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ISSN (E) 2790-9352
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VOLUME 06 ISSUE 01

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Published by:
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VOLUME 06 ISSUE 01

PJHS
Pakistan Journal of Health Sciences
Lahore

ISSN (E) 2790-9352
ISSN (P) 2790-9344

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Published by:
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DOI: https://doi.org/10.54393/pjhs.v6i1.2835

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

The Rise of Polycystic Kidney Disease (PKD): Early Detection and New Treatment Options

OPEN ACCESS

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ARTICLE INFO

How to Cite:

Mumtaz, S. U. (2025). The Rise of Polycystic Kidney Disease (PKD): Early Detection and New Treatment Options. Pakistan Journal of Health Sciences, 6(1), 01. https://doi.org/10.54393/pjhs.v6i1.2835

Polycystic Kidney Disease (PKD) is a hereditary disorder that results in the formation of fluid-filled cysts in the kidneys. Cysts can cause damage or worse renal failure over time. Although PKD has no cure, recent developments have helped in early detection and provided additional therapies that can control the condition and improve the quality of life of the affected. Early detection is essential to slow its progression and maintain renal function. It is inherited in an autosomal dominant pattern so the children of the afflicted parents have a 50% chance of developing this condition. The symptoms include kidney infections, flank pain, high blood pressure, and frequent urination, they don't show up until later in life. Cyst formation may start sooner in childhood, and the condition may advance more quickly in certain instances. PKD can be confirmed by performing genetic testing in families with a history of the condition. Imaging methods such as MRI and ultrasound are essential in early diagnosis. Ultrasonography can be used to visualize the cyst. If this condition is diagnosed early medical professionals can treat the patient and control the symptoms while delaying kidney impairment. Some medications can delay its progression, but currently, no cure is there. There is a drug called Tolvaptan which inhibits the growth of kidney cysts and aids in maintaining renal function, is considered one of the noteworthy achievements. It has shown promising results in delaying the need for dialysis or kidney transplants by inhibiting the hormone vasopressin, a hormone responsible for the formation of cysts. Hypertension can worsen renal damage so drugs such as ACE inhibitors and angiotensin receptor blockers (ARBs) are prescribed to maintain blood pressure levels.

Stem cell researchers are working on the repairing and renewal of damaged kidney tissue. Research on this subject has just started but the potential of this research can be foreseen in producing novel medicines that could revolutionize PKD care shortly. Life style plays an important role in controlling PKD, kidney strain can be reduced by maintaining a healthy life style, eating a diet that is low in proteins, and avoiding smoking.

Frequent exercise can improve health and blood pressure. PKD is a health concern that affects people significantly but early detection and new treatments like tolyaptan and ongoing research are the hope for patients.

Although no cure is available advancements in managing the disease can improve the quality of life and delay renal failure. With early intervention and the right treatment approach, PKD patients can lead healthier and more fulfilling lives.

DOI: https://doi.org/10.54393/pjhs.v6i1.1990

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
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Original Article

OPEN ACCESS

Prevalence of Tardive Dyskinesia and Its Association with Antipsychotic Drug and Depression in Geriatric Population in Lahore, Pakistan

Maria Mustafa[1*], Kanzul Kamal[1], Irsa[1], Minahil[1], Laiba Azam[1] and Aira Eman[1]

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ARTICLE INFO

Keywords:
Tardive Dyskinesia, Depression, Antipsychotic Drugs, Geriatric Population, Prevalence

How to Cite:
Mustafa, M., Kamal, K., Irsa, ., Minahil, ., Azam, L., & Eman, A. (2025). Prevalence of Tardive Dyskinesia and Its Association with Antipsychotic Drug and Depression in Geriatric Population in Lahore, Pakistan: Tardive Dyskinesia's Association with Antipsychotic Drug and Depression. Pakistan Journal of Health Sciences, 6(1),02-06. https://doi.org/10.54393/pjhs.v6i1.1990

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Received date: 30th August, 2024
Acceptance date: 8th January, 2025
Published date: 31st January, 2025

ABSTRACT

Tardive Dyskinesia" is the subtle onset of rhythmic, stereotype, repetitive movement of the face, mouth, and tongue. The basic pathology behind this disease is hypersensitization of dopamine receptors. **Objective:** To find out the prevalence of tardive dyskinesia and its association with depression and antipsychotic drug administration in the geriatric population. **Methods:** A cross-sectional descriptive study was conducted for a period of four months from February 2023 to May 2023. The data were collected from different hospital settings in Lahore. A sample size of 150 elderly individuals aged 55-80 years were included. Depression was evaluated through Geriatric Depression Scale whereas abnormal involuntary movement Tardive Dyskinesia is evaluated through AIMS scale. Chi square test was used to determine the association between variables Depression, Antipsychotic drug and Tardive Dyskinesia. Informed consent and ethical approval were taken from all participants. **Results:** Out of 150 respondents, 78(52%) male and 72 (48%) were female. Mean age was 65 years ± 7.21 SD. Among all individuals 20% experienced mild, 42.7% with moderate and 37.3% experienced severe depression.27.3% of the population taking antipsychotic drug experienced Tardive dyskinesia while it was absent in 22.67% of the individuals who were taking antipsychotic drug.20.67% of old individuals with severe depression were with Tardive dyskinesia. **Conclusions:** It is concluded from above study depression is common among geriatric population. Antidepressant drugs used to treat depression for longer duration because abnormal movement called tardive dyskinesia. There is significant relation of Tardive Dyskinesia with depression and antipsychotic drugs.

INTRODUCTION

Tardive syndrome is a vast term and includes different categories of movement disorders. It majorly encompasses tardive dyskinesia and tardive dystonia [1]. The Term "Tardive Dyskinesia" was first introduced by Faurbye in 1964. Tardive means arriving or coming late. Dyskinesia means abnormal involuntary movements which are more prominent around the mouth, and jaw and later can be developed in the upper limb, lower limb, and pelvis. The first case of Tardive Dyskinesia was reported in 1957 by Joseph while the first anti-psychotic chlorpromazine was introduced in 1952 [2]. "Tardive Dyskinesia" is the subtle onset of rhythmic, stereotype, repetitive movement of the face, mouth, and tongue (frowning of the forehead, puckering of lips, abnormal chewing, tongue protrusion) and also frequently involves the trunk and lower extremities (like piano playing a movement of fingers and in the trunk like pelvic gyration shrugging of shoulders, etc.) resulting from prolonged used of antipsychotic drugs [3]. Vesicular Monoamine transporter type 2 is responsible for wrapping dopamine present in the cytoplasm of presynaptic neurons in vesicular form. After stimulation of dopaminergic neurons, dopamine is discharged from presynaptic neurons and binds to postsynaptic D2 receptors and generates the response but when the patient uses dopaminergic blocking agents, dopamine can't bind to D2 receptors. In feedback response, there are

DOI: https://doi.org/10.54393/pjhs.v6i1.1990

more expressions of D2 receptors on postsynaptic neurons. Because of this more dopamine is released and there is hypersensitization of D2 receptors producing Dyskinesia (abnormal movements) which is the clinical presentation of Tardive Dyskinesia. While considering antipsychotics, second-generation has fewer adverse effects as compared to first-generation drugs of high potency with higher dopamine receptor activity [4]. Risk factors for tardive dyskinesia are broadly classified into two major categories i.e. modifiable and non-modifiable. Major modifiable risk factors include class of dopamine receptor blocking agent (either first generation or second generation), duration of illness, the dosage of the drug, length of exposure to DARBs, alcohol consumption, and smoking. Non-modifiable risk factor comprises of elderly population, female gender, African ethnicity, patients suffering from schizophrenia, and having neurological problems or mood disorders [5]. Tardive dyskinesia is rarely reported in the Asian population or there may be inadequate published research available for this ethnicity [6]. The rating tool to assess TD which is most frequently used is the "Abnormal Involuntary Movement Scale" (AIMS). According to the Schooler-Kane standard to diagnose TD is, a) Involuntary movement or symptoms of TD appear after at least 3 months of therapy with antipsychotic drugs, b) Abnormal, uncontrolled movement present in almost 2 or more body parts in case of mild but should be present in at least 1 body region with moderate severity, c) There should be no other cognitive impairment that can cause abnormal uncontrolled movement [4]. Tardive dyskinesia is not a rare disease. Its incidence rate is increasing by 3%-5% per annum and recently its prevalence is found to be about 20-30% [7]. 15-40% lifetime prevalence of tardive dyskinesia is reported among patients who are taking antipsychotic drugs and it is more prevalent in the elderly aged>55 and in postmenopausal women [8]. Patients taking first-generation antipsychotics are more prone to develop tardive dyskinesia than second-generation antipsychotics. A meta-analysis review showed that TD is 30% prevalent in patients taking first-generation antipsychotics and 21% prevalent in patients who are being treated with second-generation antipsychotics [9]. According to the guidelines from the American Psychiatric Association, patients should be checked for symptoms of TD before starting DRBA treatment. For patients on DRBAs, examinations should be conducted at least twice a year. Additionally, assessments should be done whenever there's a change in the DRBA dosage or type, or if new movement symptoms are noticed [10]. Pharmacological therapy for tardive dyskinesia includes VAMT2 (vesicular monoamine transporter 2) inhibitors which majorly include drugs like trabenazine, valbenazine, and tetrabenazine [11]. Substitution of antipsychotics with low potency DARBS and the use of amantadine may also prove effective in treating TD [12]. Deep brain stimulation has proven effective in the treatment of tardive dyskinesia [13]. The Tardive Dyskinesia Impact Scale (11-item questionnaire) is formulated to assess the impact of disease on a patient's quality of life [14]. Tardive dyskinesia affects a person's mental well-being, and professional life, and also interferes with their social activities [15]. Patients suffering from tardive dyskinesia may experience the exacerbation of psychological problems, increased incidence of chronic illness, and problems with speech, gait, respiration, etc. [16].

METHODS

It was cross-sectional descriptive study that was conducted on geriatric population from different hospital settings of Lahore, i.e. General Hospital, Jinnah Hospital, Fountain House, and Mayo Hospital. The study was of 4 months' duration after approval of the Ethical committee of university and respected HOD i.e. 16th January, 2023 with Reference no. RE-010-2023. After approval of Ethical Committee, it was started from January 2023 to May 2023. The information was collected from the geriatric population aimed to determine the prevalence of Tardive Dyskinesia in the geriatric population and its association with depression and antipsychotic drugs. Non probability purposive sampling technique was used for data collection. A sample of 150 geriatric individuals aged 55-80 years both male and female were included in the study. The sample size was calculated by using WHO calculator with 11% population proportion, 95% confidence level, and 5% margin error. Individuals taking antipsychotics were either diagnosed with schizophrenia, bipolar disorder or substance abuse were screened. However, only those patients who scored greater than 5 on Geriatric depression scale and antipsychotic drug was prescribed in their medical records, were included. Before participation, the consent of patients was taken after giving a comprehensive understanding of the survey. Depression was assessed by the Geriatric depression scale which was filled after asking the questions from patients. Cutoff score for Geriatric depression scale was 0-4 considered normal and 12-15 indicate severe depression. The Geriatric depression scale is a 15-questionnaire scale, depending on age, education, and complaints; with 5-8 indicate mild depression; 9-11 indicate moderate depression; and 12-15 indicate severe depression. Tardive Dyskinesia was assessed by AIMS (Abnormal Involuntary Movement Scale) by observing involuntary movements in participants. Patients taking antipsychotic medications are doing so as prescribed by their doctors and are suffering from severe depression. Data were analyzed using SPSS version 24.0. Mean and standard deviation was calculated of quantitative

DOI: https://doi.org/10.54393/pjhs.v6i1.1990

variables and qualitative measures are presented in the form of frequency and pie or bar charts. Chi Square test was applied to see association between qualitative variables Tardive dyskinesia, depression and antipsychotic drug.

RESULTS

Tardive Dyskinesia was assessed in 150 geriatric populations using the AIMS (Abnormal Involuntary Movement Scale) and its association with depression using the Geriatric depression scale for measuring depression and those who were taking antipsychotic drugs. Table 1 showed the demographic values of the participants. The research study had a total of 150 participants, among them 56 percent of the participants were of 55-65 years of age and 44 percent of the participants were of 66-80 years of age. The study groups include participants of both genders 52 percent of participants were male and 48 percent were female. Among them 76.7% of the participants were married, 16.7% were widows, and 6.7% of divorced. Socioeconomic status of the study group where 7 participants belonged to the upper class, 112 participants belonged to the middle class and 31 participants were of the lower class. The total number of participants was 150, among them 50 percent of the participants had been taking antipsychotic drugs for many years and 50% of the participants were not taking any antipsychotic drug.

Table 1: Demographic Characteristics of the Study Participants

Variables	Frequency (%)
Age (Years)	
55-65 Years	84 (56%)
66-80 Years	66 (44%)
Gender	
Male	78 (52%)
Female	72 (48%)
Marital Status	
Married	115 (76.7%)
Widow	25 (16.7%)
Divorced	10 (6.7%)
Socioeconomic Status	
Upper	7 (4.7%)
Middle	112 or 74%
Lower	31 or 20.7%
Family Status of The Study Group	
Nuclear	64 (42%)
Joint	86 (57.2%)
Patient Taking Antipsychotic Drugs	
Yes	75 (50%)
No	75 (50%)

Table 2 showed the frequency of tardive dyskinesia and depression in geriatric individuals. The research findings indicate that among 150 participants 36.7% of participants 55 in numbers were aware of involuntary movement in their body Tardive dyskinesia and 63.3% of the participants 95 in numbers were not with Tardive dyskinesia and Among 150 participants 30 participants were present with mild depression, 64 participants were with moderate depression and 56 were with severe depression.

Table 2: Frequency of Tardive Dyskinesia in the Geriatric Population

Conditions	Subcategory		Frequency (%)
Tardive Dyskinesia	Present		55 (36.7%)
	Absent		95 (63.3%)
Depression	Mild	5-8	30 or 20%
	Moderate	9-11	64 (42.7%)
	Severe	12-15	56 (37.3 %)

Table 3 showed that there were 41 participants taking antipsychotic drug were with Tardive dyskinesia and 34 participants were not developed Tardive dyskinesia. A chi-square tests was applied between variable Tardive dyskinesia and with antipsychotic drug. According to chi-square tests, the p-value for tardive dyskinesia with antipsychotic drug was <0.05, which showed that there is a significant relation between tardive dyskinesia antipsychotic drugs.

Table 3: Association of Tardive Dyskinesia with Anti-Psychotic Drugs in Geriatric Population

The Patient Taking the Antipsychotic Drug	Frequency of Tardive Dyskinesia Frequency (%)		p-Value
	Present	Absent	
Yes	41 (27.3%)	34 (22.67%)	<0.05
No	14 (9.33%)	61 (40.67%)	
Total	55 (36.67%)	95 (63.3%)	

Table 4 showed that there are highest number of participants developed moderate depression and Tardive dyskinesia was more observed in participants having moderate to severe depression. A chi-square tests was applied between Tardive Dyskinesia and Geriatric Depression Scale to see association between them. According to chi-square tests, the p-value for tardive dyskinesia with depression was <0.05, which showed there is a significant association of tardive dyskinesia with depression.

Table 4: Association of Tardive Dyskinesia with Depression in Geriatric Population

Tardive Dyskinesia	Geriatric Depression Scale Frequency (%)			p-Value
	Mild	Moderate	Severe	
Present	0	24 (16%)	31 (20.67%)	<0.05
Absent	40 (26.67%)	30 (20%)	25 (16.67%)	
Total	40 (26.67%)	54 (36%)	56 (37.33%)	

DISCUSSION

In a study conducted in Ethiopia in 2022, they found the Prevalence of TD, and the results show that 15.4% of patients had TD who were taking antipsychotic drugs [17]. In this study, the calculated prevalence of TD is 36.67%

DOI: https://doi.org/10.54393/pjhs.v6i1.1990

which may suggest that tardive dyskinesia is more prevalent in Pakistan. In a study conducted in 2023, tardive dyskinesia was assessed by Impact-TD Scale and guided the treatment plan but we used the AIMS scale and GDS scale to assess Tardive Dyskinesia so the disease can be diagnosed either by using AIMS scale or TIDS scale [18]. A retrospective analysis was conducted whose results showed that there were higher chances of developing TD in patients those who were taking antipsychotic drugs for more than 1 year. The participants included in the retrospective analysis were adult patients with schizophrenia, major depressive disorder, and bipolar [19]. This study's results also showed that the geriatric participants who have been taking anti-psychotic medication for years are at high risk of developing TD and the prevalence of TD in these patients was 22% which is higher than those taking anti-psychotic for months this proposed that TD can develop either in adults or geriatric but the main factor is taking anti-psychotic drugs for more than 3 months. Another study showed that the diagnosis and treatment of TD are important as it is highly disrupting for both patients and their families and affects their quality of life. To differentiate TD from other diseases, they notice the use of DRBA, their duration of use, and any other neurodegenerative disease [9]. We also assessed TD based on the duration of antipsychotic administration but we excluded the patients having any other neurodegenerative disease. In 2023 it was discovered not only psychotic problems and Antipsychotic drug consumption but Traumatic brain injury can also be a cause of Tardive Dyskinesia. A case study of chronic mandibular Tardive Dyskinesia was presented which is caused by concussion with no history of Anti-Psychotic Drugs [20]. We find the prevalence of Tardive Dyskinesia in people who are old, diagnosed as depressive, or are taking antipsychotic drugs. These findings suggest that tardive dyskinesia can develop if the patient is suffering from any neurodegenerative condition with no history of antipsychotic drugs.

CONCLUSIONS

Tardive Dyskinesia is more prevalent in the geriatric population, particularly among those who were with severe depression and have been on long-term antipsychotic medications. These involuntary movements are highly distressing and can significantly impact a person's quality of life, often leading to isolation and worsening depression. There is a strong association between tardive dyskinesia, depression, and the use of antipsychotic drugs.

Authors Contribution

Conceptualization: MM
Methodology: MM, KK, I, M, LA, AE
Formal analysis: MM
Writing, review and editing: MM, KK, I, M, LA, AE

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.1990

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DOI: https://doi.org/10.54393/pjhs.v6i1.1490

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Effectiveness of Aromatherapy on Pain and Anxiety among Burns Patients at Public Hospital of Karachi

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ARTICLE INFO

Keywords:
Aromatherapy, Pain Management, Anxiety Reduction, Burn Patients, Complementary Therapy

How to Cite:
Haider, A., Micah, S., Raja, ., Khan, A. U., Kumar, S., & Bibi, A. (2025). Effectiveness of Aromatherapy on Pain and Anxiety among Burns Patients at Public Hospital of Karachi: Effectiveness of Aromatherapy in Burn Patients. Pakistan Journal of Health Sciences, 6(1), 07-11. https://doi.org/10.54393/pjhs.v6i1.1490

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Received Date: 5th April, 2024
Acceptance Date: 5th January, 2025
Published Date: 31st January, 2025

ABSTRACT

Aromatherapy is a safe supplement to reduce the pain and anxiety among burn patients. **Objective:** To determine the effectiveness of aromatherapy on pain and anxiety among burn patients at a public tertiary care teaching Hospital, Karachi, Pakistan. **Methods:** A quasi-experimental design was employed, on participants of both genders aged between 18-54 years and had burns that were less than 40% Total Body Surface Area. The sample size for this study was calculated through Open Epi version 3.0 with a proportion formula and the calculated sample size was 88. Two open accessed questionnaires Pain and Anxiety Symptom Scale (PASS-20) and Visual Analogue Scale (VAS) was used to collect the data. Wilcoxon signed-rank test was used to test the effect of the intervention (8.00 to 5.75). **Results:** The results showed that aromatherapy significantly reduced post-intervention pain (p-value0.001).The sub-scale "cognitive", "escape avoidance", and the global PASS score was significant after intervention with P-values <0.0001, 0.039, and 0.025 respectively. The mean scores of PASS in all sub-scales and the global score was significantly decreased after the intervention with a large effect size (r>0.5) using Cohen's (1988) criteria. **Conclusions:** The findings suggested that aromatherapy was a safe supplement to reduce the pain and anxiety among burn patients. Nurses can use at the clinical practice to enhance the use of aromatherapy by which the pain and anxiety can reduce among burn patients.

INTRODUCTION

Burn injuries result in excruciating agony, which is made worse by a number of variables including wound healing, physical therapy, and other invasive procedures [1]. Burn pain is an intense pain that follows an injury and is regarded by sufferers as one of the worst types of pain. Throughout the course of treatment, burn pain persists at varying intensities and, in certain situations, may develop into chronic pain. While the size and severity of the burn injury at the outset are directly associated to pain, other treatment modalities, the presence of infection, rehabilitation techniques, and the psychosocial milieu in which the patient is located all influence pain to differing degrees [2]. An anxious patient is not capable of caring of them and therefore relies on others (nurses and medical staff) to do so, which could also extend hospitalization and increase costs of care [3]. Analgesic drugs and sedatives are commonly used to treat pain and anxiety in patients who have complications such as bleeding, nausea, drowsiness, or respiratory problems [4]. Non-pharmaceutical intervention is also beneficial for the patients who do not respond well to pharmacological intervention or who had an experience regarding the side effects of medication and are cautious to take medicine [5]. Aromatherapy is a simple, safe and easy way to incorporate it into nursing practice for pain and anxiety management [6]. Aromatherapy combined with massage has been shown to decrease anxiety and pain, with some positive consequences identified for the normal mood and reducing stress [7]. An exploratory study, case analysis, and anecdotal reports support the advantages for patients

DOI: https://doi.org/10.54393/pjhs.v6i1.1490

and lay the groundwork for future studies. There are countless chances for aromatherapy research in whole-person care to promote well-being, healing possible uses for infection control, wound healing, menopause, and inflammation are particularly promising [8]. It is regarded as a holistic nursing intervention that can assist nurses in reducing pain and anxiety [9]. Aromatherapy also has effect on parasympathetic nervous system to alleviate the symptoms of pain and anxiety [10].

Therefore, this study was designed to evaluate the effectiveness of aromatherapy on pain and anxiety among burn patients.

METHODS

Quasi experimental design was utilized and the study was carried out at the Dr. Ruth K.M Pfau Civil Hospital Karachi. The study was completed in two months (August to October 2021) after the approval from Ethical Review Committee (ERC) and institutional permission with ERC reference number: 4290921AHNUR. The target population was all burn patients with the burn percentage of mild to moderate with low Body surface area, < 40% Total Body Surface Area (TBSA) or less as per "rule of nine". Burns patients who were affected from any type of burn like by Fire or flame, heat or radiation, radioactivity, electricity, friction or contact with chemicals were selected. The sample size was estimated using (OpenEpi info program version 3.0), using the Confidence Interval (CI) 95% power of study 1-β=80% and sample size was 88. Participants were divided into two groups, aromatherapy was administered exclusively to the interventional group, the control group received comprehensive standard care. The control group received standard care, which included routine medical treatment, medications, and analgesics as per hospital policy, while the interventional group received aromatherapy. The computed sample size for both groups was 44/44, based on a mean difference of 6.43, before and after aromatherapy intervention for lowering pain and anxiety among burn patients. The percentage of burns and the location of burns were obtained from hospital records and confirmed through patient reports during the initial assessment. This data was collected as part of the demographic and clinical information recorded for each participant at the start of the study. A Consecutive sampling technique was used to recruit the participants in the study. As a research instrument, a two-part questionnaire was used to collect data. The first section contained demographic information about patients, as well as disease information, such as the proportion of burns, history of burns, location, and cause of burns. The second sections contain Visual Analog Scale (VAS) and Pain and Anxiety Symptom Scale (PASS-20) to calculate patients' pain and anxiety levels [11]. The highest core indicates the severe level of anxiety experienced by the target group. The VAS score questionnaire employs numbers that correspond to the severity of pain they were experiencing. Participants were divided into two groups: the intervention group and the control group, based on their assigned wards in the burn unit. The control group received routine care, including wound care and standard analgesics per hospital policy. The intervention group received the same care along with aromatherapy using lavender oil, applied twice daily for 15 minutes over two days. Aromatherapy involved placing seven drops of lavender oil on a cotton ball positioned 20 cm from the patient's nose. This intervention duration was limited due to COVID-19 restrictions, reducing hospital stays. Data on pain and anxiety levels were collected before and two days after the intervention. Patients on regular analgesics were included, but those requiring high-dose pain medications were excluded. The Statistical Package for Social Sciences (SPSS) version 23.0 was used to analyze data. The numeric variables were expressed as mean ± standard deviation; the categorical variables were represented as frequencies and percentages. Wilcoxon signed-rank test was used to compare pain and anxiety scores in each group before and after the intervention was implemented. For all tests, the P-value of ≤ 0.05 was considered statistically significant.

RESULTS

Table 1 showed that most of the participants in both groups were aged between 18 to 30 years. The majority of participants were married, had matriculation level education, and was laborers by profession. Burn locations among participants were: Intervention group - lower trunk + multiple areas (6.81%), lower trunk (2.27%), upper trunk + multiple areas (65.90%), upper trunk (25%); Control group - lower trunk + multiple areas (15.90%), lower trunk (2.27%), upper trunk + multiple areas (54.54%), upper trunk (27.27%). All the participants did not document any type of allergy (Table 1).

Table 1: Demographic Characteristics of the Study Participants in Control and Interventional Groups

Groups	Control N (%)	Intervention N (%)
Age		
18 to 30 Years	25 (56.8%)	30 (68.2)
31 to 42 Years	9 (20.5%)	9 (20.5)
43 to 54 Years	10 (22.7%)	5 (11.4)
Gender		
Male	26 (59.1%)	30 (68.2)
Female	18 (40.9%)	14 (31.8)
Marital Status		
Married	29 (65.9%)	24 (54.5)
Un-Married	15 (34.1%)	20 (45.5)
Participants Education		
Illiterate	10 (22.7%)	0 (0.0%)
Primary	15 (34.1%)	15 (34.1%)
Matric	19 (43.2%)	27 (61.4%)

DOI: https://doi.org/10.54393/pjhs.v6i1.1490

Graduate	0 (0.0%)	2 (4.5%)
Participants Profession		
Laborer	20 (45.5%)	18 (40.9%)
House Wife	17 (38.6%)	5 (11.4%)
Student	4 (9.1%)	12 (27.3%)
Retired From Job	1 (2.3%)	4 (9.1%)
Others	2 (4.5%)	5 (11.4%)
Participants Allergy		
No	44 (100.0%)	44 (100.0%)
Yes	0 (0.0%)	0 (0.0%)
Location of Burns		
Lower Trunk + Multiple Areas	3 (6.81%)	7 (15.90%)
Lower Trunk	1 (2.27%)	1 (2.27%)
Upper Trunk + Multiple Areas	29 (65.90%)	24 (54.54%)
Upper Trunk	11 (25.00%)	12 (27.27%)

The Figure 1 showed burn locations in the intervention and control groups. Most burns were in the *Upper Trunk + Multiple Areas* (29 interventions, 24 control), followed by the *Upper Trunk* (11 interventions, 12 control). The *Lower Trunk + Multiple Areas* had 3 intervention and 7 control cases, while the *Lower Trunk* had only 1 case in the intervention group and none in the control group.

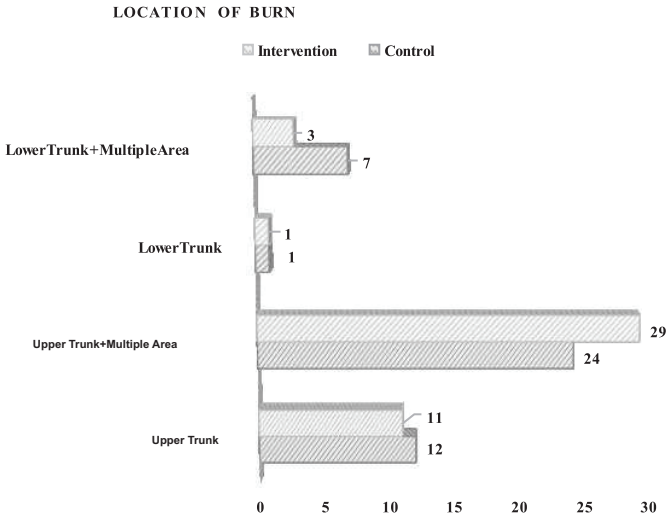

Figure 1: Distribution of Location of Burns between the Participants from Control and Intervention Group

Table 2 illustrated the causes of burns in study participants. 5 (11.36%) participant had burnt from electric, 36 (81.81%) participants had burnt from fire, 3 (6.81%) participant had burnt from scald and no any participant had burnt from acid, while in the control group 11 (25%) participant had burnt from electric, 29 (65.90%) participants had burnt from fire, 1 (2.27%) participant had burnt from scald and 3 (6.81%) participant had burnt from acid.

Table 2: Causes of Burns among Study Participants

Cause of Burn	Intervention Group N (%)	Control Group N (%)
Electric	5 (11.36%)	11 (25%)
Fire	36 (81.81%)	29 (65.90%)
Scald	3 (6.81%)	1 (2.27%)
Acid	0 (0%)	3 (6.81%)

Table 3 presented the severity of pain among study participants in both groups, measured using the Visual Analog Scale (VAS). All participants reported some level of pain. In the control group, 19 (43.2%) experienced severe pain, while in the interventional group, 24 (54.5%) reported very severe pain and 16 (36.4%) reported unbearable pain. Overall, the interventional group had a higher pain score compared to the control group. After the intervention, the median pain score was 6 for both groups. Most participants in each group experienced severe pain, often following very severe pain.

Table 3: Severity of Pain among Participants (VAS Scale)

Severity of Pain	Intervention Group N (%)	Control Group N (%)
Severe	0	19 (43.2%)
Very Severe	24 (54.5%)	0
Unbearable	16 (36.4%)	0
Median Pain Score	6	6

Table 4 expressed the Wilcoxon signed-rank test to evaluate the changes in the intensity of pain before and after intervention in both the control and interventional group. The results exhibited that the post-intervention mean score of pain has significantly decreased after aromatherapy (p-value <0.001*) with a large effect size (r = 0.61) using Cohen's (1988) criteria.

Table 4: Comparing the Changes in the Mean Scores before and after the Aromatherapy in Control and Intervention group by Wilcoxon Signed-Rank Test

Groups	VAS-Score	Mean	Mean Rank	Z	R	p-Value
Control	Vas Score Pre-Intervention	6.16	305.00	-1.793	0.19	0.073
	Vas Score Post-Intervention	5.84	-	-	-	-
Intervention	Vas Score Pre-Intervention	8.00	4.50	-5.805	0.61	<0.001*
	Vas Score Post-Intervention	5.75	-	-	-	-

Table-5 compared the changes in anxiety mean scores before and after the intervention in the control group of burn patients using the Wilcoxon signed-rank test. The results showed significant changes in the Cognitive sub-scale ($p < 0.0001$), Escape/Avoidance sub-scale ($p = 0.039$), and Global Score ($p = 0.025$). However, no significant changes were observed in the Fear sub-scale ($p = 0.286$) and Physiological Anxiety sub-scale ($p = 0.330$).

DOI: https://doi.org/10.54393/pjhs.v6i1.1490

Table 5: Comparison in Anxiety Mean Scores before and after the Intervention in the Control Group

Pain and Anxiety Symptom Scale	Pre-Intervention Mean Score	Post-Intervention Mean Score	Z	R	p-Value
Cognitive	19.7727	18.8409	-3.493	0.37	<0.0001*
Escape/Avoidance	19.3409	18.7500	-2.061	0.22	0.039*
Fear	19.8636	19.4773	-1.068	0.11	0.286
Physiological Anxiety	19.4545	19.1591	-0.974	0.10	0.330
Global Score	78.4318	76.2273	-2.248[b]	0.24	0.025*

Table 6 presented the changes in anxiety mean scores before and after the intervention in the interventional group of burn patients. The results, analyzed using the Wilcoxon signed-rank test, show significant reductions in anxiety across all sub-scales and the global score (all p-values < 0.001). The anxiety scores for Cognitive, Escape/Avoidance, Fear, Physiological Anxiety, and the Global Score all decreased notably after the intervention, indicating a significant improvement in anxiety levels among the participants.

Table 6: Comparison in Anxiety Mean Scores Before and After the Intervention in Interventional Group

Pain and Anxiety Symptom Scale	Pre-Intervention Mean Score	Post-Intervention Mean Score	Z	R	p-Value
Cognitive	22.2273	17.6136	-5.365	0.57	<0.0001*
Escape/Avoidance	21.5227	16.8182	-5.573	0.59	<0.0001*
Fear	22.5227	17.8864	-5.313	0.57	<0.0001*
Physiological Anxiety	21.4318	17.1364	-5.239	0.56	<0.0001*
Global Score	87.7045	69.4545	-5.374	0.57	<0.0001*

DISCUSSION

This study was conducted to determine the effectiveness of aromatherapy on pain and anxiety among burns patients. In the current study, males as (68.2% -31.8%) had a higher prevalence of burn. Another research study conducted in Pakistan found similar results [11]. Similarly, the American Burns Association (ABA) reported that male has the higher prevalence of burns compared with females (68% vs. 32%) in the United States [12]. In the current study, more than half of the participants, 24 (54.5 %) in the control group and 29 (65.9 %) in the intervention group, had the upper trunk and multiple areas burn injuries. However earlier studies showed differed burn injury location i.e. the extremities, particularly the upper extremities, were the most potential sites for suffering burn injuries [13]. Another study found that the trunk and lower limbs were mostly affected by burn injuries [14]. Although pain and anxiety scores decreased in both groups in the current study, the decrease was more prominent in the intervention group than in the control group. This difference could be attributed to the aromatherapy program, which was provided to the intervention group. The pain score on VAS has significantly reduced from 8.00 to 5.75 after the intervention in experimental group with significant p-value (<0.001). The mean global anxiety scores of (Cognitive anxiety, Escape/Avoidance, Fear of pain, Physiological anxiety) subscales on PASS has significantly decreased in the interventional group (all has p-value < 0.001). These findings were congruent with another study, indicating the effectiveness of aromatherapy to reduce pain and anxiety [15]. A meta-analysis on effectiveness of the aromatherapy also reported similar findings [8]. Moreover, another study exhibited remarkable effectiveness of aromatherapy for pain management but not anxiety [16]. Furthermore, another study found that burn victims' subjective pain intensity and anxiety levels were reduced when they inhale aromatherapy with Damask rose essence [1]. However, other studies supported the remarkable effectiveness of aromatherapy for the reduction of anxiety [17, 18]. While another meta-analysis found that patients with burns may experience less anxiety while using aromatherapy [19]. Another study also found that anxiety was reduced by using Rose Damascene inhalation aromatherapy [20].

CONCLUSIONS

In conclusion, the intervention led to significant reductions in anxiety levels across all sub-scales and the global score in the interventional group of burn patients, with all p-values being less than 0.001. This indicates that the intervention was effective in reducing cognitive, escape/avoidance, fear, physiological anxiety, and overall anxiety.

Authors Contribution

Conceptualization: SM, AM
Methodology: R, SM
Formal analysis: AUK, AH
Writing, review and editing: AH, SK, AB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.1490

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DOI: https://doi.org/10.54393/pjhs.v6i1.2028

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Thyrotoxicosis: What is the Cause in Our Population?

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ARTICLE INFO

Keywords:
Thyrotoxicosis, Graves' Disease, Toxic Adenoma, Toxic Multinodular Goiter, Endocrinology

How to Cite:
Ali, A., Khan, S., Anees, ., Hassan, T., & Mufti, F. (2025). Thyrotoxicosis: What is the Cause in Our Population? Causes of Thyrotoxicosis. Pakistan Journal of Health Sciences,6(1), 12-16. https://doi.org/10.54393/pjhs.v6i1.2028

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Received date: 25th September, 2024
Acceptance date: 10th January, 2025
Published date: 31st January, 2025

ABSTRACT

Thyrotoxicosis is an endocrine disorder in which excess amount of thyroid hormone is secreted in the blood stream and causes its action at the tissue level. Thyrotoxicosis highly affects the quality of life of patients suffering from the disease in carrying out daily activities. Proper treatment of thyrotoxicosis requires an accurate diagnosis. **Objective:** To determine the causes of thyrotoxicosis in patients reported for evaluation and management to specialized endocrine unit. **Methods:** This was a descriptive cross sectional observational study conducted by convenient sampling in Outpatient Department (Endocrinology Clinic) Khyber Pakhtunkhwa in six month's duration (15th December 2023 to 15th May 2024) having sample size n=118. Thyrotoxicosis was labeled if patient has high T3, T4 (thyroxine and/or triiodothyronine) levels and suppressed thyroid stimulating hormones TSH levels. Information was gathered from the patients regarding their clinical signs and symptoms and anthropometrics. Laboratory investigations of thyroid function tests were obtained and analyzed. **Results:** The mean age of 118 patients was 40.39 ± 13.69 years, 28% male and 72% female patients were in enrolled in the study. Graves' disease was most common form thyrotoxicosis making count of 50% of patients followed by toxic adenoma, toxic MNG, thyroiditis 16% and 14 % respectively. Anti-thyroid drugs count 43% of most of the patient's treatment offered followed by radioactive iodine 28%. **Conclusions:** In conclusion, the main cause of thyrotoxicosis, includes grave's disease, toxic adenoma and toxic MNG in Pakistani population. Thyrotoxicosis was more prevalent among female population as compared to males.

INTRODUCTION

Thyrotoxicosis is an endocrine disorder in which excess amount of thyroid hormone is secreted in the blood stream and causes its action at the tissue level [1]. The term "thyrotoxicosis" is high T3, T4 (thyroxine and/or triiodothyronine) levels and suppressed TSH levels [2]. Hyperthyroidism is observed in female more as compared to males with a ratio of (5:1). The overall prevalence of hyperthyroidism in female is 1.3% however it increases in age and in older females it is estimated to be 4% to 5% [3]. Literature showed that prevalence of hyperthyroidism is higher among smokers as compared to nonsmokers [4]. Young females are most prone to graves' disease while toxic nodular goiter is more prevalent in older women. Thyrotoxicosis has various etiologies, manifestations, and potential treatments [5]. Treatment of each type requires accurate diagnosis. Furthermore, β-blockers can be used in almost all forms of thyrotoxicosis, whereas Anti-Thyroid Drugs (ATDs) are useful in only some patients [6]. For appropriate treatment of thyrotoxicosis, exact diagnosis of the cause and its associated medical conditions should be dig out and patient preference for utmost priority [7]. It is difficult to diagnose exact cause of thyrotoxicosis as symptoms can mimic many other diseases and this can lead to inappropriate diagnoses and timely management of the disease [8]. For all the above reasons, literature studied showed that many globally surveys and endocrinologist opinions from different geographical areas unveiled important ambiguities in AIT causing, diagnosis and treatment is concern. Thyrotoxicosis exhibit collective clinical manifestation, caused by excessive serum thyroid hormones particularity thyroxin [9]. The clinical signs and symptoms of thyrotoxicosis exists variable feathers like weight loss fatigue and weakness like cardiovascular disorders neuromuscular disorder and gastrointestinal

DOI: https://doi.org/10.54393/pjhs.v6i1.2028

disturbance. Mostly worldwide thyrotoxicosis is diagnosed on laboratory investigations, levels of thyroxin, triiodothyronine and thyroid stimulating hormones associated with other investigations for medical condition. In general thyrotoxicosis elevated levels of serum level of thyroid hormones and thyroxin [10]. Management of thyrotoxicosis rely on the cause and severity of the disease. The treatment options of hyperthyroidism include anti-thyroid medicines, radioiodine therapy and thyroid surgery. The radioiodine treatment aims to dominate radioiodine and recovers thyroid over weeks to months. Medical treatment of Hyperthyroidism include medicine like as methimazole can temporally controls disease, β-blockers also control cardiovascular symptoms. Lastly surgical removal of thyroid gland is mainly applied on cancerous condition and has higher prevalence among female then males and younger age groups [11]. Worldwide, patients with thyrotoxicosis are examined and managed in specialized endocrine clinics. Being the super specialty clinics of endocrinology in this part of the country, endocrine patients from nearby areas are managed here in super specialty clinics.

This study aimed to find the causes of thyrotoxicosis in population in this part of the world. The current study added and improved the existing knowledge of medical physicians on thyrotoxicosis, its evaluation and management, especially in this region, thus improving the general health and quality of life of the population being affected by this endocrine disease.

METHODS

This was a descriptive cross sectional observational study conducted in Out-Patient Department (Endocrinology Clinic) Khyber Pakhtunkhwa in six month's duration (15th December 2023 to 15th May 2024). The sample was calculated by open Epi sample size calculator. The previously reported prevalence of hyperthyroidism in Pakistan is 8.38% as reported by previous literature [12]. The minimum required sample size was 118 participants at 95% confidence interval, 5% margin of error and 80% power. All those patients who were reported at OPD of Department of Endocrinology and Metabolic Disorder for evaluation and management of thyrotoxicosis were included in the study using convenient sampling technique. Those patients who were already on anti-thyroid medications and had no record of thyroid scan were excluded from study. The researcher collected the data after approval of proposal from ethical committee of college of family medicine Pakistan, approval letter issued (IRB-CFMP/22/2023). Participants were enrolled according to inclusion and exclusion criteria. Informed consent was taken from each participant, who met the inclusion criteria. Before consent, the purpose and benefits of the study were explained to participant using the patient information sheet. Trained phlebotomist took 5cc blood to carryout blood analyses. Samples/data were collected using Non-Probability Consecutive Sampling Technique from all included patients presenting to the Department of Endocrinology, Hayatabad Medical Complex Peshawar for thyrotoxicosis. Data regarding socio demographic aspects, hematological, biochemical findings and radiographic images (Thyroid Uptake Scan and Ultrasound) of thyroid gland were collected on the specially designed tool to analyze hyperthyroid patients. Thyrotoxicosis was evaluated using blood tests for thyroid function tests using immunoassay test kits. Thyrotoxicosis was labeled if patient has high T3, T4 (thyroxine and/or triiodothyronine) levels and suppressed TSH levels. Information was gathered from the patients regarding their clinical signs and symptoms and anthropometrics. The data collected was analyzed using SPSS version 21 and interpreted in tables. Frequencies, means and standard deviation were calculated for continuous variables. The Chi Square test was used for association of categorical variables. P value < 0.05 was considered statistically significant.

RESULTS

The mean age of 118 patients was 40.39 ± 13.69 years, 28% male and 72% female patients were in enrolled in the study table 1. Duration of the disease history was 13.81 ± 21.84 months. Mean thyroid function tests recorded was as T3 2.55 ± 2.92, T4 16.59 ± 7.53, TSH 1.05 ± 9.25. Inflammatory markers mean ESR was 74 ± 33. Among biochemical interpretation overt hyperthyroidism was higher 51% followed by subclinical 39% T3, 9% T4 thyrotoxicosis 1%. In appropriate treatment was taken by 20% of the thyroid patients. Goiter was found among 55% while Sjogrens' syndrome signs were among 83% of patients. TSH receptors antibodies test TRAB carried out was positive among 38% of thyroid patients.

Table 1: Baseline Characteristics of Patients (n=118)

Variable		Mean ± SD / N (%)
Age (Mean)		40.39 ± 13.69
Gender	Female	33 (28%)
	Male	85 (72%)
Duration of Disease (Months)		13.81 ± 21.84
T3 (µLU/mL)		2.55 ± 2.92
T4(µLU/mL)		16.59 ± 7.53
TSH (µLU/mL)		1.05 ± 9.25
ESR (mm/Hr)		74 ± 33
Biochemical Interpretation		
Sub Clinical		39%
Overt		51%
T3 Thyrotoxicosis		9%
T4 Thyrotoxicosis		1%
In Appropriate Treatment Taken		
Yes		20%

DOI: https://doi.org/10.54393/pjhs.v6i1.2028

No	80%
Goiter	
Yes	55%
No	45%
Sjogrens' Syndrome	
Yes	83%
No	17%
TSH Receptors Anti Bodies Test (TRAb)	
Positive	38%
Negative	62%

Grave's disease was most common form thyrotoxicosis making count of 50% of patients followed by toxic adenoma, toxic MNG, thyroiditis 16% and 14 % respectively. All the causes Graves' disease, toxic adenoma, thyroiditis and toxic MNG were significant with p value 0.004, 0.001, 0.002 and 0.072 respectively. Drug induced and TSHoma were insignificant with p value 0.241 and 0.42 respectively table 2.

Table 2: Frequency of Different Causes of Thyrotoxicosis and Association with Gender (n=118)

Variables	Male N (%)	Female N (%)	p-Value
Graves' Disease	21 (18%)	38 (32%)	0.004
Toxic Adenoma	5 (4%)	14 (12%)	0.001
Toxic MNG	5 (4%)	12 (10%)	0.072
Thyroiditis	7 (6%)	11 (9%)	0.002
Drug Induced	1 (1%)	2 (2%)	0.241
TSHoma	1 (1%)	1 (1%)	0.423

Thyroid scan showed most significant among diffuse increased uptake followed by Low Uptake 51% and 19% respectively. All types of thyroid scan have statistical significance with gender except multifocal increase up take with (p value 0.75). These results also make graves diseases among leading cause in thyrotoxicosis table 3.

Table 3: Association of Thyroid Scan in Gender among study participants

Variables	Total N (%)	Male N (%)	Female N (%)	p-Value
Diffuse Increased Uptake (Graves)	191 (51%)	60 (16%)	131 (35%)	0.002
Solitary Increased Uptake/Toxic Adenoma	60 (16%)	25 (7%)	35 (9%)	0.001
Multifocal Increased uptake	52 (14%)	20 (5%)	32 (9%)	0.753
Low Uptake	72 (19%)	24 (6%)	48 (13%)	0.001

Table 4 described treatment offered to the patients. Anti-thyroid medications treatment was offered to 43% of the offered followed by radioactive iodine 28%. Observation and monitoring required among 12% and surgery required 10% and steroid therapy required to 7% of patients.

Table 4: Treatment Offered to the study participants

Variables	n (%)
Anti-Thyroid Drugs	51 (43%)
Radio Active Iodine	33 (28%)
Surgery	12 (10%)
Observation and Monitoring	14 (12%)
Steroid Therapy	8 (7%)

DISCUSSION

The causes of thyrotoxicosis in general population were well understood in western world, globally it was known that Graves' disease was contributing factor to thyrotoxicosis [13]. The findings of the present study also appraise this literature where it was found out that 50% of population had Graves' disease followed by toxic adenoma and thyroiditis in 16 % each of population. Literature showed that thyrotoxicosis can occur in any age, child adolescent and adults were equally affected with incidence of between ages 20 and 50 years [14]. The study finding showed that mean age of the patients with thyrotoxicosis was 40.39 ± 13.69 with male to female 28% and 78% frequency. The reason behind this was thyrotoxicosis prevalence was higher in females as compared to male by ratio of 5:1 [15]. Mean duration and treatment of disease was 13.81 ± 21.84, however this could be late presentation as in this population very limited access to specialized endocrinologist and the specialized health facility. A study conducted in Turkey found mean duration of treatment of 8.0 ± 6.9 months [16]. The biochemical interpretation of this study reveals that overt hyperthyroidism was in 51 patients followed by sub clinical 39%. A study conducted found that including 0.5% overt thyrotoxicosis and 0.7% subclinical among total of 1.2% thyrotoxicosis [17]. This study found 55% of patients with diffused goiter on thyroid scan, however Hanely P reported that 10-15% of adolescent's thyrotoxicosis were caused by diffused toxic goiter [18]. These results also found that Sjogrens' syndrome signs were positive among 83% of the study population. TSH receptor antibodies (TRAb) were antibodies directed against. The TSH receptors, it was measured to differentiate between thyrotoxicosis with hyperthyroidism [19]. In this study the TRAB was performed in patients and 38% of the results were positive. Graves' disease that was an autoimmune disorder that causes immunoglobulins to activate the TSH receptor of follicular cells [20]. The risk factors for thyrotoxicosis include family history positive, female gender, termination of pregnancy postpartum period and increasing age. These study findings showed that graves' disease was the main cause of thyrotoxicosis that accounts for 50% of patients among which 32% were female population with significant p value (p=0.004). Over all the female population in this study were affected by toxic adenoma 12 % and toxic MNG 10% with p value 0.001 and 0.07 respectively. A thyroid scan can help diagnose the cause of thyrotoxicosis, it helps to differentiate between Graves' disease, Toxic Multinodular Goiters (TMNGs), and Subacute Thyroiditis (SAT) [21]. This

DOI: https://doi.org/10.54393/pjhs.v6i1.2028

study analysis of thyroid scan showed that diffuse increased uptake was higher prevalent followed by Low Uptake 51.3% and 18.5% respectively. Technically, the aim of treatment of the thyrotoxicosis was to investigate find and remove the cause, treatment includes thyroid-stimulating immunoglobulin, anti-thyroid medications methimazole, surgery thyroidectomy, and immunosuppressive steroid therapy [22]. In the study population, the treatment offered included anti thyroid drugs count 43% of most of the patient's treatment offered followed by radioactive iodine 28%. The goal of treatment has never been to cure the thyrotoxic condition rather than making the condition euthyroid without the need for thyroid hormone or to reduce the function to below normal. In limitation, the sample size was too small as this was shorter duration of the study and due to very small population proportion larger data could not be achieved. As sample size was n=118 so this small data could not be generalized in conclusion for whole population. However, it was recommended to carry out more detail cohort, prospective, metacentric studies with larger sample size to better understand the depth of the disease.

CONCLUSIONS

In conclusion, the main cause of thyrotoxicosis, includes Graves' disease, toxic adenoma and toxic MNG in Pakistani population. Female population was more affected as compared to males. Mainly patients responded to anti thyroid medications for treatment. The management of thyrotoxicosis requires specialized consultation to correctly find the cause, diagnose the condition and treat accordingly that can significantly influence the outcome of disease and the well-being of the patient.

Authors Contribution

Conceptualization: AA
Methodology: SK
Formal analysis: A
Writing, review and editing: TH, FM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Sleep Disorders and Quality of Life in Children with Cerebral Palsy

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ARTICLE INFO

Keywords:
Cerebral Palsy, Sleep Disorders, Motor Function, Epilepsy, Gross Motor Function Classification System, Children's Sleep Habit Questionnaire

How to Cite:
Bahalkani, U., Bharo, M. A., Haque, T., Bhanbhro, B. A., Ali, K., & Ali, F. K. (2025). Sleep Disorders and Quality of Life in Children with Cerebral Palsy: Sleep and Cerebral Palsy. Pakistan Journal of Health Sciences, 6(1), 17-22. https://doi.org/10.54393/pjhs.v6i1.2582

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Received date: 18th November, 2024
Acceptance date: 15th January, 2025
Published date: 31st January, 2025

ABSTRACT

Sleep disorders are common in children with Cerebral Palsy (CP) and can adversely affect their health and quality of life. **Objective:** To investigate the factors associated with sleep disorders in children diagnosed CP with age ranged from 5 to 10 years. **Methods:** A cross-sectional study was conducted for six months from March 2024 to August 2024, with 150 children aged 5 to 10 years diagnosed with CP at Department of Pediatrics, Khairpur medical college Khairpur Mir's. Data on demographics, type of CP, motor function levels (GMFCS), epilepsy presence, physiotherapy intensity, co-sleeping practices, and sleep disorder prevalence were collected. Odds Ratios (OR) and Adjusted Odds Ratios (Adjusted OR) were calculated using chi-square tests and multivariate analysis. **Results:** Participants were predominantly aged 8 to 10 years (53.3%), with spastic CP being the most common type (56.7%). Significant associations were found between sleep disorders and several factors: type of CP (OR = 2.57, P = 0.004), GMFCS levels III and IV (OR = 2.94, P = 0.001), epilepsy (OR = 2.67, P = 0.01), and low physiotherapy intensity (OR = 3.11, P < 0.001). Multivariate analysis confirmed that the type of CP (Adjusted OR = 2.45, P = 0.007) and motor impairment severity (Adjusted OR = 3.10, P = 0.001) were significant risk factors for sleep disorders. **Conclusion:** The study highlighted a high prevalence of sleep disorders among children with CP, emphasizing the need for targeted interventions addressing specific risk factors to improve sleep quality and overall well-being.

INTRODUCTION

Worldwide, Cerebral Palsy (CP) affects about 1 in 300 live births and is a set of permanent mobility disorders that first manifest in early childhood and are characterized by the impairment of muscle coordination and control. One of the many secondary health issues that children with cerebral palsy frequently face is sleeping difficulties. Sleep disorders are prevalent in this demographic and have a substantial influence on the general well-being, development, and quality of life of afflicted children as well as their families [1]. Sleep difficulties affect a significant number of children with Cerebral Palsy (CP); estimates range from 30% to 80% of this population developing sleep problems. These conditions can show up as resistance to going to bed, delayed initiation of sleep, frequent night awakenings, and trouble staying asleep. These disruptions have serious ramifications; they can cause behavioural issues, daily drowsiness, and difficulties with cognitive and emotional development [2]. A non-progressive, chronic movement impairment that manifests before the age of two years old and is brought on by brain damage is known as cerebral palsy. Brain palsy can impact musculoskeletal function, sight, language, learning, perception, and so on [3, 4]. There are several different causes that might lead to sleep disturbances in children with cerebral palsy. A higher frequency of sleep problems has been linked to specific varieties of cerebral palsy (CP), including the spastic and

DOI: https://doi.org/10.54393/pjhs.v6i1.2582

dyskinetic variants. This association is probably caused by underlying neurological abnormalities that impact the brain regions in charge of regulating sleep [5]. Furthermore, there is evidence linking sleep disorders to the severity of motor impairments as categorized by the Gross Motor Function Classification System (GMFCS). Children with higher GMFCS scores, which are associated with more mobility limitations, frequently experience more severe challenges when it comes to getting a good night's sleep [6, 7]. Additional variables that can worsen sleep difficulties include the existence of epilepsy, which affects of children with cerebral palsy. Difficulties sleeping may also be caused by the drugs used to treat epilepsy [8, 9]. Additionally, children's sleep habits may be impacted by the type and intensity of their physical therapy. Lower intensity therapy has been associated with less favorable sleep effects, for example. While it is believed that sleeping together fosters a sense of security and closeness among family members, the benefits of this practice for children with impairments in terms of better sleep quality have been disputed. According to certain research, co-sleeping may not be able to significantly reduce sleep disruptions; therefore, tailored approaches to sleep management should be examined more closely [10]. By assisting healthcare professionals and caregivers in putting into practice practical methods to enhance sleep quality, the study's findings are meant to add to the expanding corpus of research on sleep in children with cerebral palsy. In the end, children with cerebral palsy may benefit from increased sleep in terms of their quality of life, functionality, and health.

This study was investigating the factors associated with sleep disorders in children diagnosed CP with age ranged from 5 to 10 years.

METHODS

This was a cross-sectional study, conducted for six months from March 2024 to August 2024 at Department of Pediatrics, Khairpur Medical College, Khairpur Mir's. Utilizing the Children's Sleep Habit Questionnaire (CSHQ), a primary data was gathered from patients at the Children's Health Department Outpatient Clinic. Stratified sampling was employed to select participants meeting specific inclusion criteria related to ensuring relevant data for genetic analysis. Children with cerebral palsy aged 5–10 years and having a primary caregiver capable of providing information about their daily activities and sleep patterns were included, while those with chronic diseases such as cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, or malignancy were excluded; parents completed the 33-item Children's Sleep Habits Questionnaire (CSHQ) to assess eight types of sleep problems. A three-point rating system was used for each question; 1 represented infrequently, 2 represented occasionally, and 3 represented always. A sleep problem was indicated by a total score of 41 or higher. Using the scores, it was determined that the percentage of sleep problems. Participants were assessed using tools like the Gross Motor Function Classification System (GMFCS) for CP severity, the Sleep Disturbance Scale for Children for sleep disorders, and the Pediatric Quality of Life Inventory (PedsQL) and CP-QoL for quality of life (QoL). Parent proxy reports were included for children unable to self-report. A reasonable sample size calculation that is frequently used for research involving proportions (like prevalence studies) is as follows, based on the technique outlined in your study where you are evaluating sleep disturbances in children with Cerebral Palsy (CP): $n=Z2 \cdot p \cdot (1-p)/ E2$, Confidence Level: 95% ($Z=1.96$), Estimated proportion of the population ($p=0.5$ can be used for maximum variability), Margin of Error: $E=0.1$, then total number were obtained of participants was 150. A demographic information was gathered, details about physiotherapy intensity, co-sleeping, and sleep habits from parents. Secondary data included the type of CP, severity of motor dysfunction (assessed by the Gross Motor Functional Classification System or GMFCS), presence of epilepsy, and medications that could affect sleep. The independent variables were the type of CP, GMFCS, and physiotherapy intensity. Data analysis was performed using SPSS 21 software, including descriptive, bivariate (Chi-square), and multivariate (logistic regression) analyses. The study was approved by the Institutional Review Board (IRB) under the reference number (KMC/RERC/106). Informed consent was obtained from all study participants prior to enrollment in the study.

RESULTS

The demographic characteristics of the participants are summarized in Table 1. Of the children, 46.7% were between the ages of 5 and 7, and the majority (53.3%) were between the ages of 8 and 10. There were marginally more females (53.3%) than males (46.7%) in terms of gender distribution. With regard to the various types of Cerebral Palsy (CP), dyskinetic CP (20.0%), ataxic CP (13.3%), and other forms (10.0%) were the most prevalent, accounting for 56.7% of the participants. Using the Gross Motor Function Classification System (GMFCS), the gross motor functional level was determined for each participant. Level I accounted for 26.7% of the participants, level II for 33.3%, and smaller percentages were at levels III (20.0%), IV (13.3%), and V (6.7%). 18% children did not have epilepsy, but twenty percent of them had it. While 53.3% of the families did not co-sleep, 46.7% of the households reported doing so. 40.0% of children underwent low-intensity physiotherapy, 33.3% underwent moderate-intensity therapy, and 26.7% participated in high-intensity physiotherapy programs (Table 1).

DOI: https://doi.org/10.54393/pjhs.v6i1.2582

Table 1: Demographic Characteristics of Study Participants

Variables	Category	N (%)
Age (Years)	5-7	70 (46.7%)
	8-10	80 (53.3%)
Gender	Male	70 (46.7%)
	Female	80 (53.3%)
Type of Cerebral Palsy	Spastic CP	85 (56.7%)
	Dyskinetic CP	30 (20.0%)
	Ataxic CP	20 (13.3%)
	Other	15 (10.0%)
Gross Motor Functional Level	GMFCS I	40 (26.7%)
	GMFCS II	50 (33.3%)
	GMFCS III	30 (20.0%)
	GMFCS IV	20 (13.3%)
	GMFCS V	10 (6.7%)
Presence of Epilepsy	Yes	30 (20.0%)
	No	120 (80.0%)
Co-Sleeping	Yes	70 (46.7%)
	No	80 (53.3%)
Physiotherapy Intensity	Low	60 (40.0%)
	Moderate	50 (33.3%)
	High	40 (26.7%)

Footnote Statistical: Calculate Frequencies and Percentages, **Chi-Square Test:** Used for Categorical Variables

Figure 1 represents the distribution of different sleep problems in 150 kids with cerebral palsy. Night waking (affecting 26.7% of the children) was the most common problem, followed by reluctance to bedtime (20%) and delayed sleep onset (16.7%). Ten percent of the individuals reported having sleep anxiety, while 13.3% reported having problems with duration of their sleep. Daytime drowsiness and sleep-disordered breathing were both recorded in 3.3% of patients, while parasomnias (6.7%) were less common problems. The results of this study underscore the fact that children with cerebral palsy experience nighttime awakenings and trouble falling asleep, which makes focused interventions necessary to address these particular sleep disruptions in this population (Figure 1).

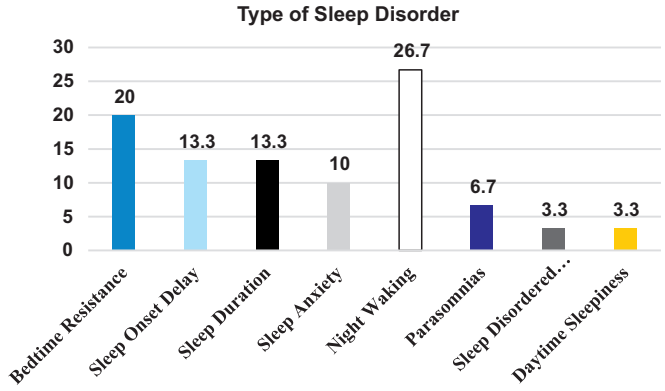

Figure 1: Different Types of Sleep Disorders among Study Participants

Table 2 presented the causes of sleep disturbances in children with cerebral palsy (N=150). A strong correlation was found between the kind of cerebral palsy and sleep disorders; children with specific types had odds of sleep disruptions 2.57 times higher (OR = 2.57, 95% CI: 1.35–4.87, P = 0.004). A child's motor function level also affected their sleep; according to the GMFCS, children at levels III and IV had nearly three times the odds of experiencing sleep disturbances than children at levels I and II (OR = 2.94, 95% CI: 1.56–5.52, P = 0.001). The existence of epilepsy was another significant risk (OR = 2.67, 95% CI: 1.22–5.83, P = 0.01), with children with epilepsy 2.67 times more likely to have sleep difficulties. The intensity of physical therapy was found to have a significant impact as well; children experiencing low-intensity therapy had 3.11 times higher odds of sleep disturbances than those receiving high-intensity therapy (OR = 3.11, 95% CI: 1.67–5.80, P < 0.001). The incidence of sleep abnormalities was shown to be 2.14 times higher in those who used anti-epileptic drugs (OR = 2.14, 95% CI: 1.12–4.08, P = 0.02). Co-sleeping, on the other hand, did not significantly correlate with sleep problems (OR = 1.33, 95% CI: 0.66–2.68, P = 0.30)(Table 2).

Table 2: Factors Associated with Sleep Disorders in Children with Cerebral Palsy (N=150)

Variables	Sleep Disorder: Yes	Sleep Disorder: No	OR (95% CI)	p-Value
Type of CP	75	40	2.57 (1.35 – 4.87)	0.004
GMFCS Levels				
III and IV	60	25	2.94 (1.56 – 5.52)	0.001
I and II	40	35	-	-
Presence of Epilepsy	40	50	2.67 (1.22 – 5.83)	0.01
Physiotherapy Intensity				
Low	70	30	3.11 (1.67 – 5.80)	<0.001
High	30	25	-	-
Anti-epileptic Use	55	35	2.14 (1.12 – 4.08)	0.02
Co-sleeping	25	45	1.33 (0.66 – 2.68)	0.30

Chi-square tests were used for categorical comparisons; p<0.005 indicate significant value

Table 3 presented the results of the multivariate analysis determining the variables linked to children with cerebral palsy's sleep issues. Even after controlling for other factors, children with certain forms of cerebral palsy had 2.45 times greater odds of having sleep disruptions (Adjusted OR = 2.45, 95% CI: 1.28–4.70, P = 0.007). This association between cerebral palsy and sleep disorders persisted. Compared to children at lower levels, those with more severe motor impairments—that is, those at GMFCS levels III and IV—had over three times the likelihood of having sleep disorders (Adjusted OR = 3.10, 95% CI: 1.55–6.22, P = 0.001). Another significant risk factor was epilepsy, which increased the likelihood of sleep problems by 2.89 times (Adjusted OR = 2.89, 95% CI: 1.24–6.72, P = 0.014). There was a significant correlation between low physiotherapy intensity and sleep disruptions. Children who had low-intensity therapy had an odds of 3.45 times higher sleep problems than those who received high-intensity

DOI: https://doi.org/10.54393/pjhs.v6i1.2582

therapy (Adjusted OR = 3.45, 95% CI: 1.65–7.22, P < 0.001). There was a moderate correlation between the use of anti-epileptic drugs and sleep disturbances (Adjusted OR = 2.01, 95% CI: 1.03–3.90, P = 0.04). By contrast, an adjusted OR of 1.25 (95% CI: 0.60–2.62, P = 0.55) showed that co-sleeping was not significantly linked with sleep problems. This implies that co-sleeping did not significantly affect the population's sleep issues (Table 3).

Table 3: Multivariate Analysis of Factors Associated with Sleep Disorders in Children with Cerebral Palsy

Variables	Adjusted OR (95% CI)	p-Value
Type of CP	2.45 (1.28 - 4.70)	0.007
GMFCS Level (III and IV)	3.10 (1.55 - 6.22)	0.001
Presence of Epilepsy	2.89 (1.24 - 6.72)	0.014
Physiotherapy Intensity (Low)	3.45 (1.65 - 7.22)	<0.001
Anti-epileptic Use	2.01 (1.03 - 3.90)	0.04
Co-sleeping	1.25 (0.60 - 2.62)	0.55

Multivariate Logistic Regression Analysis Was Used to Determine Independent Predictors Of Sleep Disorders

DISCUSSION

This study highlights the prevalence and predictors of sleep disorders in children with Cerebral Palsy (CP), providing key insights into demographic, clinical, and therapeutic factors influencing sleep quality. Below is a detailed discussion of the findings, aligned with existing literature. The majority of the kids in these samples (53.3%) were between the ages of 8 and 10 years old, and there were slightly more girls (53.3%) than boys (46.7%). This distribution is consistent with other research showing that there is no persistent gender difference in CP populations, while certain cohorts have shown a slight female predominance [11]. As it turned out, 56.7% of the individuals had spastic CP, which is the most common subtype of CP. Previous research has shown that spastic CP accounts for 60–70% of cases of CP. A strong foundation was correlated between sleep problems and spastic CP (adjusted OR = 2.45, 95% CI: 1.28–4.70, P = 0.007). This study confirms previous studies' findings that children with spastic CP frequently have pain, rigid muscles, and restricted movement, all of which can lead to poor sleep quality [12]. A significant predictor of sleep disturbances was motor function, as measured by the Gross Motor Function Classification System (GMFCS). Over three times as many children at GMFCS levels III and IV experienced sleep disturbances (adjusted OR = 3.10, 95% CI: 1.55–6.22, P = 0.001). It has been shown by earlier research that kids with higher GMFCS scores typically sleep worse, probably as a result of physical restrictions, increased reliance, and a heavier caregiver load [13]. This highlights the necessity of specialized sleep therapies for kids with severe motor deficits. A significant risk factor for sleep disorders, epilepsy was found in 20% of sample of this study (adjusted OR = 2.89, 95% CI: 1.24–6.72, P = 0.014). Similar results have been documented in the literature, where it is frequently seen, that epilepsy is linked to frequent awakenings, disturbed sleep architecture, and daytime sleepiness [14, 15]. Adjusted OR = 2.01, 95% CI: 1.03–3.90, P = 0.04), the use of anti-epileptic medications was also somewhat linked to sleep disruptions. This is in line with earlier studies that have demonstrated that various anti-epileptic medications might increase sleep difficulties or induce sedation [16, 17]. These results imply that physiotherapy intensity significantly affects the quality of sleep. When comparing children undergoing high-intensity programs to those getting low-intensity therapy, the risks of sleep disturbances were 3.45 times greater (adjusted OR = 3.45, 95% CI: 1.65–7.22, P < 0.001). These findings are consistent with research showing that exercise enhances sleep quality by lowering anxiety, exhaustion, and muscular tone [18]. Additionally, high-intensity physical treatment may improve motor function and hence improve sleep indirectly. It's interesting to note that this study's adjusted OR = 1.25, 95% CI: 0.60–2.62, P = 0.55) showed no evidence of a significant effect of co-sleeping on sleep problems. Co-sleeping has shown conflicting findings in the past; while some studies have suggested that it can ease discomfort and lessen anxiety, others have shown that it may impair parents' and kids' sleep quality [19]. The samples of this study lacked of statistically significant correlation raises the possibility that co-sleeping is not the main factor influencing sleep problems in kids with cerebral palsy [20]. In this group, bedtime resistance (20%), sleep start delay (16.7%), and nocturnal waking (26.7%) were the most prevalent sleep disorders. These results are consistent with earlier studies that highlight how children with CP frequently experience physiological pain, seizures, or adverse drug reactions, which can cause them to wake up during the night or have trouble going asleep [21].

CONCLUSIONS

This research identified a number of important variables, such as the kind of CP, motor function, epilepsy, and the severity of physiotherapy, that are linked to sleep disturbances in children with CP. The significance of timely detection and customized measures in the handling of sleep disturbances in this demographic is highlighted by these results.

Authors Contribution

Conceptualization: UB
Methodology: MAB, TH, BAB
Formal analysis: MAB, FKA
Writing, review and editing: KA, FKA

All authors have read and agreed to the published version of the manuscript

DOI: https://doi.org/10.54393/pjhs.v6i1.2582

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2374

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Impact of Anesthesia Type on Stone Clearance and Morbidity in Ureteroscopy: General Versus Spinal Anesthesia

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ARTICLE INFO

Keywords:
Ureteroscopy, Stone Clearance, Spinal Anesthesia, General Anesthesia

How to Cite:
Iqbal, A., Saeed, S. J., Liaqat, K., Ovais, F., Qamber, J. H., & Nadia, S. (2025). Impact of Anesthesia Type on Stone Clearance and Morbidity in Ureteroscopy: General Versus Spinal Anesthesia: Impact of Anesthesia Type on Stone Clearance and Morbidity. Pakistan Journal of Health Sciences, 6(1), 23-29. https://doi.org/10.54393/pjhs.v6i1.2374

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Received date: 5th October, 2024
Acceptance date: 9th January, 2025
Published date: 31st January, 2025

ABSTRACT

Background: Anaesthesiologists prefer regional anesthesia for ureterorenoscopy to prevent difficulties after the procedure, whereas surgeons prefer general anesthesia in order to prevent ureteral damage. However, limited comparative data exist regarding the outcomes of these anesthesia techniques in ureteroscopy-assisted stone clearance **Objective:** To compare spinal and general anesthesia regarding efficacy, safety, and patient outcomes during ureteroscopy for ureteric stones. **Methods:** This quasi-experimental study included 90 patients aged between 20-60 years in total were chosen. Using a semi-rigid ureteroscope (8/8.4 fr), all individuals had ureteroscopic treatment for ureteric stones. Equal numbers of 45 patients were divided between the two groups. General anesthesia was administered to Group A, and spinal anesthesia was provided to Group B. The participants' demographic data, hospital stays, operating times, stone removal rates, and intra- and post-operative problems were all recorded. Data on intraoperative parameters, stone clearance, and postoperative complications were collected and analysed using SPSS 23.0. **Results:** General anesthesia significantly reduced the dilatation time (104.01 ± 12.772 vs. 130.552 ± 22.532 sec, $p < 0.001$) and time to reach the stone (126.68 ± 12.592 vs. 137.602 ± 17.841 sec, $p < 0.001$) compared to spinal anesthesia. However, no significant differences were observed in lithotripsy time, operation time, stone-free rates, or postoperative complications between the two groups. Patients in the GA group reported higher VAS scores and an increased frequency of nausea/vomiting after surgery. **Conclusion:** General anesthesia reduced the time for dilatation and stone access but showed no significant advantages in lithotripsy time, operation time, stone-free rates, or complications.

INTRODUCTION

The increasing prevalence of renal stones in modern populations is attributed to Western-style lifestyles and advancements in imaging technology. In Pakistan, this rise is further linked to higher consumption of animal protein [1]. Ureterorenoscopy has been the primary surgical method for managing ureteral calculi unresponsive to medical expulsive therapy since the 1980s [2]. It offers a better stone-clearance ratio than shockwave lithotripsy and lower complication rates compared to percutaneous nephrolithotomy [3]. The procedure's success is dependent on proper surgical techniques, advanced tools, and careful patient selection.

Ureteral access plays a critical role in the success of ureterorenoscopy, with factors such as axial pressure and preoperative preparation affecting the ease of access and stone-reaching efficiency [4]. The development of advanced surgical techniques and instruments has significantly improved the safety and success rates of ureterorenoscopy. Complication rates have decreased substantially, now ranging from 0% to 6%, while stone

DOI: https://doi.org/10.54393/pjhs.v6i1.2374

removal success rates remain consistently high [5]. Despite these advancements, potential complications persist, including ureteral perforation, urinomas, residual stone fragments, strictures, avulsions, bleeding, septic episodes, urinary retention, and postoperative pain [6-8]. Ureteral access is a critical factor for achieving successful ureterorenoscopy outcomes, as it directly impacts the ease of entry and the stone-reaching process [2]. Various techniques, including balloon dilatation, stent placement for passive dilation, and the use of α-blockers, enhance access but come with their own pros and cons [9, 10].

According to the European Association of Urology guidelines, ureterorenoscopy is typically performed under general anesthesia, although spinal and local anesthesia are feasible alternatives, particularly for distal ureteral stones [11]. Anaesthesiologists often favor regional anesthesia to minimize the risks associated with general anesthesia, while surgeons prefer general anesthesia to reduce the likelihood of ureteral injury [12, 13].

Despite advancements in ureterorenoscopy, the choice of anesthesia remains a topic of debate. Existing studies on this subject are often limited by small sample sizes and lack comprehensive analysis [9, 14]. Moreover, there is limited literature that comprehensively compares the impact of general versus spinal anesthesia on ureteroscopy-assisted stone clearance, particularly in different global, regional, and local contexts.

This study aims to address this gap by comparing stone clearance rates and associated outcomes in ureteroscopy performed under general versus spinal anesthesia. We hypothesize that general anesthesia facilitates quicker ureteral access and potentially higher stone clearance rates compared to spinal anesthesia.

METHODS

This quasi-experimental study was conducted on 90 patients undergoing ureteroscopy at the Urology Department of Jinnah International Hospital, Abbottabad, over 12 months from July 2023 to June 2024, following approval from the Institutional Review Board (JIHA/QMS/7642). The sample size was calculated using the two-proportion formula, based on stone-free rates reported in previously published studies. A study comparing ureteroscopy under general anesthesia versus spinal anesthesia reported stone-free rates of 92.3% and 71.0%, respectively [14].

$$n = \frac{\{Z_{1-\alpha/2}\sqrt{2\bar{P}(1-\bar{P})} + Z_{1-\beta}\sqrt{P1(1-P1)+P2(1-P2)}\}^2}{(P1-P2)^2}$$

P_1 (Expected stone-free rate for GA group), P_2 (Expected stone-free rate for SA group), $Z_{1-\alpha/2}$, $Z_{1-\beta}$, $\bar{P}=(P1+P2)/2$. Using these rates, with a 90% confidence level ($\alpha = 0.10$) and 80% power ($\beta = 0.2$), the calculation yielded a minimum of 45 patients per group. Convenience sampling was used due to practical limitations in patient recruitment. Each patient was informed about the study to take the consent for participation. They were given the option to select the type of anesthetic, and data were gathered by convenience sampling. The anesthesiologist and surgeon, however, had the last say over the kind of anesthesia. Patients with radiologically detected lower ureteral stones below the sacroiliac joint, aged 20 to 60, were included in the study. Patients with upper ureteral lithiasis, hemorrhage, UTIs, ASA classifications III and IV, open surgery requirements, and comorbidities that would preclude general or spinal anesthesia were excluded. To ascertain their composition, the chemical analysis of every stone that was extracted was sent. 45 patients underwent the surgery under general anesthesia, while 45 patients underwent it under spinal anesthesia. The anesthetist's recommendation and the patient's preference guided the choice of anesthesia. The majority of patients spent the night after surgery after being admitted the morning after the procedure. Every patient's whole hospital stay was documented. Prophylactic antibiotics were regularly administered to all patients. Rigid cystoscopy was performed in all cases, with a guide wire inserted into the renal system under fluoroscopy. An 8/8.4 Fr semi-rigid ureteroscope was used for all procedures. When the ureteroscope could not easily pass through the ureter, balloon dilation was performed. Stone fragmentation was achieved using a pneumatic lithoclast, and stents were placed based on the surgeon's discretion. Surgical time, defined as the duration from cystoscope insertion to ureteroscope withdrawal, was documented. Patients were closely monitored for intraoperative complications. Stone fragmentation and clearance were evaluated using KUB radiography and/or excretory urography (in cases of radiolucent stones). Postoperative complications, such as fever, pain, hematoma formation, infection, and residual stones causing obstruction, were assessed in all patients. Visual analog pain scores were recorded post-surgery. Blood cultures and sensitivity tests were conducted if an infection was suspected, and abdominal ultrasound was performed for symptomatic patients presenting with abdominal swelling or suspected hematoma formation. The total hospital stays, measured in hours from admission to discharge, was documented for each patient. The overall health of the patient, the duration of their hospital stays, any difficulties following surgery (such pain and fever), and any complications resulting from anesthesia (like headache and vomiting) were used to determine morbidity. Stone clearance was defined as the absence of residual stones at the first follow-up on the seventh postoperative day, as determined by intravenous urography (IVU) or postoperative kidney/bladder radiography (KUB). Data were analysed using SPSS version 23.0. Qualitative

DOI: https://doi.org/10.54393/pjhs.v6i1.2374

variables, such as sex, ASA status, and complication rates, were presented as frequencies (percentages). Quantitative variables, including age, stone size, and hospital stay duration were presented as mean ± standard deviation (SD). Chi square test was applied to see association of qualitative variables in relation to type of anaesthesia and same with independent sample t-test. A p-value of less than 0.05 was considered statistically significant for all comparisons.

RESULTS

Two groups of ninety patients undergoing ureterorenoscopy were created: forty-five of them underwent spinal anesthesia (SA) and forty-five of them underwent general anesthesia (GA). Before the procedure, 500 mg of levofloxacin were given to each patient twice a day for five days. A general anesthetic was delivered to patients who were 55 years of age or younger. There were no discernible variations seen in the GA and SA groups for sex, ethnicity, BMI, or preoperative clinical features. The two groups also showed identical stone features as determined by computed tomography, patient comorbidities, and hydronephrosis prior to ureterorenoscopy (p >.05 for all parameters). However, patients in the GA group were significantly older, while those in the SA group had a greater proportion of ASA status II classifications, as shown in Table 1.

Stone clearance, the study's primary outcome, was defined as the absence of residual stones upon the first follow-up, assessed via IVU or KUB radiography. At the first follow-up, 39 patients (87%) in the GA group and 38 patients (84%) in the SA group were stone-free. This difference was not statistically significant (p = 0.773). The reported stone-free rates align with the study's operational definition of stone clearance. Table 1 shows that patients in the SA group had a larger number of patients with ASA status II and that patients in the GA group were older than those in the SA group.

Table 1: Demographics, Clinical, and Pathophysiological Features of the Patients

Parameter	General Anesthesia (GA)	Spinal Anesthesia (SA)	p-Value
Number of Patients	45	45	-
Sex (%)			
Male	36 (80%)	31 (69%)	0.208
Female	9 (20%)	14 (31%)	
Age (years)			
Mean ± SD	39.79 ± 8.42	25.22 ± 1.97	<0.0001
Body Mass Index (kg/m^2)	25.22 ± 1.97	11.35 ± 1.987	0.079
Hemoglobin (g/dL)	11.28 ± 2.31	11.35 ± 1.987	0.839
Serum Creatinine (mg/dL)	0.68 ± 0.11	0.69 ± 0.15	0.053
ASA Status (%)			
I	28 (63%)	19 (42%)	<0.0001
II	17 (37%)	26 (58%)	
Stone Size (mm)	11.45 ± 3.49	11.11 ± 2.89	0.286
Stone Volume (mm^3)	553.45 ± 25.45	552.12 ± 24.48	0.051
Stone Side (%)			
Right	22 (49%)	23 (51%)	0.782
Left	23 (51%)	22 (49%)	
Stone Status (%)			
Opaque	41 (91%)	39 (89%)	0.737
Semi-Opaque	2 (5%)	3 (7%)	
Non-Opaque	2 (4%)	3 (4%)	
Stone Localization (%)			
Upper	14 (31%)	13 (29%)	0.419
Middle	14 (31%)	16 (35%)	
Lower	15 (34%)	16 (36%)	
Comorbidity (%)			
Absent	40 (89%)	38 (84%)	0.508
Present	5 (11%)	7 (16%)	
Hydronephrosis (%)			
Absent	28 (63%)	26 (58%)	0.508
Grade I	5 (11%)	6 (13%)	
Grade II	6 (13%)	7 (16%)	
Grade III	6 (13%)	6 (13%)	

*p-Value <0.05 is considered significant. Student's t-test was applied

Compared to patients in the SA group, dilatation times in the GA group were substantially lower (104.01 ± 12.772 vs. 130.552 ± 22.532 sec, p < 0.001). Additionally, the GA group required less time to reach the stone than the SA group did (126.68 ± 12.592 vs. 137.602 ± 17.841 sec, p < 0.001). The length of hospital stays, lithotripsy duration, surgery duration, and intraoperative complications were not different significantly, between the groups (p >0.05 for all parameters)(Table 2).

Table 2: Characteristics of Patients, Operation Duration, and Complications during the Surgery

Parameter	General Anesthesia (GA)	Spinal Anesthesia (SA)	p-Value
Lithotripsy Time (min)	12.06.90 ± 2.07	11.94 ± 2.35	0.359
Operation Time (min)	39.12 ± 4.25	39.92 ± 3.15	0.449
Lithotripsy Time (min)			
- Modified SATAVA Grade 1	8 (18%)	9 (20%)	0.058
Length of Hospital Stay (days)	2.08 ± 0.25	2.05 ± 0.17	0.057

*p-Value <0.05 is considered significant. Student's t-test was applied

In the first table, the mean dilatation time for patients under GA was 104.01 ± 12.77 seconds, whereas for SA, the mean dilatation time was significantly longer (p < 0.0001) at 130.55 ±22.53 seconds (Figure 1 A). Similarly, the mean time to reach the stone was 116.68 ± 8.77 seconds for GA, while

DOI: https://doi.org/10.54393/pjhs.v6i1.2374

under SA, the mean time was 137.6 ± 12.53 seconds (Figure 1 B).

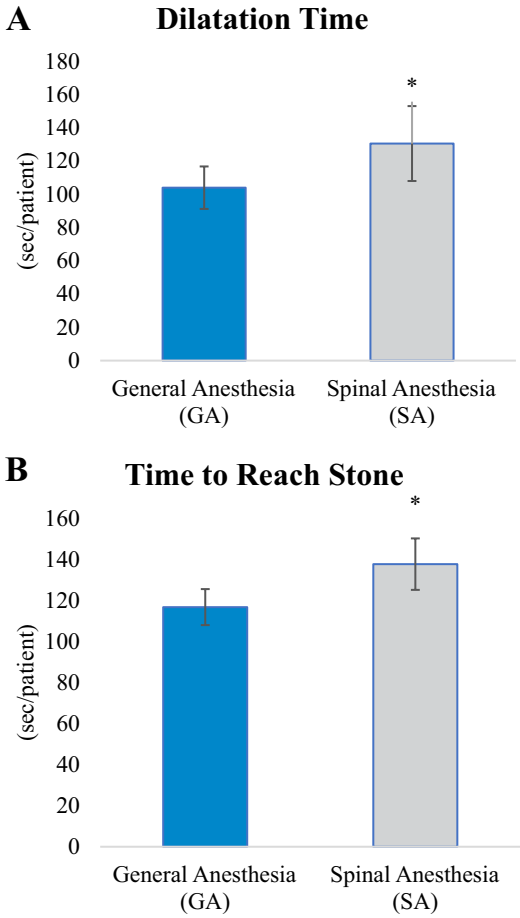

Figure 1: (A) The Time Required for Dilatation (B) Time Required to Reach the Stone

* p-value≤0.05 (Statistically significant). Student t-test was applied

Those in the GA group reported a greater VAS pain score at 8 hours post-surgery (5.01 ± 0.56 vs. 3.94 ± 0.51, p < 0.001) than those in the SA group. At the 24-hour mark following the procedure, the GA group continued this pattern, reporting higher pain levels than the SA group (3.13 ± 0.11 vs. 2.02 ± 0.39, p < 0.001) (Figure 2).

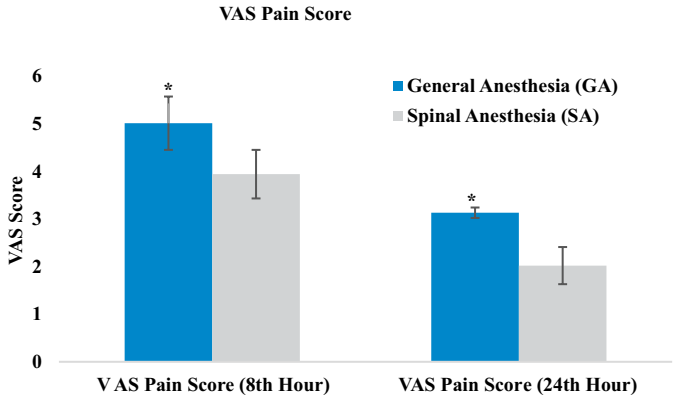

Figure 2: VAS Pain Score

* p-value≤0.05 (Statistically Significant). Student t-test was applied

Following the surgery, a total of 39 patients (87%) in the GA group and 38 patients (84%) in the SA group were clear of stones. There was no statistically significant difference in the groups' stone-free conditions (p = 0.773). Only problems classified as modified CLAVIEN I, II, IIIa, and IIIb were recorded over the 8-week postoperative period. Postoperative problems were not significantly differed between the two groups, with the exception of nausea and vomiting, which were more common in the GA group (p =0.013). According to Table 3, none of the patients had any disabilities upon discharge.

Table 3: Postoperative Complications with Modified CLAVIEN Classification Grade

Complication	General Anesthesia (GA)	Spinal Anesthesia (SA)	p-Value
Mucosal Injury (%)	5 (11%)	4 (9%)	0.859
Hematuria (%)	4 (9%)	4 (9%)	0.949
Fever (%)	1 (2%)	1 (2%)	0.859
Obstructive Diuresis (%)	1 (2%)	1 (2%)	0.975
Elevation in Renal Functions (%)	1 (2%)	1 (2%)	0.859
Retention of Urine (%)	3 (7%)	2 (4%)	0.981
Urinary Tract Infections (%)	4 (9%)	3 (7%)	0.989
Proximal Stone Migration (%)	3 (7%)	2 (4%)	0.993
Stent Migration (%)	2 (4%)	1 (2%)	-

Chi-square test was applied. p≤0.05 was considered significant

A bivariate regression analysis was conducted to evaluate the effect of various characteristics on anesthesia-related times, such as the time for dilation, time required for reaching to the stone, time for lithotripsy, surgery duration, and complications during the surgery. The analysis considered factors such as age, the American Society of Anesthesiologists (ASA) status, and stone volume (Table 4). Stone volume was a significant predictor of lithotripsy time and operation duration, with higher volumes associated with longer times (p = 0.045 and p = 0.046, respectively).

DOI: https://doi.org/10.54393/pjhs.v6i1.2374

Table 4: Effect of Anesthesia Time on Characteristics Using Independent Sample t-Test

Characteristics	Age		p-value	ASA Status		p-value	Stone Volume (mm^3)		p-value
	<55	≥55		II	I		<500	>500	
Dilation Time (min)	18.5 ± 2.3	19.7 ± 2.5	0.079	18.2 ± 2.6	19.4 ± 2.7	0.063	17.8 ± 2.2	20.1 ± 2.4	0.055
Time to Reach Stone (min)	7.4 ± 1.1	8.0 ± 1.2	0.072	7.3 ± 1.3	7.9 ± 1.4	0.074	7.1 ± 1.0	8.2 ± 1.1	0.063
Lithotripsy Time (min)	15.3 ± 1.9	16.1 ± 2.0	0.079	15.2 ± 1.8	16.2 ± 1.9	0.079	14.7 ± 1.7	16.5 ± 1.8	0.045*
Operation Time (min)	45.5 ± 4.1	47.3 ± 4.3	0.081	45.4 ± 4.2	47.5 ± 4.4	0.061	44.0 ± 3.9	48.2 ± 4.0	0.046*

The independent t-test was applied, and the results are shown as mean ± standard deviation (SD) for continuous variables and percentage {%(n)} for categorical variables. A p-value <0.05 is considered significant.

DISCUSSION

The results of our study indicate that general anesthesia for ureterorenoscopy significantly reduces both the time for dilatation and the time required to reach the stone, compared to spinal anesthesia. Specifically, the GA group had a dilatation time of 104.01 ± 12.77 seconds, while the SA group had a dilatation time of 130.55 ± 22.53 seconds ($p<0.001$). Although statistically significant, the clinical relevance of this finding is limited, as quicker dilatation did not translate into improved overall outcomes such as stone-clearance rates or postoperative recovery. These findings are consistent with previous studies that suggest general anesthesia provides better relaxation of the distal ureters, facilitating quicker and easier access to the stone [9]. Regional and spinal anesthesia may not be sufficient for optimal ureteral dilatation, which is crucial for successful stone access [15, 16]. Although medications such as α-blockers and calcium channel blockers could potentially enhance ureteral dilatation, studies examining their effects in this context are still lacking, necessitating further research [11]. Overall, general anesthesia appears to offer advantages in facilitating early ureteral dilatation and stone access [17]. However, the study results showed no significant changes between the general and spinal anesthesia groups in case of lithotripsy time (GA: 12.06 ± 2.07 minutes, SA: 11.94 ± 2.35 minutes, $p = 0.359$), duration of surgery (GA: 39.12 ± 4.25 minutes, SA: 39.92 ± 3.15 minutes, $p = 0.449$), complications during surgery, duration of hospital stay (GA: 2.08 ± 0.25 days, SA: 2.05 ± 0.17 days, $p = 0.057$), stone-clearance rates, or postoperative complications. These findings align with several prospective randomized studies that indicate intraoperative and postoperative outcomes are more closely related to individual patient recovery and surgical technique rather than the type of anesthesia used [18]. In contrast, a Quasi-experimental study reported contradictory results, likely due to a small sample size (type I error) [9]. Patients who received general anesthesia reported higher postoperative Visual Analog Scale (VAS) pain scores at 8 hours post-surgery (GA: 5.01 ± 0.56, SA: 3.94 ± 0.51, $p < 0.001$, Student's t-test) compared to those who received spinal anesthesia. At the 24-hour mark following the procedure, the GA group continued this pattern, reporting higher pain levels than the SA group (GA: 3.13 ± 0.11, SA: 2.02 ± 0.39, $p \leq 0.001$, Student t-test) [19]. These higher pain scores under GA are likely due to its shorter analgesic effect compared to spinal anesthesia and should be weighed against other procedural advantages. Age did, however, influence the anesthesia technique, as general anesthesia was only applied to individuals under the age of 55, which could affect their VAS scores as well [20]. Moreover, urinary symptoms caused by larger-diameter ureteral stents are notably worse than those caused by smaller-diameter ureteral stents. Further investigation is necessary to clarify these relationships. The research discovered that both intraoperative and postoperative characteristics were impacted by stone volume. The results of the current investigation are in line with the results of a prospective study indicating that larger stone volumes are associated with worse intraoperative and postoperative outcomes [18]. Patients having 3rd grade ASA status were not included in the present study, as those with preoperative 3rd grade ASA can experience a 58% increase in major complications and a 49% increase in minor complications following surgery [9]. Excluding these patients limits the generalizability of the findings, as they represent a significant portion of real-world surgical populations. While this study contributes valuable insights to the field of urology, several limitations should be acknowledged. The non-standardized choice of anesthesia introduces potential selection bias, as decisions were influenced by institutional practices and individual preferences. Additionally, the small sample size reduces the statistical power and increases the likelihood of type I and type II errors. Variability in surgeon techniques likely impacted procedural times, emphasizing the operator-dependent nature of these results. The study used bupivacaine for spinal anesthesia, despite reports of the vasodilation properties of levobupivacaine, which may have influenced the outcomes. In the present study, the choice of anesthesia was not standardized and varied between hospitals, sometimes based on the surgeon's preference and other times on the anesthesiologist's recommendation.

DOI: https://doi.org/10.54393/pjhs.v6i1.2374

CONCLUSIONS

In conclusion, while general anesthesia demonstrated a statistically significant reduction in the time to reach the kidney stone, the clinical significance of this difference may be limited. Further research, ideally in the form of prospective, randomized trials, is needed to better understand the implications of anesthesia choice in ureterorenoscopy.

Authors Contribution

Conceptualization: AI
Methodology: SJS, AI
Formal analysis: AI, KL, SNJ
Writing, review and editing: FO, SJS, KL, JHQ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Prevalence of the Modifiable Risk Factors of Cardiovascular Diseases in Young Adults of District Hyderabad Sindh Pakistan

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ARTICLE INFO

Keywords:

Cardiovascular Disease, Risk Factors, Physical Inactivity, Unhealthy Diet, Young Adults

How to Cite:

Shaikh, S. A., Memon, S. F., Shah, H., Rahu, H. N., Laghari, K. R., Shaikh, S. N., Laghari, Z. A., & Warsi, J. (2025). Prevalence of the Modifiable Risk Factors of Cardiovascular Diseases in Young Adults of District Hyderabad Sindh Pakistan: Risk Factors of Cardiovascular Diseases in Young Adults of District Hyderabad . Pakistan Journal of Health Sciences, 6(1), 30-35. https://doi.org/10.54393/pjhs.v6i1.2569

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Received date: 19th November, 2024
Acceptance date: 18th January, 2025
Published date: 31st January, 2025

ABSTRACT

Cardiovascular diseases are the major cause of morbidity and mortality around the world. Numerous studies concluded that populations of the subcontinent are more prone to develop cardiovascular diseases including Pakistan as compared to other countries. **Objective:** To determine cardiovascular disease risk factors in the healthy population of the Hyderabad district, Sindh. **Methods:** The cross-sectional study was conducted from July 2023 to December 2023, in this study, apparently healthy young adults of not more than 40 years of age were included. A self-designed questionnaire was set for the collection of data. Blood pressure was taken using the standard method, a mercury sphygmomanometer. South Asian standards calculated BMI, and the blood sample was taken after 10 hours of fasting for lipid profile and fasting blood sugar. Collected data were analyzed by SPSS version 23.0. **Results:** In this study, one risk factor was found in 276 (76%) of the participants, and Obesity was found in 41 (17%) and 66 (52%) respectively in group I and group II participants. Central obesity was found to be higher in group II 92 (72%) than in group I 69 (29%). Group II participants were found to have higher blood pressure than group I 61 (48%) and 61 (26%) respectively. **Conclusions:** It was concluded that 3 risk factors were found higher in females, and 4 risk factors were found higher in males, thus making the male population more prone to be affected by cardiovascular diseases even at an early age.

INTRODUCTION

Traditionally, cardiovascular diseases affect the older population. Hence, it is well documented nowadays that the higher frequency of the younger population is also caused by cardiovascular diseases [1]. Early onset of these risk factors may lead to a longer duration of exposure, thereby increasing the chances of developing cardiovascular diseases in the latter half of life. Awareness of these trends in the young adult population is necessary to prevent cardiovascular diseases [2]. The frequency of overweight and obesity in young adults has been a rising trend that significantly contributes towards the development of increased blood pressure, dyslipidemia, and insulin resistance, these all are the risk factors for cardiovascular diseases [3]. Hypertension almost remained undiagnosed and untreated in the young population, and it is a major risk factor for cardiovascular diseases [4]. Timely detection and treatment are essential to avoid the long-term development of cardiovascular diseases [5]. Abnormal lipid concentrations, including higher concentrations of low-density lipoprotein (LDL), Triglycerides (TG), and

DOI: https://doi.org/10.54393/pjhs.v6i1.2569

decreased concentrations of high-density lipoprotein (HDL) are increasingly detected in younger populations. Improper diet patterns, physical inactivity, and genetic traits mainly cause dyslipidemia [6]. Cigarette smoking and tobacco use are also significant contributors to cardiovascular diseases. The new rising trend of vaping as an alternative to traditional smoking is also a bigger contributor, as the use of both causes endothelial dysfunction and the development of atherosclerosis [7]. Physical Inactivity prevalent among young adults, is linked to obesity, hypertension, and other cardiovascular risk factors. Promoting physical activity is crucial for cardiovascular health [8]. Consumption of unhealthy diets, like diets with increased saturated fats, increased sodium, and higher levels of sugar is linked with increased cardiovascular diseases. On the other hand, a diet rich in fruits, vegetables, whole grains, and lean proteins has protective effects against cardiovascular disease [9]. Therefore, early diagnosis and treatment of risk factors can prevent the development and progression of any type of cardiovascular disease [10]. Limiting the risk factors in the young population can lead to significant long-term health benefits, reducing the overall burden of cardiovascular diseases on the healthcare system [11]. Understanding these risk factors benefits in developing targeted health strategies among the young population, thus promoting healthier generations in the future [12]. Hence, the increasing frequency of cardiovascular disease risk factors among the young population is a public health concern that needs urgent consideration. This article was previously posted to the Research Square preprint server on 19 August 2024" in the last section of the introduction.

This study aims to find out the association of cardiovascular disease risk factors among the young healthy population.

METHODS

This comparative cross-sectional study was conducted in the Physiology Department of the University of Sindh Jamshoro. The Epi info software was used for sample size, with a 5% error margin and, a 95% confidence interval. The formula for sample size calculation was $n=Z^2.P.(1-P) / E^2$. Before enrollment, informed consent was taken from volunteers, inclusion criteria, residents of district Hyderabad, individuals aged between 20 to 40 years, individuals without cardiovascular disease, non-smokers, those without pregnancy, and no drug history. Exclusion criteria, non-residents of Hyderabad, individuals aged more than 40 years, individuals with any heart disease, individuals with pregnancy, active smokers, and drug addicts. All the procedures were carried out according to the guidelines and regulations of the University's research and ethical committee letter no: IRB/PHY1/=55. This study was conducted from July 2023 to December 2023. About 415 healthy participants were approached and finally, 363 (87.46%) participants agreed and provided the necessary data. A random sampling technique was used to collect data and participants were approached. Two sittings were done with all subjects in whom complete information was recorded in the pre-designed questionnaire and blood samples were taken under acceptable conditions using steroid syringes for fasting blood, and lipid profile in a fasting condition. The questionnaire included: sociodemographic characteristics, height, and weight measurements to calculate body mass index (BMI), questions about physical activities, and dietary habits, and questions to collect information about cardiovascular diseases. The BMI was calculated by standard method and South Asian scale was used for the measurement of BMI and blood pressure readings were taken by standard method. Blood pressure was measured by the mercury sphygmomanometer (Made in Shanghai, China). The chemistry analyzer (Micro lab 300) was used to fast blood sugar levels. Data were analyzed with a statistical package for the social sciences (SPSS Version 23.0). Statistical assumptions were tested before. Descriptive statistics, t-test and chi-square performed (mean, standard deviation, frequencies) were calculated for the baseline characteristics. Statistical significance was set at $p<0.05$.

RESULTS

The basic characteristics of the participants were divided into two groups according to their age. Group I includes participants aged 20 to 29, and Group II includes participants aged 30 to 40. Out of 363, 236 (65.01%) male belonged to age group I, while 127 (34.98%) belonged to age group II. In both groups, male participants were more numerous than female participants (Table 1).

Table 1: Sociodemographic Characteristics of the Participants

Variables	Frequency (%) (n=363)
Gender	
Male	236 (65.01%)
Female	127 (34.98%)
Age	
The Age Group I (20-29Years)	236 (65.01%)
Male	139 (58.89%)
Female	97 (41.10%)
Age Group II (30-39Years)	127 (34.98%)
Male	93 (73.22%)
Female	34 (26.77%)
Education	
Low	103 (28.37%)
High	260 (71.62%)
Social Status	
Low	98 (26.99%)
Middle	200 (55.09%)
High	65 (17.90%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2569

A t-test performed between 2 groups, the overall age of the participants was 29.05 ± 1.01, while the mean age was higher in group II. The mean height was 1.6 ± 0.1 and no significant difference in both groups as well. The mean weight was 66.2 ± 13.4 and it is higher in group II. The mean BMI was 24.7 ± 4.2 and it increased in age group II. The mean Waist circumference was 86.0 ± 11.7 and it is increased in group II. The mean Systolic blood pressure was 122.4 ± 11.0 and it is higher in group II. The mean Diastolic blood pressure was 83.4 ± 9.4 and it is more in group II. The mean Total cholesterol was 140.9 ± 34.7 which is more in group II. The mean low-density lipoprotein was 91.6 ± 21.9 and it increased in group II. The mean Triglycerides was 140.8 ± 54.5 and it is higher in group II. The mean High-density lipoprotein was 50.5 ± 17.2 which is higher in group II. The mean blood sugar was 99.5 ± 26.8 which is higher in group II (Table 2).

Table 2: Mean and Standard Deviation of Variables in Age Groups I and II

Parameters	Group I (n=236)	Group II (n=127)	Total (n=363)
Age (Years)	25.7 ± 2.3	33.24 ± 3.3	29.05 ± 1.01
Height (cm)	1.63 ± 0.1	1.6 ± 0.1	1.6 ± 0.1
Weight (kg)	63.2 ± 10.5	71.9 ± 16.3	66.2 ± 13.4
BMI (kg/m2)	23.8 ± 3.1	26.5 ± 5.2	24.7 ± 4.2
WC (cm)	82.7 ± 10.3	92.3 ± 11.7	86.0 ± 11.7
SBP (mmHg)	120.4 ± 10.9	126 ± 10.4	122.4 ± 11.0
DBP (mmHg)	81.3 ± 9.1	87.2 ± 8.9	83.4 ± 9.4
TC (mg/dl)	135.9 ± 30.7	150.2 ± 40.1	140.9 ± 34.7
LDL (mg/dl)	91.2 ± 20.2	92.4 ± 25.2	91.6 ± 21.9
TG (mg/dl)	131.5 ± 54.3	157.96 ± 51.7	140.8 ± 54.5
HDL (mg/dl)	48.1 ± 7.7	54.8 ± 26.9	50.5 ± 17.2
FBS (mg/dl)	98.6 ± 26.4	101.2 ± 28.1	99.5 ± 26.8

WC=Waist Circumference, SBP=systolic Blood Pressure, DBP=Diastolic Blood Pressure, TC=Total Cholesterol, FBS=Fasting Blood Sugar

Almost all risk factors were prevalent in age group II, with central obesity being most prevalent with 92 (72.44%) of subjects having increased waist circumference (p=0.0001). Dyslipidemia was almost twice more frequent in age group II and results were statistically significant for all but one parameter, LDL. The same goes for hyperglycemia with 14 (11.023%) sufferers in group II, in comparison to 09 (3.81%) in group I. However statistical significance failed to reach (Table 3).

Table 3: Comparison of Individual Risk Factors between Age Groups

Age Group	Group I (n=236)	Group II (n=127)	p-value
Individual Risk Factors			
Obesity	40 (16.94%)	66 (51.96%)	<0.05
Central Obesity	69 (29.23%)	92 (72.44%)	<0.05
Hypertension	61 (25.84%)	61 (48.03%)	<0.05
Increased TC	09 (3.81%)	17 (13.8%)	<0.05
Increased LDL	10 (4.2%)	15 (11.81%)	>0.05
Increased TG	66 (27.96%)	61 (48.03%)	<0.05
Hyperglycemia	09 (3.81%)	14(11.02%)	>0.05
Less Than Required HDL	50 (21.18%)	47 (37.00%)	<0.05
Inactive Lifestyle	186 (78.81%)	83 (65.5%)	<0.05

Participants had one risk factor found in 276 (760.3%) of the study population. No risk factor was found in 24% of participants. Only 87 (23.96%) of the participants were found to have 2 risk factors, 40 (11.01%) of the participants were found to have 3 risk factors, and more than 3 risk factors were found in 66 (18.18%) of subjects (Table 4).

Table 4: Clustering of Risk Factors in Total Subjects

Frequency of Risk Factors	Prevalence (%) (n=363)
0 Factors	8 (23.96%)
1 Factor	83 (22.86%)
2 Factor	88 (24.24%)
3 Factors	40 (11.0%)
4 Factors	36 (9.91%)
5 Factors	22 (6.03%)
6 Factors	04 (1%)
7 Factors	03 (0.94%)

*0 Factor=Obesity,1 Factor=Central Obesity, 2 Factor= Hypertension, 3 Factor=Increased TC, 4 Factor =Increased LDL, 5 Factor=Increased TG, 6 Factor =Hyperglycemia, 7 Factor=Decreased HDL.

The difference was much higher in the frequency of risk factors when age group I was compared with age group II. Increasing age showed the increasing frequency of CVD risk factors. Subjects in the older age group (II) had risk factors more. A total of 78 (33.05%) of subjects of the age group I were free from CVD risk factors, while only 10 (7.87%) of subjects of age group II had no risk factor. A whopping percentage (92.15%) of subjects belonging to age group II had at least one risk factor (Table 5).

Table 5: Comparison of Clustering of Risk Factors between Age Groups

Age Group	Group I (20-29 Years)	Group II (30-40 Years)
Frequency of RF, n (%)		
0 Factors	78 (33.05%)	10 (7.87%)
1 Factors	66 (27.96%)	15 (11.81%)
2 Factors	57 (24.15%)	31 (24.40%)
3 Factors	26 (11.01%)	15 (11.81%)
4 Factors	00 (0.0%)	36 (28.34%)
5 Factors	05 (2.1%)	15 (11.81%)
6 Factors	00 (0.0%)	05 (3.93%)
7 Factors	05 (2.1%)	00 (0.0%)

The results for awareness of CVD risk factors were almost equal in both groups. Only 90 (24.79%) were aware of CVD risk factors; the rest of the 273 (75.20%) subjects did not know CVD risk factors and their effects (Table 6).

DOI: https://doi.org/10.54393/pjhs.v6i1.2569

Table 6: Awareness of Cardiovascular Risk Factors in Male and Female Subjects

Gender	Group I	Group II	Total
Awareness About CVD Risk Factors			
Yes	56 (23.73%)	34 (26.78%)	88 (25.25%)
No	180 (76.27%)	93 (73.22%)	275 (75.75%
Total	236 (100%)	127 (100%)	363 (100%)

DISCUSSION

At present, limited studies have been conducted to find out the frequency of diseases associated with cardiovascular and their risk factors in the young healthy population of Pakistan. In this study, we assessed the overall prevalence of risk factors in young adults (<40 years of age). The increase in the prevalence of risk factors with increasing age was also examined. The results achieved with this study are mostly in agreement with the majority of the literature available. More risk factors were available in male subjects, a fact widely accepted is that the male population is higher at risk for cardiovascular disease. A similar trend was found by Tran *et al.*, [13]. Another vital finding was the increase in the prevalence of risk factors with increasing age; which has been consistent time and again in other investigations, similarly Vasan *et al.*, conducted a Framingham study with a sample size of 317849 [14]. Thus, concluding that males are more at risk for developing CVDs and this risk becomes higher with increasing age. Obesity is one of the major CVD risk factors. Pakistan was ranked as the 9th most obese country in the world. In this study, obesity was found as one of the most prevalent CVD risk factors. 30% of all subjects were found to be overweight or obese according to BMI. The prevalence of obesity was less in males (29%) as compared to females (30%). The finding of this study is inconsistent with different Tran *et al.*, conducted cross-sectional population-based research from 2011 and 2017 found increased BMI major cause of CVD risk factor [13]. Dikaiou *et al.*, conducted a prospective study in Sweden and documented a slightly J-shaped association of BMI with CVD risk factors [15]. Studies were done in Pakistan that have found the prevalence of obesity in young adult Pakistanis in between 25 -35% by Sabiha *et al.*, and obesity as being more prevalent in female as compared to males with only a small margin of difference [16]. Later findings also match several studies which show a higher prevalence of obesity in female in comparison to male by Khan *et al.*, Asif *et al.*, [17, 18] and Ibrahim *et al.*, [19]. We found waist circumference as being more prevalent in females than in male subjects and there was an increase in waist circumference with increasing age. These results highly matched the investigation done by Gadekar *et al.*, who also observed higher waist circumferences in females which were found to increase with increasing age [20]. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure in their seventh report has emphasized that systolic more than diastolic Blood Pressure is strongly related to CVDs. The combined overall frequency of pre-hypertension and hypertension combined was 34%. These results were similar to a study done by Tran *et al.*, who found the prevalence of hypertension in people above 40 years of age to be 38% [13]. The difference in age group is sufficient to address this slight difference in prevalence. The incidence of hypertension was found higher in males as compared to female subjects at 22%; these results were in agreement with studies done by Mills *et al.*, and Riaz *et al.*, [21, 22]. Another important risk factor, dyslipidemia was prevalent in 35% of participants with increased triglycerides as the most prevalent of all cholesterol types. Similar results were achieved by Duran *et al.*, and Basit *et al.*, who diagnosed 31% of subjects with dyslipidemia and found impaired triglyceride levels as most prevalent [23, 24]. Diabetes not only directly affects the integrity of the vascular system, but also impacts other cardiovascular risk factors. A satisfying number of studies have revealed higher levels of Dyslipidemia in diabetics as compared to non-diabetics. The prevalence of hyperglycemia was 7% in total subjects with being higher prevalent in male subjects. No diabetics were found in this study, a possible explanation for this might be the limited sample size. Metro-ville Health Study (MHS) study by Dennis *et al.*, showed hyperglycemia in 8-10% of subjects [25]. A sedentary lifestyle leads to increased deposits of fat in the body causing obesity and subsequent risk factors. This risk factor was found to be prevalent in 74% of total subjects. Hayes *et al.*, compared activity levels among the Indian and Pakistani populations with that of Europe and found that Europeans were more physically active than Indians, Pakistanis, or Bangladeshis [26]. Their study showed that 52 per cent of European men did not meet the required levels of physical activity, compared to 71 per cent of Indians, 88 per cent of Pakistanis, and 87 per cent of Bangladeshis. Similar findings were documented for women. In conclusion, European men and women participated more frequently in moderate to intense sports and exercise activities as compared to Pakistani and Indians. Thus lack of exercise combined with inappropriate diet are responsible for the growing epidemic of obesity in Pakistan. Females were less active as compared to male subjects. Furthermore, awareness about cardiovascular risk factors was less in the majority of subjects. Only 24% of subjects were moderate to high level aware of cardiovascular risk factors. The remaining did not know whatsoever about cardiovascular risk factors and their destructive effects on health. The lack of awareness co-relates with the increased incidence of cardiovascular risk factors. The less a person is aware of risk factors, the more he will succumb.

DOI: https://doi.org/10.54393/pjhs.v6i1.2569

CONCLUSIONS

It was concluded that 76% had at least one risk factor. Such a high prevalence of cardiovascular risk factors in young adults is an alarming finding. Young adults with a lack of exercise, poor quality, high-fat diet, and lack of awareness about cardiovascular diseases and cardiovascular risk factors are moving towards the development of an unhealthy generation. These risk factors not only lead to cardiovascular diseases but also compromise the quality of life. Inactive lifestyle, Central obesity, Dyslipidemia, hypertension, and obesity were the most prevalent cardiovascular risk factors. Furthermore, 4 risk factors were more prevalent in male subjects; increased Triglycerides, Hypertension, Hyperglycemia, less than desired HDL, and increased LDL, as compared to female subjects. These results indicate male population is slightly more at risk for developing CVDs.

Authors Contribution

Conceptualization: SAS
Methodology: HS, HNR, SNS, ZAL, JW
Formal analysis: SFM, KRL
Writing review and editing: SAS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2364

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Perceptions of Medical Students Towards Artificial Intelligence

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ARTICLE INFO

Keywords:
Artificial Intelligence, Medical Education, Students, Technology Driven

How to Cite:
Rizwan, S., Rizwan, S., Rizwan, M., Hashim, A., Nawal, .,& Batool, S. (2025). Perceptions of Medical Students towards Artificial Intelligence: Medical Students Towards Artificial Intelligence. Pakistan Journal of Health Sciences,6(1), 36-41.https://doi.org/10.54393/pjhs.v6i1.2364

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Received date: 12th November, 2024
Acceptance date: 16th January, 2025
Published date: 31st January 2025

ABSTRACT

The incorporation of technological advancements, particularly Artificial Intelligence has transformed healthcare systems globally, especially post-COVID-19. Medical education faces challenges in incorporating AI due to instructor shortages and high software costs. Understanding medical students' attitudes towards AI is crucial for its successful integration into medical practice and education. **Objective:** To evaluate the attitude of medical undergraduate students towards AI in medicine. **Methods:** A descriptive, online cross-sectional study was executed among undergraduate medical students utilizing a non-probability convenience sampling. The questionnaire, distributed to 340 participants, included demographic details, perceptions towards artificial intelligence, and its effect on medical education. A total of 252 responses were received, receiving a 74% response rate. Data analysis was executed through SPSS version 26.0. **Results:** Demographic characteristics of 252 subjects revealed a mean age of 23.5 years, with a majority being female (74.2%) and in their first to third year of study (58.3%). Participants generally had intermediate computer literacy (75.7%) and used technology consistently for learning (57.5%). Regarding perceptions of AI, most students strongly agreed that AI will significantly impact healthcare (48.8%) and that all medical students should be educated about it (31.3%). Additionally, a substantial majority believed that integrating AI into medical education would enhance its quality (66.6%) and facilitate the learning experience (57.9%). **Conclusions:** It was concluded that students have positive perceptions regarding AI systems, demonstrating enthusiasm for expanding their knowledge of AI within their medical education.

INTRODUCTION

The healthcare systems worldwide have experienced significant transformations with the integration of technological advancements, especially in the aftermath of COVID-19 [1]. In recent years, artificial intelligence has garnered the attention of medical experts and practitioners due to its extensive applications in healthcare [2]. AI holds the promise of being a valuable medical resource in diagnostics and scientific decision-making, thanks to its remarkable ability to synthesize large amounts of data [3]. The applications of AI in medicine can facilitate a range of functions, including clinical research, treatment, administrative tasks, and drug development, owing to its capacity to learn from wide-ranging datasets [4]. Across the globe, numerous nations have started to adopt AI to improve the efficiency of healthcare distribution systems. Numerous healthcare professionals are optimistic about the implementation of AI in diagnostics, prognostics as well as therapeutic interventions [5]. Nevertheless, as AI systems become more prevalent in the healthcare sector, concerns regarding the ethical implications of utilizing technology are becoming gradually significant [6]. The COVID-19

DOI: https://doi.org/10.54393/pjhs.v6i1.2364

pandemic has underscored AI's influence on medical education, providing medical students with interactive learning experiences and enabling virtual simulations and training, which allow them to practice complex procedures on simulated patients without risking harm to real patients. However, many educational institutions face challenges in effectively integrating AI into their curricula due to a shortage of qualified instructors, the high costs of AI software, and ethical considerations [7]. The advent of Chat GPT 4, which is a novel AI-powered language technology, has showcased the potential to assist a community of students in grasping challenging scientific concepts while also raising ethical concerns [8]. As AI applications are set to profoundly impact medical pieces of training, all the alertness is being directed towards preparing the health workforce for the transition by exploring the perspectives of healthcare professionals and medical students [9]. Numerous studies have examined knowledge, perceptions, as well as attitudes of medical and healthcare specialists or students regarding AI in various states, including the Republic of Korea, Germany, the United Kingdom, Canada, the United States, Pakistan, Australia, New Zealand, Malaysia, Turkey, Saudi Arabia, United Arab Emirates, and Kuwait [10]. A noticeable knowledge gap exists in the area of Pakistan, which needs to be addressed due to the anticipated rise in Artificial intelligence utilization within the medical field. Understanding the attitudes as well as behaviours of medical students to be future consumers of AI applications is crucial for the successful integration of AI in health-related and medical education. Furthermore, assessing students' perceptions of AI is vital to determine if further workshops will be necessary, as they will frequently engage with clients and utilize technologies. However, to our information, there has been insufficient current literature focusing on the perceptions of medical students regarding the addition of AI into medical education.

This study aims to recognize the attitudes of medical students towards AI, explore current AI training prospects, investigate the necessity for AI addition in medical courses, and ascertain favoured means for educating AI-related content. Outcomes will inform choices regarding the application of medical AI and the future growth of medical syllabi.

METHODS

A descriptive, cross-sectional, online questionnaire-based study was conducted for a six months period in Lahore. The target population consisted of undergraduate medical students registered in the faculty of medicine at either private-sector or public-sector universities. Non-probability convenient sampling was utilized as the sampling technique. Informed consent was taken from each participant. Data were collected through a questionnaire. The questionnaire comprised three sections: (1) demographic baseline details, (2) perception of AI, and (3) effect of AI on medical education. These are measured through a point Likert scale. It was adapted from a previous literature [11]. The data collection questionnaire was designed in an electronic pattern using online Forms. Criteria for participant selection were: Students currently listed in the faculty of medicine at private sector or public sector university in Lahore, undergraduate students of any year, Undergraduate students who transferred from the faculty of medicine to other programs like Faculty of Science, Health sciences, D-Pharmacy, or Nursing) and have education experience for a minimum of a year in the faculty of medicine. Exclusion criteria were graduated medical students who completed their medical studies, and medical students who have withdrawn from their education. The sample size for our study was determined using the formula for cross-sectional studies: n=Z2·P (1–P) /E2. Where: n=Required sample size, Z=Z-score for a 95% confidence level (1.96), P=Assumed prevalence of awareness or positive perceptions of artificial intelligence (50% or 0.5, as no prior studies were available in this context) and E=Margin of error (5% or 0.05). Adjusting for a finite population of approximately 1,000 medical students at the institutions. n adjusted= n/1+n−1/N =278. To account for potential non-responses, the sample size was increased by 20%, resulting in a target of 334 participants. The questionnaire was distributed to 340 participants and received 252 complete responses, achieving a response rate of 74%. The questionnaire was distributed among 340 participants. 252 responses were received, depicting a response rate of 74%. To minimize bias and reduce the risk of students overstating their comfort and understanding of artificial intelligence, the questionnaire was administered anonymously to ensure that participants felt secure in providing honest responses without fear of judgment. Data analysis was executed via SPSS version 26.0. Descriptive statistics were utilized to formulate frequency and percentage tables. The chi-square test was applied to analyze the difference in perception of students with years of education.

RESULTS

The mean age of the respondents was 23.5 years (± 2.2 years). Among the participants, 25.7% were male (n=65), and 74.2% were female (n=187). The distribution of participants by their current year of study showed that 58.3% (n=147) were in their first to third year, while 41.6% (n=105) were in their fourth to final year. Regarding computer literacy, the majority (75.7%, n=191) had an intermediate level of proficiency, while 18.2% (n=46) reported basic literacy and 5.8% (n=15) advanced skills.

DOI: https://doi.org/10.54393/pjhs.v6i1.2364

Most participants (57.5%, n=145) consistently utilized technology for learning purposes, 39.2% (n=99) used it occasionally, and only 3.1% (n=8) reported rare usage. A summary of the demographic and technological characteristics of the study participants was provided in Table 1.

Table 1: Demographic Characteristics of Participants (n=252)

Characteristic	n (%)
Age (in years)	
Mean ± Standard Deviation	23.5 ± 2.2
Sex	
Male	65 (25.7%)
Female	187 (74.2%)
Current Year of Study	
First to Third-Year	147 (58.3%)
Fourth to Final Year	105(41.6%)
Level of Computer Literacy	
Basic	46 (18.2%)
Intermediate	191 (75.7%)
Advanced	15 (5.8)
Frequency of Technology Utilization for Learning	
Consistently	145 (57.5%)
Occasionally	99 (39.2%)
Rarely	8 (3.1%)

A significant majority (91.2%) agreed or strongly agreed that AI would have a profound impact on the future of healthcare, with 48.8% strongly agreeing. Half of the participants (50.7%) agreed that AI could replace certain medical specialities during their lifetime, while 27.7% disagreed. Regarding personal understanding, 53.9% agreed to have a basic grasp of AI concepts, although only 6.3% strongly agreed. Most participants (63.8%) felt comfortable with AI-related terminology, and 57.1% were aware of AI's limitations. AI was seen as beneficial for professional development by 93.1% of respondents, and 81.6% agreed or strongly agreed that all medical students should be educated about AI. Confidence in using AI applications and integrating AI into clinical practice by the end of training was less pronounced, with 44.8% and 46.8% agreeing, respectively. A smaller proportion (47.2%) believed they would gain a clear understanding of evaluating AI performance by the end of their medical education. Outlines of participants' perceptions of artificial intelligence (AI) in healthcare and medical education are given in Table 2.

Table 2: Perceptions of Participants Regarding Artificial Intelligence

Characteristics	Strongly -agree n (%)	Agree n (%)	Disagree n (%)	Strongly-Disagree n (%)
AI significantly impact the future of healthcare	123 (48.8%)	107 (42.4%)	17 (6.7%)	5 (1.9%)
AI could potentially replace certain medical specialties in my lifetime	44 (17.4%)	128 (50.7%)	70 (27.7%)	10 (3.9%)
I have a basic understanding of AI concepts	16 (6.3%)	136 (53.9%)	88 (34.9%)	12 (4.7%)
I feel at ease with AI-related terminology	74 (29.3%)	161 (63.8%)	16 (6.3%)	1 (0.3%)
I am aware of the limitations of AI technology	26 (10.3%)	144 (57.1%)	74 (29.3%)	8 (3.1%)
Learning about AI will enhance my professional development	73 (28.9%)	162 (64.2%)	17 (6.7%)	0 (0.0%)
All medical students should be educated about AI	79 (31.3%)	127 (50.3%)	46 (18.2%)	0 (0.0%)
I will be confident consuming AI applications after medical training	36 (14.2%)	113 (44.8%)	90 (35.7%)	13 (5.1%)
I will gain a clearer understanding of how to evaluate healthcare AI performance by the end of my medical training	20 (7.9%)	119 (47.2%)	95 (37.6%)	18 (7.1%)
I will acquire the skills necessary to integrate AI into clinical practice by the end of my medical education	30 (11.9%)	118 (46.8%)	90 (35.7%)	14 (5.5%)

A significant majority of respondents (96.7%) agreed or strongly agreed that AI technologies enhance the quality of medical education, with 66.6% agreeing and 30.1% strongly agreeing. Similarly, integrating AI into medical training was viewed positively by 91.9% of participants, with 34.1% strongly agreeing and 57.9% agreeing that AI would facilitate the learning experience. Regarding AI's potential to prepare students for practical clinical scenarios, 87.2% agreed or strongly agreed, while 25.7% strongly agreed and 61.5% agreed. On the other hand, the statement that AI may take over some responsibilities of future physicians received mixed reactions, with 78.5% disagreeing (49.6% disagreed and 28.9% strongly disagreed), and only 21.3% agreeing (3.9% strongly agreed and 17.4% agreed). Participants' perceptions regarding the influence of artificial intelligence (AI) on medical education are presented in Table 3.

Table 3: Influence of AI upon Medical Education

Characteristics	Strongly -agree n (%)	Agree n (%)	Disagree n (%)	Strongly-Disagree n (%)
AI technologies enhance the quality of medical education	76 (30.1%)	168 (66.6%)	7 (2.7%)	1 (0.3%)
Integrating AI into medical training would facilitate the learning experience	86 (34.1%)	146 (57.9%)	14 (5.5%)	6 (2.3%)
Utilizing AI in medical education will equip me for practical clinical scenarios	65 (25.7%)	155 (61.5%)	52 (20.6%)	10 (3.9%)
AI may take over some responsibilities of future physicians	10 (3.9)	44 (17.4)	125 (49.6)	73 (28.9)

DOI: https://doi.org/10.54393/pjhs.v6i1.2364

The p-values indicate significant differences in some of the responses between the two groups. For the statement "AI technologies enhance the quality of medical education," a higher percentage of students in the Fourth to Final Year (73.3%) agreed compared to those in the First to Third Year (61.9%), with a p-value of <0.05, suggesting a statistically significant difference. Similarly, in the statement "Integrating AI into medical training would facilitate learning," a higher percentage of Fourth to Final Year students (62.8%) agreed compared to First to Third Year students (54.4%), with a p-value of <0.05, also indicating statistical significance. Regarding the statement "Utilizing AI in medical education will equip me for clinical work," 69.5% of Fourth to Final Year students agreed, while 55.7% of First to Third Year students agreed, with a p-value of 0.04, again showing a significant difference between the groups. In contrast, for the statement "AI may take over some responsibilities of future physicians," a higher percentage of students in the First to Third Year (55.7%) disagreed, compared to 40.9% in the Fourth to Final Year group. The p-value of 0.02 highlights a statistically significant difference between the two groups. The results of a Chi-square test comparing the year of study (First to Third Year vs. Fourth to Final Year) with participants' views on the influence of AI on medical education are displayed in Table 4.

Table 4: Chi-Square Test Comparing the Year of Study with Influence of AI On Medical Education

Characteristics	Response	First to Third-Year	Fourth to Final Year	p-value
AI technologies enhance the quality of medical education	Strongly Agree	46 (31.2%)	30 (28.5%)	<0.05
	Agree	91 (61.9%)	77 (73.3%)	
	Disagree	8 (5.4%)	2 (1.9%)	
	Strongly Disagree	2 (1.4%)	0 (0%)	
Integrating AI into medical training would facilitate learning	Strongly Agree	57 (38.7%)	29 (27.6%)	<0.05
	Agree	80 (54.4%)	66 (62.8%)	
	Disagree	8 (5.4%)	6 (5.7%)	
	Strongly Disagree	2 (1.4%)	4 (3.8%)	
Utilizing AI in medical education will equip me for clinical work	Strongly Agree	40 (27.2%)	25 (23.8%)	0.04
	Agree	82 (55.7%)	73 (69.5%)	
	Disagree	20 (13.6%)	32 (30.4%)	
	Strongly Disagree	5 (3.4%)	3 (2.8%)	
AI may take over some responsibilities of future physicians	Strongly Agree	8 (5.4%)	2 (1.9%)	0.02
	Agree	22 (15.0%)	22 (20.9%)	
	Disagree	82 (55.7%)	43 (40.9%)	
	Strongly Disagree	35 (23.8%)	38 (36.1%)	

DISCUSSION

Artificial Intelligence (AI) has recently garnered considerable attention in the healthcare sector and is emerging as a crucial element in the coming era of medicine, with implementations spanning several domains like pharmaceutics, informatics, imaging analysis, and medical aids [12]. A large majority of students believe that AI would play a vital part in health sciences. Comparable results were observed in studies conducted in the United Kingdom (UK) and the United States (USA), where over seventy-five per cent of medical students felt that AI would have a moderate to significant impact on the field of medicine throughout their professions [13]. Current study results were not astonishing in that a substantial number of pupils believed that AI education would enhance career prospects. It aligns with prior research [14]. However, the literature also documents instances of AI failures, for instance, IBM's Watson for Oncology which is an AI-driven decision support gadget that was initially implemented by several hospitals but ultimately withdrawn due to its subpar performance after substantial financial investments [15]. Furthermore, experts have indicated that AI and healthcare professionals can work synergistically; while AI is poised to transform medical practice, it is improbable that it will fully replace human practitioners shortly if ever [16]. In our study, approximately 2/3rd of participants thought that AI might supplant certain domains within health care during the lifespan, echoing comparable sentiments found among nearly half of UK students in another study [17]. Conversely, a significant majority (96.6%) of students in a German study did not agree with the concept that AI could substitute practitioners in foreseeable times [18]. It is essential to recognize that while AI may serve as an alternative for certain tasks performed by human physicians, such replacements are unlikely to be total. Rather, AI abilities might likely enhance the care provided to physicians in patient treatment and management [19]. Additionally, as AI continues to evolve, clearer guidelines for its integration into medical practices and patient pathways will likely emerge [9]. In our research, students generally reported a comprehension of AI language, restrictions, and values. Parallel results were reported in a UK study where students indicated a basic understanding of the computational principles related to AI and its limitations, although they expressed discomfort with AI vocabulary [20]. In another study, a majority of medical students (78.9%) claimed to have a solid grasp of AI; however, this study utilized correct/incorrect assessments that comprised both truths and misconceptions regarding AI, ultimately revealing that a significantly lower percentage truly understood the subject [21]. The majority of participants in the current study highlighted that by the conclusion of medical education, the capability to use AI tools will be, applied in everyday medical practices along with evaluating performances of health AI. One possible description for perceptions is that medical students at the University in Kuwait may have an overly simplified view of AI, although

DOI: https://doi.org/10.54393/pjhs.v6i1.2364

the robustness of this consideration was not quantitatively evaluated in this study, representing a limitation [13]. This is further supported by the observation that only a small fraction of the sample had gained AI information through formal training ways. In the unit of UK medical students, answers differed significantly and many expressing doubts about their readiness to engage with AI or confidence in utilizing AI tools when needed. Undoubtedly, technology can change individual's lives, and participate in technology within specific contexts. Strong belief in the prospective of AI apps to revolutionize medical curricula was evident among students. Numerous means via AI could improve education settings comprise intellectual coaching systems that identify knowledge limitation areas and provide solutions for them, computer-generated enablers, statistics mining and smart feedback mechanisms [22]. Current study, a significant bulk of students conveyed optimistic attitudes regarding the influence of AI on medical education and assumed that it would facilitate the education process. A study conducted in Pakistan highlighted several challenges that may need to be addressed when integrating AI into Pakistan's healthcare system. These challenges span various areas, including government-related issues, healthcare provider concerns, and technical difficulties. Given the scarcity of AI research in the country, healthcare providers may also lack trust in its accuracy and reliability [23]. However, the current study suggests that students recognized the value and influence of AI organizations as helpful tools in their educational journey. Their optimistic outlook was underscored by the fact that a large majority expressed a willingness to engage with AI in medical studies.

CONCLUSIONS

It was concluded that students have positive perceptions regarding AI systems, demonstrating enthusiasm for expanding their knowledge of AI within their medical education.

Authors Contribution

Conceptualization: SR1,
Methodology: SR1, SR2, MR, AH
Formal analysis: SR2
Writing review and editing: N, SB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2581

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Autoimmune Hemolytic Anemia in Children: Clinical Profile and Outcome

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ARTICLE INFO

Keywords:
Autoimmune Hemolytic Anemia, Pediatric Patients, Treatment Responses

How to Cite:
Ali, K., Ahmed, B., Bharo, M. A., Khuhro, A., Bahalkani, U., & Kamran, F. (2025). Autoimmune Hemolytic Anemia in Children: Clinical Profile and Outcome: Hemolytic Anemia in Children. Pakistan Journal of Health Sciences, 6(1), 42-47. https:/ /doi. org/ 10.5 43 93/pjhs.v6i1.2581

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Received date: 18th November, 2024
Acceptance date: 19th January, 2025
Published date: 31st January, 2025

ABSTRACT

Autoimmune Hemolytic Anemia (AIHA) is an idiopathic condition marked by red blood cell destruction. **Objective:** To compare the clinical features, laboratory parameters, treatment approaches, and responses between idiopathic and secondary AIHA in pediatric patients, with the aim of identifying key distinctions that can inform the development of tailored diagnostic and therapeutic strategies. **Methods:** This was cross sectional study and conducted for six months from April 2024 to September 2024 at Department of pediatrics at Khairpur medical college khairpur mirs. Data were collected on demographics, presenting symptoms, laboratory findings (hemoglobin, bilirubin, LDH levels), antibody profiles, and treatment outcomes. SPSS 23 was used for statistical analysis to compare treatment responses and clinical characteristics between idiopathic and secondary AIHA patients. Chi-square tests were used for categorical variables and t-tests for continuous variables. **Results:** The mean age of participants was 6.8 years, with 58% male. Patients with idiopathic AIHA had higher hemoglobin levels (7.5 g/dL versus 6.9 g/dL for secondary, p=0.03) and lower bilirubin (3.6 mg/dL versus 4.1 mg/dL, p=0.02). Treatment varied significantly: 89% of idiopathic patients received steroids compared to 86% of secondary patients. Secondary patients were more likely to receive IVIG (51% versus 34%, p=0.04) and rituximab (37% versus 11%, p<0.01). Complete response rates were higher in idiopathic AIHA (83% versus 63%, p=0.01). **Conclusions:** Significant differences exist in the clinical presentation and treatment responses of idiopathic versus secondary AIHA. Tailored treatment strategies on AIHA type are essential for improving patient outcomes, warranting further research into these distinctions and new therapies.

INTRODUCTION

Autoimmune Hemolytic Anemia (AIHA) is a hematological condition defined by the premature death of red blood cells caused by the immune system's erroneous attack on them. This illness can cause major morbidity and, in severe situations, fatality, particularly in pediatric populations. AIHA in children can be divided into two categories: idiopathic and secondary. Idiopathic AIHA has no obvious cause, whereas secondary AIHA is caused by underlying illnesses such as infections, cancer, or autoimmune diseases [1]. The clinical manifestations of AIHA in children are pallor, jaundice, fatigue and splenomegaly; based on the degree of hemolysis and general condition of a child these can be mild or severe. It is important to diagnose AIHA as soon as possible; untreated, the disorder may cause life-threatening complications, including organ failure and impaired immunity [2]. Corticosteroids, including prednisone, are often the initial treatment choice for autoimmune hemolytic anemia. These medications work by suppressing the immune system and reducing inflammation. The initial approach to rapidly treat the symptoms of anemia is to start at a high dose of corticosteroids. Often within days or weeks, patients will see a response characterized by an increase in hemoglobin levels and reduction of hemolysis. The dose of corticosteroids can be tapered gradually as symptoms improve to minimize unwanted side effects. However

DOI: https://doi.org/10.54393/pjhs.v6i1.2581

chronic administration of corticosteroid can lead to life threatening side effects like weight gain, increased risk for infection, osteoporosis and metabolic derangement (like diabetes) [3]. When corticosteroids alone have not produced the desired effect in patients with AIHA who are steroid-dependent, an immunosuppressive medication called azathioprine may be given. By preventing DNA synthesis, azathioprine inhibits the growth of immune cells that create autoantibodies against red blood cells [4]. Usually, it is applied as a second-line therapy, especially for persistent AIHA. Azathioprine can cause side effects such as liver toxicity, bone marrow suppression, and an increased risk of infections, even though it is beneficial for certain people. Throughout treatment, routine blood count and liver function testing is crucial [5, 6]. Splenectomy, or the surgical removal of the spleen, may be considered in cases of AIHA that do not respond well to medication therapy. Red blood cell survival and hemoglobin levels can be increased by eliminating the spleen, which is involved in a major portion of the breakdown of red blood cells. For patients with warm AIHA, this method is quite helpful. Splenectomy is not appropriate for every patient, and before undergoing this surgical procedure, one must carefully weigh the advantages and disadvantages [7]. In children, type secondary is frequently associated with lymphoreticular malignancy, autoimmune disease, primary immunodeficiency and rare drugs. Around 80% of kids have an intense and also self-limiting illness, that often improves with treatment for only a few days with steroids. In the presence of systemic disease, it takes a chronic relapsing course requiring prolonged immunosuppression. Secondary Autoimmune Hemolytic Anemia (AIHA) is not a disease in itself but a manifestation of other underlying disorders. Often associated with lymphmotoreticular malignancies; these neoplasms may', however, impair immune system function and create autoantibodies against red blood cells Lymphomas and leukemias [8]. This means that some cases of AIHA can occur due to immune systems gone haywire, which attack their own tissues including red blood cells (as is the case with autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus [SLE]). Furthermore, in individuals with primary immunodeficiency disorders, impaired immunity may lead to production of autoantibodies and subsequent development of secondary AIHA [9]. Some less common medicines that can cause AIHA include nonsteroidal anti-inflammatory drugs (NSAIDs), some anti-seizure drugs and antibiotics. These therapies stimulate an immune response that misidentifies red blood cells as targets. Because hemolytic anemia can improve with treatment of the underlying disease, knowledge of secondary AIHA triggers, and specific therapy for the respective trigger is important in optimizing therapy and management [10].

While previous studies have focused on either idiopathic or secondary AIHA individually, there is a lack of direct comparisons between these two forms, particularly in the pediatric population. This study aims to fill this gap by providing a comprehensive analysis of both forms of AIHA, thereby aiding clinicians in better understanding the distinct clinical and laboratory profiles, treatment responses, and management strategies for each type. These findings may help guide more personalized and effective therapeutic interventions for children with AIHA.
The aim of this study was to shed some light on the demographic, clinical, laboratory data and management and outcome in children with AIHA. With this information, we hope to achieve an awareness and a better understanding of the incidence among children affected.

METHODS

This was cross sectional study and conducted for six months from April 2024 to September 2024 at Department of pediatrics at Khairpur Medical College, Khairpur Mirs. A consecutive sampling method was used to select pediatric patients diagnosed with autoimmune hemolytic anemia. Inclusion criteria were: age between 1 and 18 years, direct Coombs test positive, hemolysis raised bilirubin level, decreased haemoglobin levels and increased reticulocyte count. Exclusion criteria: Patients with hemolytic anemia due to other known reasons (for example, hereditary spherocytosis, glucose6-phosphate dehydrogenase lack of ability and/or medicine created hemolysis). The sample size calculation on prevalence: n=Z2×p× (1–p)/ d21, Z = 95% (1.96), p = Prevalence assumed (10%) for AIHA in pediatric hospitalized patients) and d = margin of error (5% or 0.05). Consequently, a sample size of at least 138 cases was needed. Demographics, presenting symptoms (such as pallor, jaundice, and hepatosplenomegaly), and laboratory parameters (such as hemoglobin levels <11 g%, total bilirubin >1.2 mg/dL, LDH >280 U/L, Reticulocyte count >2.5%, Coombs test results, and antibody profiles) were recorded during the review of medical records and direct patient assessments. The methods of treatment were also recorded, including the kinds of medication administered (rituximab, plasmapheresis, intravenous immunoglobulin (IVIG), steroids), the length of the steroid therapy course, the need for transfusions, and the length of hospital stay. Treatment responses were classified as total or partial, and any relapses were noted during the follow-up. Data were analyzed using SPSS. 23. Descriptive statistics (mean, standard deviation, frequency, percentage) summarized demographic and clinical characteristics. Independent t-test for comparing continuous variables (e.g., age, hemoglobin levels) between the two groups, assuming normal distribution of data. Chi-square test for categorical variables (e.g., gender, response to treatment) to

DOI: https://doi.org/10.54393/pjhs.v6i1.2581

determine the association between group status and clinical outcomes. A p-value of <0.05 was considered statistically significant. The ethical approval for this study was obtained from the Ethical Review Board and the approval letter was issued under reference number [KMC/RERC/104].

RESULTS

The data highlighted the differences between idiopathic and secondary AIHA in terms of demographic features, clinical presentation, and laboratory findings. Table 1 reveals the descriptive statistics of study variables for n=138 patients. The average age of participants was 6.8 ± 2.4 years, suggesting that children in this sample were mainly in lower primary grades. The patients had a mean hemoglobin level of 7.1 ± 1.5 g/dL, indicating a notable degree of anemia in this population. The mean total bilirubin was 3.8 ± 1.2 mg/dL, which by definition constituted mild hyperbilirubinemia. While the mean hospital stay was 8.2 ± 3.5 days, indicating the clinical severity and complexity of patient management they reflected. Demographic characteristics showed a preponderance of male patients 80 (58%) versus female patients 58 (42%) for the cohort. The most common presenting symptom was pallor 127 (92%) patients and other frequent findings included jaundice 108 (78%) patients and hepatosplenomegaly 48 (35%). The types of Autoimmune Hemolytic Anemia (AIHA) were analyzed and 89 (64%) of the patients had idiopathic AIHA, while secondary AIHA was found in 49 (36%). These results described the clinical and demographic characteristics of the patient population within this study, noting also a significant presence of anemia and related symptoms.

Table 1: Descriptive Statistics of Study Variables (n = 138)

Variable	Mean ± SD / Frequency (%)
Age (Years)	6.8 ± 2.4
Hemoglobin (Hb) (g/dL)	7.1 ± 1.5
Total Bilirubin (mg/dL)	3.8 ± 1.2
Hospital Stay (Days)	8.2 ± 3.5
Gender	
Male	80 (58%)
Female	58 (42%)
Presenting Symptoms	
Pallor	127 (92%)
Jaundice	108 (78%)
Hepatosplenomegaly	48 (35%)
AIHA Type	
Idiopathic AIHA	89 (64%)
Secondary AIHA	49 (36%)

Descriptive analysis, frequency and percentage;

P<0.005 indicate significant values;

Bar graph represented the Etiological Spectrum of Secondary Autoimmune Hemolytic Anemia (AIHA). Infections would have the tallest bar, followed by Autoimmune Disorders and Malignancies, illustrating their significance as leading causes (Figure 1).

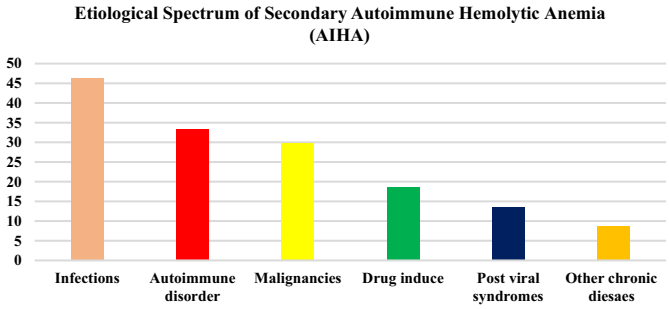

Figure 1: Etiological Spectrum of Secondary Autoimmune Hemolytic Anemia (AIHA)

Table 2, revealed that the examining laboratory parameters and antibody profiles between patients with idiopathic versus secondary AIHA is shown in Table 2. In total, 138 patients were recruited, with 64 having idiopathic AIHA and 41(39%) secondary AIHA; the mean hemoglobin level was significantly higher in the former (hemoglobin A1c g/dL [0.13 mmol/L]): idiopathic: 7.5 versus secondary: 6.9 (P =.03). Furthermore, total bilirubin level (3.6 mg/dL versus 4.1 mg/dL) was lower in idiopathic AIHA than secondarily-related AIHA (p=0.02). Reticulocyte count was 4.5% on average (range, 2-25%) in idiopathic cases and 5.0% (2-20%) in secondary cases but this difference did not reach significance level (p = 0.09). Lactate dehydrogenase (LDH) levels were notably lower in the idiopathic group (620 U/L) than in the secondary group (780 U/L), with a p-value of 0.01, indicating a significant difference. When assessing the antibody profiles, the direct Coombs test positivity was similar in both groups, with 81% of idiopathic cases and 82% of secondary cases testing positive (p = 0.87). However, a higher percentage of patients with secondary AIHA tested positive on the indirect Coombs test (57%) compared to those with idiopathic AIHA (40%), approaching statistical significance (p = 0.05). The presence of warm antibodies (IgG) was slightly higher in idiopathic AIHA (79%) than in secondary AIHA (69%), but this difference was not statistically significant (p = 0.18). Cold antibodies (IgM) were found in 21% of the idiopathic group and 31% of the secondary group (p = 0.23). Notably, a mixed antibody profile was more prevalent in secondary AIHA, with 16% of patients exhibiting this profile compared to 6% in idiopathic cases, achieving statistical significance with a p-value of 0.04. Overall, these findings suggest that there are significant differences in certain laboratory parameters between idiopathic and secondary AIHA, particularly in hemoglobin, bilirubin, and LDH levels, as well as in the prevalence of mixed antibody profiles.

DOI: https://doi.org/10.54393/pjhs.v6i1.2581

Table 2: Comparison of Laboratory Parameters and Antibody Profile in Idiopathic versus Secondary AIHA (n=138)

Variables	Idiopathic AIHA Mean ± SD/N (%)	Secondary AIHA Mean ± SD/N (%)	p-value
Hemoglobin (g/dL)	7.5 ± 1.3	6.9 ± 1.7	0.03
Total Bilirubin (mg/dL)	3.6 ± 1.1	4.1 ± 1.3	0.02
Reticulocyte Count (%)	4.5 ± 1.2	5.0 ± 1.4	0.09
LDH (U/L)	620 ± 220	780 ± 250	0.01
Direct Coombs Test Positive	72 (81%)	40 (82%)	0.87
Indirect Coombs Test Positive	36 (40%)	28 (57%)	0.05
Warm Antibodies (IgG)	70 (79%)	34 (69%)	0.18
Cold Antibodies (IgM)	19 (21%)	15 (31%)	0.23
Mixed Antibody Profile	5 (6%)	8 (16%)	0.04

Independent t-test used to compare mean between lab parameters

Chi-square test used for categorical variables;
P<0.005 indicate significant values;

Table 3 compared various treatment parameters between patients with idiopathic and secondary autoimmune hemolytic anemia (AIHA). The initiation of steroid therapy was high in both groups, with 89% of idiopathic AIHA patients and 86% of secondary AIHA patients receiving treatment, resulting in a p-value of 0.62, indicating no significant difference. However, the administration of intravenous immunoglobulin (IVIG) therapy was significantly more common in the secondary AIHA group (51%) compared to the idiopathic group (34%), with a p-value of 0.04. In contrast, rituximab was used significantly more often in patients with secondary AIHA (37%) than in those with idiopathic AIHA (11%), achieving a p-value of less than 0.01. Similarly, plasmapheresis was performed in 16% of secondary AIHA cases compared to only 3% of idiopathic cases, with a p-value of 0.01, highlighting a substantial difference in treatment approaches. Regarding transfusion requirements, 58% of idiopathic AIHA patients needed transfusions, while this figure was higher in secondary AIHA patients at 78%, with a statistically significant p-value of 0.02. The duration of steroid therapy was also significantly longer in the secondary AIHA group (45 days) compared to the idiopathic group (34 days), with a p-value of less than 0.01. Hospital stays were similarly prolonged for secondary AIHA patients (10 days) compared to idiopathic patients (7 days), with a p-value of less than 0.01, indicating a higher clinical burden in secondary cases. In terms of treatment response, a complete response was observed in 83% of idiopathic AIHA patients compared to 63% of secondary AIHA patients, with a p-value of 0.01, suggesting a better overall response in idiopathic cases. Partial responses were reported in 11% of idiopathic patients and 29% of secondary patients, although this difference was not statistically significant. Relapse occurrence was similar between groups, with 20% of idiopathic and 24% of secondary patients experiencing a relapse, resulting in a p-value of 0.57, indicating no significant difference. Overall, these results suggest that while both groups receive steroid therapy at similar rates, secondary AIHA patients require more aggressive treatment strategies, including IVIG, rituximab, and plasmapheresis, and experience longer hospital stays and steroid therapy durations.

Table 3: Comparison of Treatment Parameters in Idiopathic versus Secondary AIHA (n=138)

Treatment Variables	Idiopathic AIHA Mean ± SD/N (%)	Secondary AIHA Mean ± SD/N (%)	p-value
Steroid Therapy Initiated	79 (89%)	42 (86%)	0.62
IVIG Therapy Administered	30 (34%)	25 (51%)	0.04
Rituximab Used	10 (11%)	18 (37%)	<0.01
Plasmapheresis Performed	3 (3%)	8 (16%)	0.01
Transfusion Requirement	52 (58%)	38 (78%)	0.02
Duration of Steroid Therapy (days)	34 ± 12	45 ± 18	<0.01
Hospital Stay (days)	7 ± 2	10 ± 3	<0.01
Response to Treatment Complete	74 (83%)	31 (63%)	0.01
Partial Improvement	10 (11%)	14 (29%)	
Relapse Occurrence	18 (20%)	12 (24%)	0.57

Independent t-test used to compare mean between lab parameters;

Chi-square test used for categorial variables;
P<0.005 indicate significant values;

DISCUSSION

The hematological condition known as Autoimmune Hemolytic Anemia (AIHA) is caused by decompensated acquired hemolysis, which is brought on by the host's immune system attacking self-red cell antigens. Autoantibodies, whether or not complement activation is present, are directed against erythrocytes [11]. In patients with idiopathic versus secondary Autoimmune Hemolytic Anemia (AIHA), this study sought to assess the clinical and laboratory features, therapeutic parameters, and response to therapy. The present findings offer important new information about patient demographics, test results, therapy modalities, and treatment outcomes. These details can be compared with previously published research to make relevant inferences [12]. The average age of 6.8 years for this study of 138 patients corroborates to previous studies reporting a predominance of AIHA in a paediatric population. Autoimmune disorders tend to have a slightly male bias, which is aligned with the majority of patients (58%) being male. The high prevalence of pallor (92%) and jaundice (78%) indicates severe hemolytic anemia symptoms among the patients. This aligns with the findings from (Voulgaridou and Kalfa *et al.*, in 2021), stating

DOI: https://doi.org/10.54393/pjhs.v6i1.2581

that young AIHA patients often present with symptoms like pallor and jaundice [13]. In the present study finding that the mean hemoglobin level of 7.1 g/dL confirmed the severity of anemia. The total bilirubin level of 3.8 mg/dL in this case, which is also shown to be classical in AIHA patients by (Gabelli *et al.*, in 2022) further represents the hemolytic process [14]. These results are important as they were for idiopathic AIHA which was the most prevalent type, to be precise 64% in idiopathic and 36% in secondary showed to have concordance. In the current study to found that laboratory parameters, including hemoglobin, total bilirubin and LDH levels were significantly different between idiopathic versus secondary AIHA. The hemoglobin level in idiopathic AIHA patients was higher than that in secondary patients (7.5 versus 6.9 g/dL), suggesting less pronounced anemia at the time of presentation among idiopathic cases [15]. Weli *et al.*, in 2020 previous study consistent with the observations by the secondary AIHA typically has a more severe clinical presentation and worse test values [16]. It is also possible that lower total bilirubin (3.6 mg/dL) in idiopathic AIHA than secondary AIHA (4.1 mg/dL) suggests less hemolysis among the former group. The results of the substantial difference in LDH level (620 U/L idiopathic versus 780 U/L secondary) between the two groups, which is further corroborating conclusions proposed by other authors, as LDH is involved in oxidizing redox reaction and, therefore an important marker of hemolysis severity [17]. Consistent with the findings of (Delesderrier *et al.*, in 2020) for secondary AIHA patients, the antibody profiles displayed a wider spectrum of reactivity, capturing underlying diseases. In fact, secondary AIHA had higher occurrence rates of mixed antibody profiles (16%) than idiopathic AIHA (6%) [18]. For treatment, initial steroid therapy was given to 89% of idiopathic and 86% secondary AIHA patients, denoting equivalence in commencing management. In contrast, there were significant differences in the use of complementary therapies. According to previous study that had a secondary AIHA, because of the association of such with other underlying disorders, usually needs a more intense therapy. The increased usage of IVIG (51% in secondary AIHA) and rituximab (37% in secondary AIHA) suggests a more aggressive therapy approach for secondary AIHA [19]. Moreover, the duration of steroid therapy was longer in secondary AIHA patients (45 days) than idiopathic patients (34 days), indicating a longer treatment course. These results are in line with the findings of previous study of (Dei *et al.*, in 2024) secondary cases usually stay in pellet longer than primary ones [19]. Treatment response 83% of idiopathic AIHA patients had a complete treatment response, 63% of the secondary AIHA patients had a complete treatment response. The contrast with treatment response emphasizes the generally favorable course of idiopathic case [20]. This aligns with the previous literature (Mueller *et al.*, 2018), supporting that initial therapy is often more effective in idiopathic AIHA than secondary variants which may have confounding factors influencing treatment outcomes [21]. This study indicated that laboratory results, treatment strategy and response to therapy differ significantly between idiopathic and secondary AIHA patients. The results are consistent with prior studies and support the importance of individualized management strategies based on AIHA pathogenesis. Further research is needed to provide long-term outcomes, quality of life and impact of new treatments in these patients.

CONCLUSIONS

In contrast to secondary AIHA patients who often required more intensive treatment including IVIG and rituximab, the idiopathic AIHA cases are less severe and respond better. These findings emphasized the need for accurate diagnosis and individualized treatment strategies tailored to each specific form of AIHA to ultimately improve patients' outcomes.

Authors Contribution

Conceptualization: KA
Methodology: BA, MAB, AK
Formal analysis: BA, FK
Writing, review and editing: UB, FK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2277

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Assessing the Alkaline Phosphatase Levels as A Bone Biomarker in Gingival Crevicular Fluid during Semi-Rapid Expansion

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ARTICLE INFO

Keywords:
Biomarker, Gingival Crevicular Fluid, Alkaline Phosphatase, Bone Remodeling

How to Cite:
Shamim, A., Shaheen, A., Azeem, M., Atiq, N., Hussain, S., & Mahmood, S. (2025). Assessing the Alkaline Phosphatase Levels as A Bone Biomarker in Gingival Crevicular Fluid during Semi-Rapid Expansion: Alkaline Phosphatase Levels in Gingival Crevicular Fluid during Expansion. Pakistan Journal of Health Sciences, 6(1), 48-52. https://doi.org/10.54393/pjhs.v6i1.2277

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Received date: 22th October, 2024
Acceptance date: 16th January, 2025
Published date: 31st January, 2025

ABSTRACT

In orthodontics, the expansion of the maxilla is done to treat transverse maxillary deficiency in childhood. The cause of maxillary constriction may be genetic or environmental leading to crowding of teeth, cross bite and development of malocclusions. This expansion leads to increased maxillary dimensions. **Objectives:** To detect changes in alkaline phosphatase level as a bone biomarker in crevicular fluid during the phases of semi-rapid palatal expansion. **Methods:** Fifteen growing patients with an age range from 8-13 years were selected who needed maxillary semi-rapid palatal expansion as a part of orthodontic treatment. This quasi-experimental study was based on a non-probability purposive sampling technique conducted from August 2023 to July 2024. The samples were collected by inserting paper points in the gingival sulcus. The Periodontal status was evaluated before starting the sampling. The probing depths were recorded at different levels throughout the study until the completion of the retention period. The alkaline phosphatase levels in the gingival crevicular fluid were measured at buccal and palatal sites before, during and in the retention period after treatment. The alkaline phosphatase values were compared using the ANOVA test at different points in time with $p<0.05$ considered as statistically significant. **Results:** The ANOVA test showed a statistically significant increase in enzyme activity at different sites throughout maxillary semi-rapid palatal expansion treatment. **Conclusions:** It was concluded that the enzyme alkaline phosphatase as a biomarker is an indicator of active bone metabolism in growing children while going through the maxillary semi-rapid palatal expansion treatment.

INTRODUCTION

The objectives of Orthodontic and orthopedics treatment are to correct dental as well as jaw abnormalities. Tooth movement initiated by the application of orthodontic force is characterized by alteration in the dental and periodontal tissues [1, 2]. Jaws deformities can be corrected by different methods like the use of functional appliances, expansion of jaws, and correction of cross-bites in growing children. Correction of constricted jaws can be done by Rapid palatal expansion (RPE) which is an ideal technique for widening of jaws. Similarly growing children with class 2 and 3 malocclusions of increased or negative overjet can be corrected by Functional appliances if their treatment starts at proper timing [3, 4]. Once the growth spurt of growing patients is over the active growth which normally begins to end at the age of 12–13 years in female and 14–15 years in male, the procedures for growth change, rapid palatal expansion (RPE), and class 3 overjet correction are of no use. So once the patient is mature the only option left is camouflage treatment or surgical intervention to correct jaws. So the assessment of the exact timing to start an orthopedic intervention is very important. The study of bone biomarkers can give us important information in this regard. So when to start or not an orthopedic intervention on growing patients depends mainly on the identification of

DOI: https://doi.org/10.54393/pjhs.v6i1.2277

the skeletal maturation phase. The exact timing to start treatment of growing children is different in various malocclusions [5, 6]. The methods of growth assessment are cervical vertebral method, hand and wrist analysis, and assessment of chronological and dental maturation. However, with time, these methods are not reliable assessors of growth phases [7, 8]. New opportunities available for the growth assessment are biochemical markers. The collection of gingival crevicular fluid (GCF) for the assessment of biochemical markers can protect patients from extra radiographic exposure and tell us they are directly involved in the growth of bone and its remodeling [9]. Alkaline phosphatase (ALP) has been studied as a dependable biological indicator of the maturation of bones in several studies and its levels are associated with methods for the identification of skeletal development in growing patients [10, 11]. The enzyme alkaline phosphatase in bones is produced by the osteoblasts and is an extremely specific indicator of the bone-forming activity of osteoblasts. So for children with jaw deformity, it is very important to check their growth status before the start of orthopedic treatment. The compliance to wear a functional appliance for a long time in children is mandatory [12, 13].

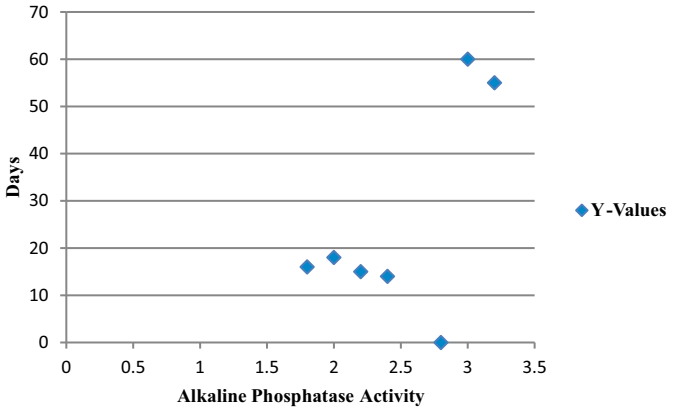
This study aims to detect changes in ALP level as a bone biomarker in crevicular fluid during various phases of semi-rapid palatal expansion.

METHODS

The institutional review board's permission was taken two months before the start of the study. The IRB number was (IBR Number 464). A written consent was taken from the patients/parents before the sampling. This quasi-experimental study was based on a non-probability purposive sampling technique due to the limited availability of patients of semi-rapid expansion. The duration was one year from 1 Aug 2023 to 31 July 2024. Patients having male gender only (to avoid gender biases), aged 10-14 years, and having narrow maxilla in transverse plane were included in the study, while, patients having any systematic disease patient or poor oral hygiene, history of undergoing any kind of oral surgery including ortho-gnathic surgery, and having a history of orthodontic treatment were excluded. The sample size of 15 was calculated by using the Open Epi sample size calculator using the following assumptions confidence level of 95%, population size of 1450, percentage frequency of outcome factor in the population of 51% and confidence limits of 5% [11]. 15 patients who visited the orthodontic department of de 'Montmorency College of Dentistry, Lahore with complaints of narrow maxilla were selected. Their oral hygiene and periodontal status were evaluated before selection for study. Also any systemic disease were ruled out. The maxillary expander was inserted in the mouth but we collected GCF one day before the insertion of the appliance. The sampling was done by inserting paper points in the gingival sulcus for collection of GCF, at all the three buccal and three lingual sides i.e. mid, mesial and distal sites. After insertion of the appliance GCF sample was also collected on day 0, day 1, and day 21. Then appliance was deactivated after completion of active semi-rapid palatal expansion for 3 months and the sample was collected again. Gingival massaging was done to activate GCF before the insertion of the appliance and whenever sampling was done to activate it. The patients were properly instructed to monitor their oral hygiene strictly and poor oral hygiene-containing patients were not included in the study. ELISA technique was utilized to analyze the ALP levels. Statistical analysis was done by entering the collected data through SPSS (Statistical Package for Social Sciences) version 21.0. The enzyme alkaline phosphatase activity was calculated and measured and the mean values of the enzyme were determined. The ANOVA test was applied for enzyme activity to check any significance of values. A value of $p \leq 0.05$ was considered a statistically significant reading.

RESULTS

A total of 15 male patients were observed between the ages of 10 and 14 years, to avoid gender bias we included only males in the current study. All the patients were in the growing age. ANOVA test was used to investigate the levels of alkaline phosphatase at Day 0, Day 1, Day 7, and Day 21 till the end of 03 months. It was observed a statistically significant difference ($p<0.05$) in mean levels of alkaline phosphatase. The mean alkaline phosphatase level rises from day 0 to day 90. It was also observed that there was a statistically substantial increase in levels between day 21 and day 0. The results also showed a noteworthy increase in alkaline phosphatase levels even till termination of 03 months of the retention period which is suggestive of increased osteoblastic activity. No significant differences were found in the selected patients of 10-14 years of age (Figure 1).



DOI: https://doi.org/10.54393/pjhs.v6i1.2277

Figure 1: Alkaline Phosphatase Activity at Different Levels

The mean values of ALP activity at each time point are presented in Table 1. The data revealed a progressive increase in ALP levels, with statistically significant differences observed between the time points ($p < 0.05$).

Table 1: Mean Alkaline Phosphatase Activity at Different Time Points

Time Point	Mean ALP Levels (± SD)
Day 0 (Baseline)	0.52 ± 0.10
Day 1	0.85 ± 0.12
Day 7	1.25 ± 0.15
Day 21	2.05 ± 0.20
After 3 months	2.90 ± 0.25

DISCUSSION

Orthodontic treatment of growing children at an exact time is very important. Most of the children at growing age seek orthodontic advice due to jaw deformity or crowding of teeth [13]. The main problems of jaws in growing age are proclined upper anterior teeth, negative overjet, crowding of teeth, cross bites and constricted upper jaws [13, 14]. The etiology of these discrepancies is many like hereditary factors, environmental factors and sometimes a combination of these two. If these ailments are addressed at the proper time most favorable results are achieved. Similarly, constriction of maxillary dentition is a common reason for irregular crooked dentition. The contributing features may be genetics, environmental or functional factors [15-18]. Rapid Palatal Expansion using semi-rapid protocol is the method which can correct it. A rapid palatal expander is an appliance which is fitted in the oral cavity. Many patients are not compliant enough to bear an appliance in their mouth for long period. So the chances of the patient drained out are high. So it is very important to know the exact status of growth before the placement of the appliance in the oral cavity. Long duration of the appliance in the mouth can also promote the accumulation of plaque and poor oral hygiene [15]. The semi-rapid palatal expansion of the palate can be done by a bonded or banded hyrax expander [6]. Typically, the RPE is done in growing patients to get skeletal effects but in patients who are skeletally mature option left is semi-rapid palatal expansion through surgical intervention [19]. These days' the role of biomarkers is increasing for the assessment of growth status in growing children. Their advantage is extra radiographic rays are avoided and the exact status of growth may be known for the start of the orthopedic intervention [14]. Enzyme alkaline phosphatase is considered a bone biomarker. Its increased levels can predict active bone turnover so that orthodontic and orthopedic intervention can be carried out [8, 12]. The raised levels of ALP are related to active bone formation which can play a vibrant role in the indication to start the exact treatment timings of orthopedic intervention. Any change in levels of alkaline phosphatase can be a sign of active bone conversion during orthodontic movement of teeth [20-23]. In current study, we tried to find out the growth status of children by checking their alkaline phosphatase levels before the start of treatment to get the maximum benefits of active growth. The frequency of bone formation through osteoblasts is broadly connected with the activity of ALP [24]. As the use of orthodontic and orthopedic appliances takes enough time to get beneficial skeletal effects so early removal of the appliance may lead to a relapse of lengthy treatment leading to incorrect results. Similarly, the early start of orthopedic intervention can also lead to non-compliance in the second phase of treatment. Batra and other researcher colleagues also noticed a decreased alkaline phosphatase level on the 21st day [20]. The results of current study are consistent with findings reported by Batra *et al.*, who observed a peak in ALP levels during the initial phase of orthodontic treatment, followed by a gradual decline as the bone stabilized [20]. However, unlike Batra's study, present findings indicate that ALP levels remained elevated even after 3 months of retention, which may suggest that the semi-rapid protocol induces prolonged osteoblastic activity. Similarly, studies by López *et al.* and Wang *et al.* have documented increased ALP levels during rapid palatal expansion, emphasizing its role in monitoring bone turnover [22, 23]. In contrast, some researchers have reported a decline in ALP activity within a shorter retention period [24]. This discrepancy could be attributed to variations in appliance design, expansion protocols, and patient-specific factors such as age and skeletal maturity. Present study focused exclusively on male patients aged 10–14 years, a group characterized by active skeletal growth, which may account for the prolonged elevation in ALP levels observed. Overall, current findings underscore the importance of biochemical markers in orthodontic treatment planning. Further studies with larger sample sizes and diverse patient populations are warranted to validate these results and explore their implications for clinical practice. In Present study the level of alkaline phosphatase was still raised till the completion of 3 months of retention period. It indicated that active osteoblastic activity was going on even after 3 months of retention period. This result shows us that we can increase the time of retention up to 6 months leading to a minimal relapse [25, 26]. Early removal of the appliance may lead to a relapse of treatment leading to incorrect results [26]. The advantage of using a Hyrax expander for the semi-rapid expansion of the palate is that it does not exasperate the mucosa of the palate and is more hygienic. The reason for selecting palatal expansion cases was to avoid extra

DOI: https://doi.org/10.54393/pjhs.v6i1.2277

retention of the appliance in the mouth as it is a lengthy procedure with a high relapse history. So biomarkers are an important means of knowing active bone formation going on in growing patients.

CONCLUSIONS

It was concluded that the enzyme alkaline phosphatase as a biomarker is an indicator of active bone metabolism in growing children while going through the maxillary semi-rapid palatal expansion treatment.

Authors Contribution

Conceptualization: AS[1]
Methodology: AS[1], AS[2], MA, NA, SH, SM
Formal analysis: AS[2]
Writing review and editing: AS[1], AS[2], MA, NA, SH, SM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2498

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Endometrial Hyperplasia on Rising Trends among Peri-Menopausal Women

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ARTICLE INFO

Keywords:

Abnormal Uterine Bleeding, Endometrial Hyperplasia, Perimenopause, Histopathological Findings

How to Cite:

Tabassum, S., Aziz, A., & Suman, F. (2025). Endometrial Hyperplasia on Rising Trends among Peri-Menopausal Women: Endometrial Hyperplasia among Peri-Menopausal Women. Pakistan Journal of Health Sciences, 6(1), 53-57. https://doi.org/10.54393/ pjhs.v6i1.2498

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Received date: 1st November, 2024
Acceptance date: 13th January, 2025
Published date: 31st January, 2025

ABSTRACT

Endometrial hyperplasia demonstrates a uterine pathology characterized by a range of endometrial morphological remodeling. The clinical importance of endometrial hyperplasia lies in its progression to endometrial carcinoma. **Objectives:** To analyze histopathological findings of endometrial biopsy in perimenopausal women having abnormal uterine bleeding and to observe the correlation of various risk factors with endometrial hyperplasia. **Methods:** The cross-sectional study was conducted at the Department of Gynaecology, Nishtar Medical University, Pakistan. Two hundred and fifty-five perimenopausal women having abnormal uterine bleeding of 3-12 months' duration were included. The participants were subjected to histopathological analysis of endometrial biopsy obtained by dilatation and curettage. All the information and the histopathology report were entered on a specific proforma. Data analysis was performed using SPSS software version 26.0. **Results:** Out of a total of 255 patients, the mean age was 48+/-6 years. A vast majority was grand multiparous (n=163, 64%). Out of a total of 255 endometrial samples, the majority (n=88, 34.5%) turned out to be proliferative endometrium, indicating hormonal imbalance like unopposed estrogen stimulation. In total, 66 (25.9%) samples fulfilled the criteria of endometrial hyperplasia. 54 (21.7%) had endometrial hyperplasia without atypia, while 12 (4.2%) had atypical endometrial hyperplasia. Regarding atypical uterine bleeding, the commonest symptom was heavy regular cycle (n=74, 29%) followed by irregular vaginal bleeding (n=70, 27.5%). **Conclusions:** It was concluded that atypical uterine bleeding in the peri-menopausal life period is alarming. All such women should undergo endometrial histopathological examination to detect endometrial hyperplasia to prevent its progression to endometrial carcinoma.

INTRODUCTION

The endometrium corresponds to the innermost layer of the uterus, which undergoes a series of cyclical changes during the menstrual cycles of a woman's reproductive years. This takes place due to a complex display between two hormones, namely estrogen and progesterone. The estrogen causes cellular proliferation of the endometrium, leading to uterine wall thickness, while progesterone causes cellular differentiation in the endometrium. If the equilibrium between the intricate display of the two hormones is disturbed, it results in chronic estrogenic stimulation of endometrium, unopposed by progesterone, leading to the marked thickness of the uterine wall [1]. Endometrial hyperplasia (EH) corresponds to a uterine pathology characterized by a range of morphological changes in the endometrium. The hallmark of EH is an exacerbation of the endometrial gland-to-stroma ratio in comparison to normal proliferative endometrium [2]. EH mostly presents with abnormal uterine bleeding. It may be in the form of heavy menstrual bleeding, inter-menstrual bleeding, postmenopausal bleeding, irregular bleeding or unexpected bleeding on hormone replacement therapy. It is estimated that EH is responsible for 15% of post-menopausal bleeding [3]. The ultimate diagnosis of endometrial hyperplasia is based on histopathological evaluation of the endometrium. The endometrial specimen can be obtained by Pipelle sampling, endometrial curettage, or hysteroscopic guided endometrial sampling. EH is a non-physiological, non-invasive precursor of endometrial carcinoma. According to the World Health Organization, there are two types of EH: EH without atypia

DOI: https://doi.org/10.54393/pjhs.v6i1.2498

and atypical EH [4]. The anticipated risk of progression to endometrial carcinoma is much more frequent with atypical hyperplasia as compared to EH without atypia. So far, studies have revealed that endometrial cancer is the most common gynaecological malignancy prevailing in developed countries and second only to cervical carcinoma when estimated worldwide [5, 6]. The prevalence rate is 21% for endometrial hyperplasia in Pakistan, while it is 20.3% in Iran [7, 8]. Endometrial hyperplasia, a precursor of endometrial carcinoma, is of great clinical significance, and its detection can provide opportunities to prevent endometrial carcinoma [9]. The causative factors leading to endometrial hyperplasia are the same as those for endometrial carcinoma. These include increased body mass index with excessive adipose tissue conversion of androgens to estrogen, polycystic ovary syndrome with associated anovulation, estrogen replacement therapy, or estrogen-secreting tumor. Obesity is specifically considered the strongest risk factor for EH and endometrial carcinoma. Endometrial carcinoma is three times more common in obese or overweight women, and the risk increases by 50% for every 5 units of body mass index (BMI) increase [10]. The prevalence of endometrial carcinoma has surged in recent years, partially due to rising trends of obesity and also due to changes in female reproductive patterns [11]. Endometrial carcinoma has historically been considered a disease of post-menopausal age group. Owing to increasing trends of obesity in women, we are observing a shift of rising trends of EH and consequent EC in pre- and peri-menopausal age group [12]. The importance of pre-cancer detection and patient risk stratification cannot be overlooked and is the key to the detection and prevention of cancer. Currently, no screening test is available for endometrial carcinoma [13]. Despite the increasing frequency of EH, there is scanty awareness among the general population and little or no local research work as compared to its social burden.

This study aims to analyze histopathological findings of endometrial biopsy in peri-menopausal women having abnormal uterine bleeding and to observe the correlation of various risk factors with EH. Consequently, we explored the prevalence of EH in peri-menopausal women so that measures can be taken to prevent its progression to endometrial malignancy.

METHODS

This cross-sectional study was conducted in the Department of Gynaecology, Nishtar Medical University, Pakistan from July 2023 to June 2024. Ethical approval was granted by the Institutional Ethical Review Board vide letter number (18675) to conduct this study. The sample size was calculated using the WHO sample size calculator using the formula, n=E2Z2.P.(1-P).The primary outcome variable for sample size calculation was the prevalence of endometrial hyperplasia among peri-menopausal women having atypical uterine bleeding in a similar population. It was set at 21% based on prior studies [7]. Non-probability consecutive sampling was used. A total of 255 perimenopausal women in the age range of 40-55 years, having abnormal uterine bleeding spanning 3-12 months' duration, were included in the study. Women with bleeding disorders like von Willebrand disease, Idiopathic Thrombocytopenic Purpura, and taking drugs like warfarin and aspirin were excluded. Hypothyroidism, pelvic inflammatory disease, fibroid, polyp, and cervical pathology (cervical polyp, cervicitis) were also excluded factors. Informed consent was obtained from patients regarding their inclusion in the study. They were ensured regarding confidentiality and the fact that there was no anticipated risk involved to the patient while participating in the current study. A detailed history was inquired and participants were subjected to endometrial sampling (both outpatient clinic procedures and inpatient procedures under anesthesia). The sample was preserved in 10% Formalin solution. The consultant pathologists performed the histopathological analysis based on morphometric study and standard WHO criteria. A structured proforma was used to gather all the information, including demographic details (age, BMI), clinical history (bleeding pattern, parity, history of diabetes mellitus, hormonal intake or polycystic ovaries), and histopathological findings. Data analysis was accomplished by using SPSS software version 26.0. The primary outcome variable was the presence or absence of EH. The secondary variables were age, parity, BMI history of diabetes mellitus, polycystic ovaries, or hormonal intake. Frequency and percentages were calculated for these variables. A chi-square test was used to calculate the significance of the test. A p-value <0.05 was taken as significant.

RESULTS

Among the total 255 patients, the mean age was 48 ± 6 years. A vast majority were multiparous (n=210, 84.4%) and obese (n=133, 52.2%). Out of all those, 32 (12.5%) had Diabetes Mellitus, and 79 (31%) were also diagnosed to have polycystic ovaries (Table 1).

Table 1: Correlation of Various Characteristics with Endometrial Hyperplasia

Characteristics		Frequency (%)	p-value
Age (Years)	40-45	82 (32.1%)	0.615
	45-50	141 (55.3%)	
	50-55	32 (12.5%)	
Parity	Nullipara	40 (15.6%)	0.024
	Multipara1-4	52 (20.4%)	
	Grand Multipara >4	163 (64%)	

DOI: https://doi.org/10.54393/pjhs.v6i1.2498

BMI (Kg/m^2)	18.5-24.9	48(18.8%)	<0.001
	25-29.9	74 (29%)	
	30 or More	133 (52.2%)	
Diabetes Mellitus	Yes	32 (12.5%)	<0.001
	No	223 (87.5%)	
Polycystic Ovaries	Yes	79 (31%)	<0.001
	No	176 (69%)	
History of Hormonal Intake	Yes	34 (13.3%)	--
	No	221 (86.7%)	

Regarding abnormal/atypical uterine bleeding, the commonest symptom was heavy regular cycle (n=74, 29%) followed by irregular vaginal bleeding (n=70, 27.5%) (Table 2).

Table 2: Pattern of Abnormal Uterine Bleeding

Pattern of Abnormal or Atypical Bleeding	Frequency (%)
Regular Heavy Menstruation	74 (29%)
Frequent Heavy Menstruation	43 (16.9%)
Irregular Menstruation	70 (27.5%)
Infrequent Menstruation	21 (8.2%)
Continuous Vaginal Bleeding	47 (18.4%)

Out of a total of 255 endometrial samples, the majority (n=88, 34.5%) turned out to be proliferative endometrium, indicating hormonal upset like unopposed estrogen stimulation. In total, 66 (25.9%) samples fulfilled the criteria of endometrial hyperplasia. 54 (21.2%) had EH without atypia, while 12 (4.7%) had atypical EH (Table 3).

Table 3: Histological Findings in Endometrial Sample

Histological Finding	Frequency (%)
Proliferative Endometrium	88 (34.5%)
Secretory Endometrium	55 (21.6%)
Fibroids	25 (9.8%)
Polyps	14 (5.5%)
Endometrial Hyperplasia without Atypia	54 (21.2%)
Atypical Endometrial Hyperplasia	12 (4.7%)
Endometrial Carcinoma	7 (2.7%)

Out of total 66 EH histopathological reports, 42(63.6%) were obese and 43(65.1%) had polycystic ovaries (Table 4).

Table 4: Correlation Between Endometrial Hyperplasia and Contributing Factors

Characteristics		Histopathology of EH:n-66 (%)	p-value
BMI (Kg/m^2)	18.5-24.9	6 (9.1%)	0.026
	25-29.9	18 (27.3%)	
	30 or More	42 (63.6%)	
Diabetes Mellitus	Yes	22 (33.3%)	0.00026
	No	44 (66.7%)	
Polycystic Ovaries	Yes	43 (65.1%)	0.00094
	No	23 (34.8%)	

DISCUSSION

Perimenopause is the time interval that encompasses the final years of a woman's reproductive life. It is the period that commences in the early years after 40 and lasts for almost two years after the final menstrual cycle. It is accompanied by the symptoms of declining ovarian function. Abnormal uterine bleeding is the hallmark of this transitional phase. It is a wide-ranging phrase used to narrate irregularities in the menstrual cycle that may imply frequency, regularity, duration frequency, regularity, duration, and volume of flow and has negative repercussions on the quality of life. A total of 255 women with abnormal uterine bleeding after the age of 40 years were subjected to endometrial sampling. The histopathology report revealed EH in 25.9% of the cases. This result is quite high when we compare it with the study conducted by Bakos *et al.* almost 25 years ago when it was found to be around 12% [14]. In current study, EH without atypia was observed in 54 (21.2%) cases. This is quite close to that appraised by Munir S (21%) in a study conducted in Pakistan [7]. Another study conducted by Bakos *et al.*, in Pakistan yielded similar results (21%) [15]. The closer findings obtained can be explained by the fact that the inclusion criteria for the participants were almost alike, and the diagnostic modality used in these studies was similar, i.e., diagnostic curettage. These figures are quite high when we take a glance at a study conducted by Takreem *et al.* in Pakistan almost 15 years ago when endometrial hyperplasia incidence was reported to be 13% [16]. The recent rise in endometrial hyperplasia is largely linked to changing lifestyles, including junk food and lack of physical activity, leading to obesity, polycystic ovarian syndrome, and eventual endometrial hyperplasia. Qureshi *et al.*, from India, reported an incidence of 33%, higher than current findings [17]. This variation might be due to the reason that they conducted a study on those patients who underwent hysterectomy. This provides the opportunity for visual analysis of the whole specimen and biopsy of grossly suspected areas, resulting in higher detection rates. In present study, atypical hyperplasia was observed in 12 (4.7%) cases. However, a similar study conducted in India reported that the incidence of atypical hyperplasia was 5.4% [18, 19]. The high rates in the later studies might result from hysteroscopic guided endometrial sampling in most cases, as it allows a more accurate selection of unhealthy-looking areas for biopsy. The incidence observed is quite high compared with the 0.4% found in the study conducted by Jetley almost 10 years back [20]. In current study, endometrial carcinoma was eminent in 7 (2.7%) cases. The equivalent (2%) was observed by Masood *et al.*, [21] and Manzoor *et al.*, [22]. The most common risk factor for EH is obesity. In present study, 63.6 % of those diagnosed with

DOI: https://doi.org/10.54393/pjhs.v6i1.2498

EH were obese, while polycystic ovaries were detected in 65.1% of current cases. It is quite high when compared to that calculated by Wang *et al.*, (35%) [23]. Chi-square crosstab analysis yielded a p-value<0.05 for obesity, diabetes mellitus and polycystic ovaries, indicating a strong association. Both obesity and polycystic ovaries result in unopposed estrogen leading to endometrial hyperplasia. The tendency of obesity is rising trends due to the overwhelming use of junk food along with cola drinks and a sedentary lifestyle. This can be self-explanatory regarding the risk of endometrial hyperplasia in the current study. The development of validated and non-invasive diagnostic methods for early detection of endometrial hyperplasia may reduce the need for invasive procedures and facilitate timely treatment. The current guidelines provide a framework for managing endometrial hyperplasia in perimenopausal women, but ongoing research is essential to refine these recommendations and enhance patient care.

CONCLUSIONS

It was concluded that in the peri-menopausal age group, AUB should be considered, and endometrial sampling must be performed to rule out endometrial hyperplasia or endometrial malignancy. As obesity and polycystic ovaries are consistently being increased, so are the rising trends of endometrial hyperplasia. Time is needed to implement targeted public health interventions. Timely diagnosis can enable the patients to have surveillance or treatment, thus preventing future endometrial carcinoma development. Future research should explore innovative diagnostic tools and preventive strategies to manage this growing health challenge

Authors Contribution

Conceptualization: ST
Methodology: ST, FS
Formal analysis: ST, AA, FS
Writing review and editing: ST, AA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.1899

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Potential Obstacles to Achieve Successful Outcomes Following Stuttering Interventions

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ARTICLE INFO

Keywords:
Barriers, Intervention, Speech Therapist, Stuttering

How to Cite:
Hassan, A., Shah, S. T., & Saqulain, G. (2025). Potential Obstacles to Achieve Successful Outcomes Following Stuttering Interventions: Potential Obstacles for Stuttering Interventions. Pakistan Journal of Health Sciences,6(1), 58-63. https://doi.org/10.54393/pjhs.v6i1.1899

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Received date: 13th August, 2024
Acceptance date: 5th January, 2025
Published date: 31st January, 2025

ABSTRACT

Stuttering is a common speech problem affecting all age groups. Speech-language pathologists face barriers in attaining favourable therapeutic results. Identification of these barriers could help attain therapy results. **Objectives:** To identify the perceived barriers that speech-language pathologists encounter in achieving successful outcomes following stuttering interventions. **Methods:** The current qualitative study was conducted at Riphah International University from September 2023 to February 2024. A sample of n=10 speech-language pathologists was taken from Rawalpindi and Islamabad using purposive sampling. The sample included qualified speech-language pathologists of both genders, any age, practicing for at least 05 years with clients having fluency disorder. The study involved semi-structured interviews with the option of face-to-face and online interviews using an interview guide. Information obtained was transcribed followed by thematic analysis. **Results:** The study revealed six major themes including collaborative approaches in intervention and the role of various professionals, Patient engagement and empowerment for successful intervention outcomes, empowering families for effective communication and support in successful intervention, strengthening speech-language pathologists' practices, therapeutic accessibility and holistic approach to stuttering intervention. The findings demonstrated that speech-language pathologists understanding of stuttering especially their unique roles within it, is somewhat restricted due to barriers including i). Diverse perspective held by the speech-language pathologists, ii) Clinical challenges, iii) Systematic and environmental factors and iv) lack of collaboration and support. **Conclusions:** It was concluded that speech-language pathologists perceive the following main barriers i) Diverse perspectives held by the speech-language pathologists, Clinical challenges, Systematic and environmental factors and lack of collaboration and support.

INTRODUCTION

Stuttering or stammering is a speech disorder that features disruptions or interruptions in the flow of speech, characterized by repetitions of words, sounds, or syllables; prolongations of sounds; or blocks in speech. Stuttering can vary in severity and may be associated with secondary behaviours like facial twitching or erratic body movements [1]. Patients with stuttering (PWS) are managed by speech therapy. A speech-language pathologist (SLP) tries to make a PWS fluent and enhance his/ her communication. An SLP may use breathing exercises, relaxation techniques, and controlled speaking. In addition, SLPs also deal with the psychological and emotional aspects of stuttering to build confidence in a stuttering patient by using different strategies [2]. Stuttering is commonly seen between 3-8 years of age and is usually cured before puberty. It is not uncommon in adulthood. Distinguishing stuttering from dysfluency in infancy can be quite challenging [3]. The beginning of Stuttering and its persistence most likely result from a complicated and multi-faced disease impacted by so many interrelated

DOI: https://doi.org/10.54393/pjhs.v6i1.1899

causes, which may result from a confluence of factors like environment, neurologic and hereditary with stuttering being a heterogeneous disorder having diverse etiologies [4]. There isn't yet a Food and Drug Administration agency-recognized medicine for treating stuttering, despite some evidence in favor of medicines with dopamine-blocking effects [5]. SLPs rely on methods like syllable stretching, soft starting of speech, and diaphragmatic breathing [6], with barriers perceived by SLPs in stuttering management [7]. Stuttering is a common speech problem affecting all age groups being highly prevalent in pre-school children (5%) with males being more commonly affected [8]. Stuttering though common in younger age groups, may also persist into adulthood with prevalence in adults being estimated around 1% [9]. Though stuttering is low in adulthood, stuttering has a very high lifetime prevalence of around 5 to 10% [10]. A local study reported a prevalence of 11% with a higher prevalence in males in the 5 to 18 years old population [11]. While a 24% prevalence of stammering among speech issues has been reported in another local study [12]. There is a lack of comprehensive data regarding nationwide prevalence in Pakistan, hence, there is a need to research to obtain local data on stuttering in Pakistan [13]. Speech-language pathologists are key in the management of stuttering with skills to evaluate, diagnose and treat stuttering utilizing a wide variety of methods and tactics to cater to stuttering. The skills, knowledge, and advice of SLPs are crucial for stutterers to achieve fluency and speech confidence [14]. Even though SLPs do provide effective therapeutic interventions, however, they may face several barriers to attaining favourable results. Including external factors i.e., patients' motivation level and access to therapeutic services but internal factors as well like bias and belief regarding stuttering, hence it is necessary to understand the SLP's point of view regarding the management of stuttering as well as to enhance therapeutic services [15].

This study aims to identify the perceived barriers that speech-language pathologists (SLPs) encounter in achieving successful outcomes following stuttering interventions. To explore such barriers six step data analysis as framed by Braun and Clarke, 2006 is required including i) Data Familiarization, ii) code generation, iii) Developing themes, iv) Review of themes, v) determination of the significance of these themes, vi) reporting [16]. The current study is of immense importance since finding barriers and roadblocks will result in overall improvement in patient care and help in research as well as help develop approaches to overcome the hurdles faced by SLPs during stuttering.

METHODS

The qualitative research design was conducted at Riphah College of Rehabilitation and Allied Health Sciences, Riphah International University, and National Institute of Rehabilitation Sciences, Islamabad over 6 months from 1st September 2023 to 29th February 2024, following ethical approval of the Research Ethics Committee vide Reference no RCRAHS-ISB/REC/MS-SLP/01628. The study recruited a sample of n=10 SLPs from Islamabad and Rawalpindi, Pakistan using non-probability purposive sampling. A sample size of n=11 was calculated using the Qualitative Sample Size Calculator [17], with a no-show-up rate=0.10. However, a sample of n=10 was used as one participant later refused consent and dropped out. The sample included SLPs of both genders and any age who have been practicing for at least 05 years with clients having fluency disorder and had a postgraduate diploma or higher qualification in speech-language pathology. While SLPs with a caseload of fluency with any comorbid condition like speech sound disorders, and language disorders were excluded from the study. The interview guide was created in the English language by literature search and tested with two SLPs to assess how the formulated questions led to discussion. It contained easy and comprehendible questions with the probes. Research participants were approached through email and phone calls. They were briefed and provided essential information about the study. Following this, a meeting was arranged with the participants who indicated interest in the study. Informed consent was taken from the interested participants before the interview. Semi-structured interviews were conducted with the option of face-to-face or online depending upon feasibility. The interview included seven questions with probes. These questions focused on the therapist's perceptions regarding successful outcomes following therapy including potential obstacles, the role of a speech therapist, caregiver factors, client factors, and collaboration with other professionals. For each question, ample time was allowed for the participant to give a response and interviews were recorded using a digital recorder after obtaining permission from the participant. Prompts were utilized to obtain essential information. Additionally, written notes were also maintained. Information obtained was transcribed for further analysis of data maintaining the confidentiality of the participant throughout the research. The data were analyzed for speech therapists' perceptions as regards possible barriers to successful treatment results after the intervention was done as per the following six phase steps for thematic analysis as described by Braun and Clarke after transcribing audio recordings and written text. This was done to ensure that interview content was easy to

DOI: https://doi.org/10.54393/pjhs.v6i1.1899

access for analysis; i) To familiarize, the data records of interview transcripts were read and reread, which helped me understand the depth and breadth of the responses of the SLPs; iii) Thematic coding was conducted to find out recurring themes, their patterns, and key concepts, and codes were assigned to particular data segments that reflected common themes relating to the barriers; iv) The coded segments were categorized into broad categories depending upon the identified themes which involved organizing coded data into categories with meaningfulness and coherence to detect the range of barriers perceived by SLPs; v) the, the data were coded and categorized for interpreting the findings was analyzed, involving delving further into the thematic content, identification of the relationship among various themes, and conclusions were drawn vi) and finally the analyzed content was compiled into comprehensive report highlighting identified themes, important findings and insights gathered from SLPs perceptions. Frequency and Percentages were calculated for demographic variables. SPSS Version 26 was used for data analysis.

RESULTS

The current research to explore the speech therapist's perception regarding potential obstacles to achieving successful outcomes following stuttering intervention utilized a sample of n=10 participants with the majority 6 (60%) female with 5 (50%) having qualified in both SLP and Psychology and remaining 5 (50%) in SLP alone. Most 5 (50%) had experience of 9-11 years (Table 1).

Table 1: Demographic Characteristics of Sample Population (n=10)

Variables	Category	n (%)
Gender	Male	4 (40)
	Female	6 (60)
Masters	SLP and Psychology	5 (50)
	SLP	5 (50)
Experience	5 to 8	1 (10)
	9 to 11	5 (50)
	11 to 15	2 (20)
	16 to 20	2 (20)

The study revealed six (06) major themes including i) collaborative approaches in intervention and the role of various professionals, ii) Patient engagement and empowerment for successful intervention outcomes, iii) Empowering families for effective communication and support in successful intervention, iv) Strengthening SLP practices and addressing societal challenges in Pakistan v) therapeutic accessibility, vi) holistic approach to stuttering intervention across the lifespan (Table 2).

Table 2: Themes and Subthemes

Themes	Sub-Themes	Codes /Keywords	Representative Quotes
Collaborative Approaches in Intervention and the Role of Various Professionals	Enhancing Communication	SLPs Play the Main Role	SLPS Have to Give Solutions to Stuttering Patients.
	Multidisciplinary Team	Teamwork	Teamwork Makes the Therapy More Effective.
	Bridging the Communication Gap	SLPS Expertise	An SLP Should be an Expert to Build Connections and Conduct Control Sessions
	Fostering A Learning Environment	Teacher's Concern	If the Teacher Motivates the Child and Gives Attention to Him, He Can be cured.
	Understanding the Emotional and Psychological Aspects	Interference of Psychologists	Only Psychologists Can Deal with Those Patients Who Have Stuttering Because of Anxiety
	Demystifying the Roles and Contributions of SLPS, Psychologists, and Other Professionals in Intervention	Medication for Brain Weakness	They Give Them Medicines for Brain Weakness
	Co-Occurring Psychological Conditions	Patient Motivation	If the Patient Is Motivated, Then Definitely He Will Overcome His Disorder.
Patient Engagement and Empowerment For Successful Intervention Outcomes	Encouraging Patient Participation and Active Involvement in Therapy	Motivated Intervention	He Can Overcome This Disorder If He Intentionally Complies with the Guidelines
	Addressing Resistance to Therapy	Duration of Treatment	They Do Not Come Due to Long Duration
	Relapse After Treatment	Relapse	They Relapse After the Treatment
	Engagement and Regularity in Intervention	Chance of Recovery	Regular Follow-Up Improves the Chances of Recovery
Empowering Families for effective communication and support in successful Intervention	Encouraging Patient Participation and Active Involvement in Therapy	Motivated Intervention	He Can Overcome This Disorder If He Intentionally Complies with the Guidelines.
	Addressing Resistance to Therapy	Duration of Treatment	They Do Not Come Due to Long Duration

DOI: https://doi.org/10.54393/pjhs.v6i1.1899

	Relapse After Treatment	Relapse	They Relapse After the Treatment
	Engagement and Regularity in Intervention	Chance of Recovery	Regular Follow-Up Improves Chances of Recovery
Bolstering SLP Practices	Knowledge Gap	Lack of Knowledge	A Lot of Knowledge Gaps among SLPS Exists
	Lack of Accurate Information About SLPS in Pakistani Society	Muscular Disorder	This Is Only a Disease of the Muscles, Weakness, Or Ghostly Shadow.It Was His Grandfather and Uncle That Caused This Issue
	Advancement in Research and Training Speech-Language Pathology	Seminar	Seminars and Meetings On Specific or Important Cases
	Social Stigmatization	Criticized	Society Mock, Criticize Tags and Make Their Parodies
Therapeutic Accessibility	Financial Distress	Financial Issues	Those People Who Have Financial Issues Cannot Afford Therapy.When the Patient Starts Recovery, ParentsLeave Therapy Because They Cannot Afford It.
	Addressing the Skilled SLP Shortage	Qualified SLPS	In Small Cities, There Are No SLPs. If There Are Then They Are Not Well Qualified
	Enhancing Accessibility of Therapy Clinics	Big Cities Transportation Issues	Parents Who Bring Their Children from Far Away Face Transportation Problems
A Holistic Approach to Stuttering Intervention Across the Lifespan	Age Factor	Early Age	It Is Very Easy to Overcome This Disorder in Early Age as Compared to Adulthood.
	Generalization of Goals Across Natural Settings	Techniques	They Will Not Generalize the Rules in Different Settings, they will not succeed

DISCUSSION

The current study revealed six themes regarding barriers that speech-language pathologists (SLPs) encounter in achieving successful outcomes following stuttering interventions. According to Iqbal *et al.*, there is a significant association between stuttering awareness and self-therapy, which reveals that the patient is better able to cope and find therapy techniques helpful for him, hence a better outcome [18]. Empowering families can result in establishing a strong supporting network. This will also result in developing resilience and bringing positive changes [19]. According to Bishop and High, the visibility of stigma impacts strategies chosen to seek support [19]. Also, it was essential to boost the knowledge of SLPs by applying current research in SLPs for all such disorders [20]. As regards the theme "Holistic approach to stuttering intervention across the lifespan", the current study revealed that compared to adulthood it is much easier to overcome stuttering at an early age, which complies with the literature [21]. The study revealed the SLP's view of the following main barriers: Environmental barriers and systemic support issues exist which according to SLPs affect therapy results. This was also evident from a local study involving an internally displaced population, where the environmental conditions resulted in increased prevalence of stammering and it made their treatment even more difficult [22]. SLPs also face clinical challenges as they have to cater to avoidance behaviours, manage conditions which co-occur, and treatment needs to be adopted for a diverse populace as well as navigate individualized intervention plans. This complies with literature on issues like overt stuttering behaviour, different views of stutterers, and the main outcome for stuttering not established [15]. SLPs also realize the need for specialized training and confidence. A current study revealed that deficient Collaboration and support barriers. This complies with literature where collaboration between PWS and SLP is essential and goals and procedures may be framed and followed by both and support is important and useful in cutting down the negative influence of stuttering [23].

CONCLUSIONS

It was concluded that SLPs perceive the following main barriers i) Diverse perspectives held by the SLPs, Clinical challenges, Systematic and environmental factors and lack of collaboration and support.

Authors Contribution

Conceptualization: GS
Methodology: AH
Formal analysis: AH
Writing review and editing: STS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v6i1.1899

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DOI: https://doi.org/10.54393/pjhs.v6i1.1659

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Variation of Epithelial and Nuclei Morphohistology in Oral Submucous Fibrosis Patients

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ARTICLE INFO

Keywords:

Oral Submucous Fibrosis, Histological Changes, Epithelial Textural Properties, Nuclear Morphology, Premalignancy

How to Cite:

Ahmed, R. R., Qureshi, M. F., Bashir, S., Abideen, Z. U., Zafar, A., Hafeez, R., & Haque, M. U. (2025). Variation of Epithelial and Nuclei Morphohistology in Oral Submucous Fibrosis Patients: Epithelial and Nuclei Morphohistology in Oral Submucous Fibrosis Patients. Pakistan Journal of Health Sciences, 6(1), 64-68. https://doi.org/10.54393/pjhs.v6i1.1659

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Received date: 12th May, 2024
Acceptance date: 10th January, 2025
Published date: 31st January, 2025

ABSTRACT

In the background of oral submucous fibrosis, oral cancer is the most commonly present malignant transformation in South Asian regions. Alteration of tissue architecture contributes significantly to determine the exact pathological state of the disease. **Objective:** To evaluate histological changes in structure of oral submucous fibrosis patients in context of textural properties of epithelium and morphology of nuclei. **Methods:** A total of 50 subjects were inducted in this cross-sectional study performed at dentistry department of Jinnah Postgraduate Medical Center (JPMC) in Karachi. Punch biopsy samples were taken from buccal mucosa followed by preparation of tissue blocks and slide preparation to analyze histology of premalignancy and record abnormal features present in normal oral tissue. Results were analyzed through SPSS version 23.0 and p value of ≤0.05 was considered as statistically significant. **Results:** 37 (74%) subjects had prominent Oral Submucous Fibrosis histologically out of which abnormal epithelial parameters such as stratified squamous, hyperplastic, keratotic, and neoplastic were noted in 5 (10%), 31 (62%), 10 (2%), 0 (0%) subject respectively. p value 0.041 was calculated using Chi square analysis for qualitative data which depicted relevance of hyperplastic epithelium in Oral Submucous Fibrosis. 29 (87.9%) subjects showed pleomorphism in nucleus and 8 (47.1%) showed normal/round nucleus in Oral Submucous Fibrosis subjects with a p value of 0.003. **Conclusions:** Histological analysis which is not routinely performed in oral submucous fibrosis patients could visualize accurate extent of disease through structural variability of epithelium and nucleus.

INTRODUCTION

In Asia and a few pacific Islands people consume Betel Quid (BQ) on a regular basis in some form which is clinically linked to rigid oral mucosa and pathologically characterized by inflammatory epithelial response and fibroelastic variations [1]. Development of Oral Submucous Fibrosis is strongly linked to causative factors of consuming Areca Nut [2]. Disruption of balance of extracellular matrix is due to flavonoids, alkaloids and copper present in Areca nut therefore it is certainly a prime factor in genesis of Oral Submucous Fibrosis as Flavonoids (tannins and catechins) block collagenase and stabilize fibers of collagen recruiting mucosal inflammation [3]. During chewing mechanism of areca nut products there is chemical stimulation by toxic components leading to trauma to the underlying tissues through physical frictional damage. These factors affect oral mucosal epithelium which in reaction responds and becomes hyperplastic in contrast to the conventional findings of atrophy in epithelium. Epithelial cells which survive the harsh trauma exhibit heterogenicity, variable nucleus and cytoplasmic ratio, abnormal mitosis and

DOI: https://doi.org/10.54393/pjhs.v6i1.1659

cellular irregularities [4]. Cytokines are predominantly associated to contribute to pathogenesis of OSMF such as increased expression of Tissue Growth Factor (TGF- β). Cytotoxic effects of areca nut products lead to epithelial cell apoptosis and promote avascularity. This pathomechanism yet needs to be further elucidated [5, 6]. OSMF is a chronic form of oral disorder which produces scarring of tissue through its fibrosis potential. Oral Submucous fibrosis is classified as a precancerous lesion by WHO having a highest rate of transformation into Oral Squamous Cell Carcinoma (OSCC). This premalignancy is prevalent most in Southeast Asia with relevant burden of disease in China, India, Pakistan and Taiwan while in USA and other European population, only a few cases have been documented that too because of migratory Asians [7]. The premalignant nature of OSMF also characterizes high frequency of epithelial dysplasia in OSMF [4]. Various risk factors are attributed to bear causative role in OSMF etiology. This includes malnourishment, genetic predisposition, alteration of salivary composition, chewing areca nut, intake of chilies, collagen defects and autoimmune disorder [5, 6]. Areca nut is the 4th ranked social drug following ethanol, nicotine, and caffeine. Hence, therefore it is accepted as the prime risk factor for OSMF. Betel quid and areca nut usage is a native habit in subcontinent and most prevalent risk factor having a significant contribution for OSMF development [5]. Overconsumption of oral mucosal irritants induce inflammatory reaction to initiate OSMF which further leads to chronic inflammation in the form of abundant deposition of collagen in connective tissue and muscular degeneration along with reduced vascularization of blood vessels present in connective tissue and dense hyalinized area [8]. As a result, there is increased synthesis of collagen as a principle underlying factor contributing to OSMF [7, 9]. Xu HQ *et al.*, states that pathological changes in connective tissue of OSMF are likely to affect overlying epithelium [10]. The conventional image of OSMF pathology suggests that epithelial surface becomes thin and occupies state of epithelial atrophy where as in seventy years' history of OSMF pathology, facts related to malignancy conversion of atrophic epithelium is contestable and contrary to the classic pathology, oral mucous membrane subjected to trauma by chemical exposure of betel quid showed physical trauma locally which is later compensated by hyperplastic epithelial tissue in early phase of OSMF [11].

The aim of this research was to have an insight through histological features present in epithelium and nucleus of oral submucous fibrosis patients to elucidate effective understanding of pathogenesis, diagnosis and management strategies for it.

METHODS

This cross-sectional study was conducted for data collection at the dentistry department of Jinnah Postgraduate Medical Center, Karachi after approval from the scientific ethical review board of the institute, No.F.2-81/2020-GENL/48908/JPMC and ethical review committee of Bahria University Medical and Dental College Karachi, No:FRC-BUMDC-13/2020-Ana-113.Data was systematically collected from January to August 2021. Subjects who gave written consent were included. Sample size was calculated using open epi software online by using prevalence 4.47% of oral submucous fibrosis worldwide [12]. The confidence interval was kept at 95% and precision was set at 6%. The sample size calculated was 46 but 50 patients were enrolled. Informed written consent was obtained from all subjects of the research. Data were systematically collected for 6 months using a detailed questionnaire proforma to confirm cases of Oral Submucous Fibrosis and consideration for histological analysis of nucleus and epithelium. Subjects with restricted mouth opening, burning sensation, white fibrotic bands, ulceration, and pain were included in the research. Subjects already undergoing treatment, Temporomandibular Joint disorders, any other systemic disease or carcinoma were constituted as the exclusive criteria. Paraffin embedded tissue blocks were prepared after incisional biopsy taken from buccal mucosa of clinically identified oral submucous fibrosis patients. Collected data was organized in Microsoft excel and processed with SPSS 23.0. Fisher Exact and Chi square analysis was utilized for comparison of gender, epithelium, and nuclei with Oral Submucous Fibrosis. All p values of ≤0.05 were considered to indicate statistical significance.

RESULTS

Current results has estimated high preponderance of male gender which includes 73% of total sample size but with non-significant statistical association using Chi square analysis. In total, 37 patients had active oral submucous fibrosis out of which 27% population was female as shown in table 1.

Table 1: Association of OSMF with Gender (n=50)

Gender	Count (%)	Fibrosis N (%)		Total N (%)	p-value
		Present	Absent		
Male	Within Fibrosis	27 (73.0%)	7 (53.8%)	34 (68%)	0.301
Female		10 (27.0%)	6 (46.2%)	16 (32.0%)	
Total		37 (100%)	13 (100%)	50 (100%)	

While analyzing the statistical association of epithelium, 5 (10%) symptomatic OSMF subjects showed presence of stratified squamous epithelium, 1 (2%) of subjects showed keratotic epithelium, 0 (0%) subject showed neoplastic stratified squamous epithelium while most of the sample 31 (62%) of participants were found to have hyperplastic

DOI: https://doi.org/10.54393/pjhs.v6i1.1659

stratified squamous epithelium as shown in Figure 1A. A significant correlation amongst variables was found (p value = 0.041) however the strength of statistical association was weak between epithelial variety and the disease. Chi square test was performed as shown in table 2.

Table 2: Epithelium Correlation amongst Cases of Submucous Fibrosis (n=50)

Epithelium						
Fibrosis	**Stratified Squamous N (%)**	**Hyperplastic Stratified Squamous N (%)**	**Keratotic Stratified Squamous N (%)**	**Neoplastic Squamous N (%)**	**Total N (%)**	**p-Value**
Present	5 (10%)	31 (62%)	1 (2%)	0 (0%)	37 (74%)	0.041
Absent	5 (10%)	6 (12%)	1 (2%)	1 (2%)	13 (26%)	
Total	10 (100%)	37 (100%)	2 (100%)	1 (100%)	50 (100%)	

The cells were assessed through histopathological evaluation after treatment with H and E staining techniques. The results showed that most cells 29 (87.9%) had pleomorphic hyperchromatic nuclei indicating cytotoxic cells amongst OSMF. Figure 1B showed distribution of nuclei amongst OSMF cases based on morphology of oral mucosal cells. Fisher Exact test was applied to test the difference between nuclei morphology (p = 0.003). This showed that nuclei of symptomatic OSMF cases were affected to adapt to an alteration in normal morphology (Table 3). p value ≤0.05 was considered statistically significant.

Table 3: Nuclei Morpho-Histology Distribution (n=50)

Nuclei				
Fibrosis	**Pleomorphic Hyperchromatic Nuclei N (%)**	**Normal/Round NucleusN (%)**	**Total N (%)**	**p-Value**
Present	29 (87.9%)	8 (47.1%)	37 (74%)	0.003
Absent	4 (12.1%)	9 (52.9%)	13 (26%)	
Total	10 (100%)	37 (100%)	50 (100%)	

In Figure 1A a 5µm thick H and E-stained section of OSMF oral mucosa showing hyperplastic stratified squamous epithelium due to basal cell hyperplasia overlying connective tissue core (photomicrograph 40X). while in figure 1B H and E-stained section image showing pleomorphic hyperchromatic nuclei (red circle) arranged around widespread cytoplasm of cells in an irregular pattern with multiple shaped nuclei due to wrinkling of nuclear membrane (photomicrograph 100X).

Figure 1 A: A 5µm thick H and E-stained section of OSMF oral mucosa showing hyperplastic stratified squamous epithelium due to basal cell hyperplasia overlying connective tissue core (photomicrograph 40X)

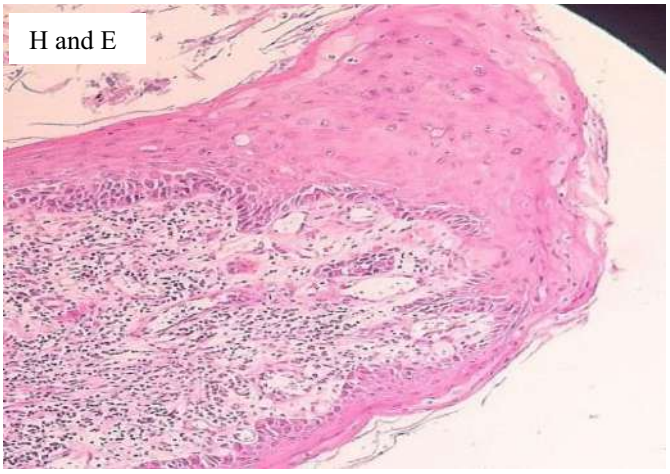
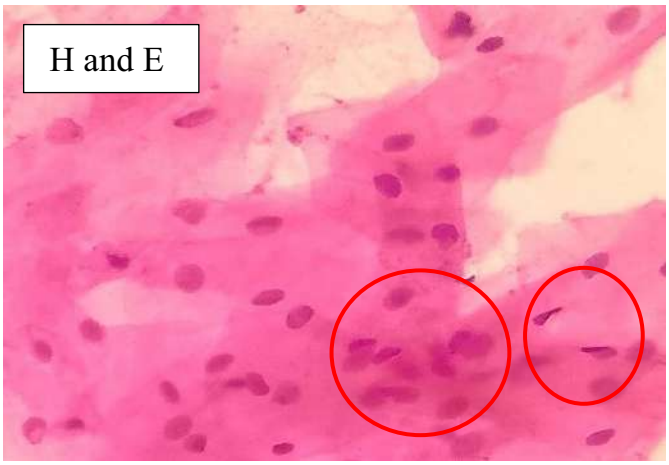


Figure 1 B: H and E-stained section image showing pleomorphic hyperchromatic nuclei (red circle) arranged around widespread cytoplasm of cells in an irregular pattern with multiple shaped nuclei due to wrinkling of nuclear membrane (photomicrograph 100X)



DISCUSSION

This research showed a non-significant statistical association of gender distribution between OSMF with greater incidence amongst male. In contradiction to these findings study by Fauzi and fellows showed 92.6% male prevalence of OSMF and while correlating gender with disease, 0.00 p value was the statistical significance which indicated that males are much likely to be affected by this disease than females [12]. These results were also inconsistent with findings of research by Sowmya and Sangavi, which revealed that majorly males are involved to have OSMF. Male predominance in OSMF could be validated due to social and traditional practices to relieve stress, freshen breath or as a stimulant [13]. Normal oral mucosa has a regenerating cell reservoir of basal stem layer for clonogenicity and self-renewal. Interruption in this cell turnover is antecedent to promote disease in the form of Oral Potentially Malignant Disorders (OPMD) and Oral

DOI: https://doi.org/10.54393/pjhs.v6i1.1659

Squamous Cell Carcinoma (OSCC) [14]. Deficiency of clonogenicity in basal stem cell surface activates epithelial atrophy which undergoes through hyperplasia amongst cells as a biological consequence [15]. Carcinogens diffuse gradually below epithelial surface. Hence, changes in epithelium are expressed and distinguished over a prolonged period of duration [16]. Present study suggests that epithelial hyperplasia, perhaps is an alternative adaptive response to local irritants to yield a greater degree of protection to the tissue present beneath. A similar study by Adhane YB *et al.*, postulated in depth observation regarding sequential adaptations in epithelial, muscular and connective tissue during gradual progressive stages of disease. To improve survival rate, it is significant to observe and identify early changes which include subepithelial inflammatory response occurring due to mucosal trauma by areca nut compounds. This inflammatory reaction consists of epithelial cell inflammatory infiltrate which is in the form of epithelial hyperplasia along with polymorphonuclear lymphocytes and plasma cells further manifesting vesicle formation and erosion [17]. Study by Jian X *et al.*, also states that OSMF pathological traits include oral epithelial tissue as either atrophic or hypertrophic while dysplastic characteristics are acquired by nucleus which becomes hyperchromatic and pleomorphic. In advanced stage of dysplasia, cellular atypia and irregularly arranged mitotic figures are present [18]. Additionally, various studies have demonstrated that OSMF transforms into malignancy through gradual changes of dysplasia amongst epithelial tissue [19]. Multifactorial etiological analysis is essential to establish corresponding therapeutic approach and integrate multidisciplinary modalities [20]. The present study is a small effort to bridge the gap between conventional concepts regarding OSMF and novel findings regarding malignisation.

CONCLUSIONS

Almost half of oral cancer conditions are diagnosed as stage III or IV during the time of first diagnosis eventually causing bad prognosis as only visual grading based on clinical parameters is insufficient and a time-consuming process. Through this study it is suggested that increased hyperplasia in epithelial layer and nuclear pleomorphism are high risk histological features of Oral Submucous Fibrosis and once these histological variations are detected, a quick strategical response to prevent oncostatic effects can be initiated timely.

Authors Contribution

Conceptualization: RRA
Methodology: MFQ
Formal analysis: SB, ZA
Writing, review and editing: AZ, RH, MH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2221

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparison of Open and Close Exposure with Orthodontic Traction of Impacted Maxillary Canine in Orthodontic Treatments

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ARTICLE INFO

Keywords:
Maxillary Canines, Impacted Teeth, Open Eruption, Closed Eruption, Orthodontic Traction

How to Cite:
Amjad Bari, M., Wajdan, N., Tariq, ., Kanju, A. H., Azeem Khan, M., & Liaquat, S. (2025). Comparison of Open and Close Exposure with Orthodontic Traction of Impacted Maxillary Canine in Orthodontic Treatments : Orthodontic Traction of Impacted Maxillary Canine. Pakistan Journal of Health Sciences, 6(1), 69–74. https://doi.org/10.54393/pjhs.v6i1.2221

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Received Date: 25th September, 2024
Acceptance Date: 21st January, 2025
Publisehd Date: 31st January, 2025

ABSTRACT

Labial impactions make maxillary canines the most affected permanent teeth after third molars, at one third. Orthodontic advice is often needed for impacted canines. **Objective:** To compare the outcomes of open and close exposure with orthodontic traction of impacted maxillary canine in orthodontic treatments. **Methods:** In this comparative prospective cohort study 54 patients with labial impacted maxillary canine were included in this study. Study was conducted from Jan 2023 - Jun 2023. Non-consecutive sampling technique was used. 27 patients were managed with open technique in group I and 27 patients with closed eruption technique in group II. The evaluation encompassed a comparison of two surgical exposure methods (open and closed) mobility, vitality, periodontal health, amount of impaction, length of orthodontic therapy, and postoperative discomfort. **Results:** Compared to the close eruption approach, the postoperative recovery time for open eruption was significantly greater ($P<0.05$). Patients reported comparable levels of postoperative discomfort; but, the closed eruption approach resulted in a more rapid resolution of that pain. The open eruption approach required less time during surgery on average compared to the closed eruption technique ($P<0.05$). In a direct correlation with the amount of impaction, the overall length of orthodontic treatment was shown to be longer for deeper levels of impaction. Both methods produced canines with comparable levels of energy and movement. **Conclusions:** In this study, the closed eruption approach took longer but reduced postoperative pain faster. Orthodontic therapy took longer with deeper impaction. Closed eruption surgeries improve periodontal tissues surrounding guided erupted teeth.

INTRODUCTION

When it comes to the structure, appearance, and function of the dental arch, canines play a pivotal role [1]. Impaction affects 2% of the population, making them the most impacted tooth in dental patient after third molars [2]. They tend to be unilateral and most often seen in the palatal area; they are more prevalent in the maxilla [3]. Impaction of the upper canine can be caused by a variety of circumstances, however the specific reason is unknown [1]. In order to diagnose impaction and plan and execute the therapy appropriately, clinical and radiographic exams are conducted, along with the determination of the site [4-6]. The location, canine angulation with respect to neighboring teeth, and presence or absence of ankylosis are factors that determine treatment prognosis [7]. Possible treatments include canine extraction and premolar relocation, auto-transplantation, prosthetic rehabilitation for occlusal harmony, or a combination of surgical and orthodontic procedures to bring the tooth into proper alignment with the jaw, among others [8]. A lack of room in the dental arch is the primary cause of buccal impaction. The genetic and guidance hypotheses have both been put out as possible explanations for palatal

DOI: https://doi.org/10.54393/pjhs.v6i1.2221

impaction. Some dental abnormalities, including hypoplasia of the enamel, microdontia of the maxillary lateral incisor, and hypodontia of the second premolar, can coexist with the eruption anomaly of the maxillary canine, which, according to genetic theory, is the consequence of a developmental disruption of the dental lamina. There is evidence for this notion in gender differences, bilateral occurrences, and families [9]. As the maxillary canines glide along their roots during eruption, the root of the lateral incisors acts as a guide, according to the guiding theory. If the directed eruption is disrupted in any way, a palatal impaction might occur. So, palatal impaction can occur if this directed eruption is interrupted. The maxillary lateral incisor missing, extra teeth, odontomas, tooth bud displacement (transposition), and cystic or neoplastic development are all examples of disorders [10]. Early detection of impacted maxillary canines is critical for reducing treatment time, expense, and complexity [11]. Radiographic imaging and clinical examination (palpation and ocular inspection) can confirm the presence of impacted maxillary canines. The dental literature has documented several clinical signs of impaction, such as the delayed eruption of the permanent canine, distal tipping, abnormal migration of the lateral incisors, absence of a labial canine bulge, presence of a palatal bulge, prolonged retention of deciduous canines, or both [12]. Therefore, it is important to determine the normal eruption timing of teeth in the examined population [13]. When caught early, impacted teeth may be able to improve their position or even spontaneously erupt with the use of interceptive orthodontic therapy, such as space formation [14]. By utilizing an apically relocated gingival flap or by entirely removing the bone and soft tissue directly overlaying the affected canine, the crown can be surgically exposed in the open approach. The next step is to use a surgical pack to cover the incision. The canine can then be let to erupt on its own or orthodontic attachments can be bonded directly to the canine for direct traction. On the flip side, the modern closed approach entails bonding an attachment to the exposed canine crown after raising a complete mucoperiostal flap. Following the first healing period, the orthodontic traction is applied and the flap is moved again. This process continues until the canine emerges in the mouth and is then directed to the dental arch. Although both methods have been around for a while, are flexible, and can be adjusted to fit any situation, there has been conflicting information on how well they compare. Pain, periodontal health, aesthetics, recuperation time after surgery, and overall performance have all been the subject of several research [15].

Using two distinct surgical exposure procedures, this study aimed to examine the final orthodontic alignment of patients with labially impacted maxillary canines and evaluate the post-treatment effects.

METHODS

This comparative prospective cohort study was conducted at CIMS Dental College/CMH Multan after getting approval on 7th Dec 2022 with reference no.786/CDC/IRB/12-04. After getting informed written consent detailed demographics were recorded. Non-consecutive sampling technique was used. The calculated sample size was via Open epi sample size calculator by taking mean surgical time in open technique 22.31 ± 1.98 min and in closed 30.87 ± 2.38 min by taking 95% Confidence interval and 80% power of test, was 4 which was too small to perform statistical test. So, 54 patients (27 in each group) were taken [16]. The inclusion criteria were impacted maxillary canines with A2 (tooth angulation to the midline 16°- 45°), V1 (vertical height of the tooth crown above the cementoenamel junction but less than half the length of the root of the maxillary lateral incisor), and O3 (medial position of the canine crown of more than half but less than the entire root width of the lateral incisor). Exclusion criteria were the medical issues that affect tooth movement or ability to use the required mechanics, the patients had no associated syndrome, alveolar cleft and/or palate, or previous tooth loss due to trauma, caries, periodontal disease, or orthodontic extraction. Over the course of six months (Jan 2023- Jun 2023) participants were chosen from a pool of patients who needed orthodontic eruption or instruction for labially impacted maxillary canines. The surgical step involved comparing two methods of guided eruption, one open and one closed. Patients were equally divided in two groups. Minor differences exist in open technique as compared to closed. In this procedure, the canine tooth is surgically exposed, but instead of bonding an attachment, a tissue window is removed to expose it. Covering the exposed area with a dressing or 'pack' After 10 days, the dressing is removed. The tooth is either left to erupt naturally or aligned with the other teeth with an orthodontic attachment above the gum. The closed method includes surgically exposing the teeth and pasting a gold chain attachment. The chain exits the mucosa when the palatal flap is adjusted and sutured. While formerly hard in the surgical theater, new self-etch adhesive bonding solutions have simplified the bonding method. After surgery, an orthodontic brace gently moves the canine into the dental arch. After emerging through the mucosa, the canine positions itself. The research team advice an Orthopantamograph (OPG) measurement of the impacted tooth's distance from the alveolar edge as a means of categorizing affected maxillary canines. Level I was assigned to distances between 1 and 5 mm from the alveolar edge, Level II to distances between 5 and 7 mm, and Level III to distances more than 7 mm. Patients' perceptions of pain during and after surgery were evaluated using a visual analog scale. The analog scale was

DOI: https://doi.org/10.54393/pjhs.v6i1.2221

used to record the following levels of pain: severe (8-10), moderate (4-7), and mild (1-3). The evaluation encompassed a comparison of two surgical exposure methods (open and closed) in terms of pain, recovery time, complications and periodontal pocket depth. To ensure root resorption and lamina dura continuity, Radiovisiography (RVG) was performed on all instances at the end of therapy. In order to determine the periodontal status of the erupted canines, measured the pocket depth on each of the four sides of the guiding tooth. Data were entered and analyzed by SPSS version 25.0. All the qualitative variable was presented by frequencies and percentages and qualitative with mean ± SD. The comparison of two surgical exposure methods (open and closed) in terms of pain, recovery time was compared by independent sample t-test and complications and periodontal pocket depth with Chi-square test. P-value <0.05 was considered as significant.

RESULTS

There were 34 (63.8%) females and 20 (36.2%) males among all cases (Figure 1).

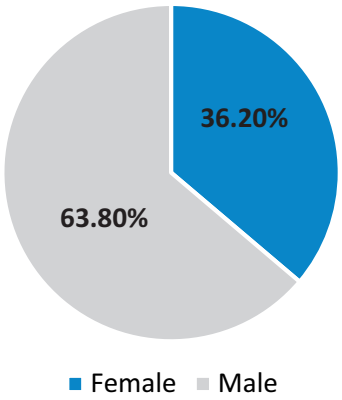

Figure 1: Gender Distribution of Presented Cases

Mean age of the cases in group I was 27.30 ± 5.75 years and in group II mean age was 25.17 ± 10.82 years. In group I right canine impaction was found in 12 (44.4%) cases and left canine in 14 (51.9%) cases while in group II right canine in 11 (40.7%) and left canine in 15 (55.6%) cases. Surgical mean time in group I was 23.17 ± 8.28 minutes and in group II mean time was 31.17 ± 10.42 minutes (Table 1).

Table 1: Demographics and Surgical Time of both Techniques (n=27)

Variables	Group I (Mean ± SD)	Group II (Mean ± SD)
Mean Age (Years)	27.30 ± 5.75	25.17 ± 10.82
Canine		
Right	12 (44.4%)	11 (40.7%)
Left	14 (51.9%)	15 (55.6%)
Bilateral	1 (3.7%)	1 (3.7%)
Surgical Time (Minutes)	23.17 ± 8.28	31.17 ± 10.42

The average pain rating for patients who underwent a closed eruption process was 3.1 ± 0.3, whereas for patients who underwent an open eruption method it was 3.12 ± 0.4, and there was no statistically significant difference (P = 0.12). The time required for recuperation following open eruption surgery was more than that of the close eruption method with p value <0.05. Post-operative, there was no any significant different was observed in complication between both groups (Table 2).

Table 2: Comparison of Pain and Recovery after Treatment (n=27)

Variables	Group I (Mean ± SD)	Group II (Mean ± SD)	p-value
Pain Score	3.1 ± 0.3	3.12 ± 0.4	0.12
Recovery Time (hour)	74.8 ± 6.18	49.04 ± 3.14	<0.05
Complications			
Yes	1 (3.7%)	2 (7.4%)	0.00
No	26 (96.3%)	25 (92.6%)	

No statistically significant difference was seen in the mobility and vitality of the guided canine between the two methods. Periodontal pocket depth evaluations revealed that closed method treated teeth exhibited superior periodontal health (Table 3).

Table 3: The Periodontal Pocket Depth

Variables	Open Technique (Mean ± SD)	Closed Technique (Mean ± SD)	p-value
Mesial (mm)	2.7 ± 1.5	2.4 ± 1.61	0.11
Distal (mm)	3.14 ± 2.12	2.3 ± 0.10	0.20
Buccal (mm)	1.9 ± 2.10	2.15 ± 10.6	0.13
Lingual (mm)	2.0 ± 0.55	2.18 ± 8.24	0.121

Independent T test was utilized

DISCUSSION

A tooth is considered impacted if it has lost its ability to erupt fully or partially into its proper location in the dental arch. The maxillary canine and third molars are among the permanent teeth that often go loose. Between one and two and a half percent of cases include the maxillary canine [17]. After a comprehensive clinical and radiographic assessment, the decision to keep or remove the impacted tooth is made. Although there is a common agreement on how to remove an impacted third molar tooth from the mandible or maxilla, a canine tooth requires a distinct approach. Because teeth are so important to the dentition, preserving them is the greatest way to keep the dental arch looking good and functioning well [18]. Collaboration is key when guiding the tooth into proper occlusion. A full-thickness mucoperiosteal incision is made and the affected tooth is exposed under local anesthetic during surgical extraction. There are two ways to accomplish this: the open technique and the closed method [19]. Re-exposure in the event of bonded connection failure is one of the key drawbacks of the closed approach, although faster healing and less aggressive bone removal are two of its primary benefits. Although the open approach has its benefits, such as the ability to easily rebound attachments

DOI: https://doi.org/10.54393/pjhs.v6i1.2221

in the event of bond failure, it also has certain drawbacks, including as the increased exposure of bone, the increased risk of infection, and the worsening of periodontal health. When all the teeth are erupted, orthodontic treatment of a malocclusion takes less time. The average pain rating for patients who underwent a closed eruption process was 3.1 ± 0.3, whereas for patients who underwent an open eruption method it was 3.12 ± 0.4, and there was no statistically significant difference (P = 0.12). Results were in line with studies conducted in past in post-operative pain score among both groups were insignificant [20-22]. The time required for recuperation following open eruption surgery was more than that of the close eruption method with p value <0.05. Post-operative, there was no any significant different was observed in complication between both groups. These were comparable to the study conducted in past [23]. In current study, surgical mean time in group I was 23.17 ± 8.28 minutes and in group II mean time was 31.17 ± 10.42 minutes. These results were agreed with previous studies conducted by Izadikhah I and Cassina C *et al* [14, 15]. However, when the maxillary canine is impacted, the process takes longer. Contrary to the findings of a previous study, which found that the time required by closed technique was significantly less than open technique, this study found that the open technique was the more time-consuming of the two surgical techniques [21]. The current study utilized MIP, which shortened the attachment bonding period. Various techniques for applying physiological pressure on impacted teeth in the upper jaw were detailed. Other supplementary mechanics enable the traction of an impacted maxillary canine into the dental arch, in addition to the standard golden chain and elastic techniques. Because the incisor is guided near to the resorptive follicle of the impacted canine and experiences a significant torque during conventional alignment, the surrounding lateral incisors may be at risk of resorption [22]. Preventing root resorptions of lateral incisors requires careful movement management of impacted maxillary canines. The temporary anchoring device described by past study can make this possible [24]. Another useful approach that may be employed both before and during the leveling process was published by Raghav *et al* [25]. The segmented arch technique's static mechanics allowed to claim an efficient and predictable output [26]. Using two distinct approaches, the initial stage of this investigation involved making enough room for the affected canine to be traced into its proper location in the arch. According to previous study,a simple biomechanical exercise can be used to tip the crown of an impacted maxillary canine into the proper position within the dental arch if its apex is in line with the arch in the buccopalatal and mesiodistal planes [27]. This study was able to include the same biomechanic because of the angulation, tilting, and vertical orientation inclusion criteria for the location of the impacted maxillary canine. In current study, no statistically significant difference was seen in the mobility and vitality of the guided canine between the two methods. Periodontal pocket depth evaluations revealed that closed method treated teeth exhibited superior periodontal health. When it comes to treating impacted canines, previously proposed that the open technique would yield better periodontal outcomes than the closed technique. This is because the former allows for better cleansability and causes less trauma to the periodontal tissue during the canine's natural eruption [28]. The results from this investigation show the opposite to be true. A Gingival Index (GI) score was used to quantify the results of a clinical assessment of gingiva color, size, and texture. The GI score was much greater in the open group compared to the closed surgical groups, indicating a worse result for the open group individuals. The dogs in the open group also showed a significantly higher plaque index compared to those in the closed group. One possible explanation for the contradictory findings is that the sample size is too small to draw any firm conclusions from the data we have collected thus far. No evidence found that participants in the open surgical group had better outcomes than those in the closed surgical group with respect to clinical attachment level. This agrees with previous study [29].

CONCLUSIONS

In this comparative study, the closed eruption approach took longer but reduced postoperative pain faster. Orthodontic therapy took longer with deeper impaction. Closed eruption surgeries improve periodontal tissues surrounding guided erupted teeth.

Authors Contribution

Conceptualization: NW
Methodology: MAB, T
Formal analysis: AHK
Writing, review and editing: MAK, SL

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v6i1.2221

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DOI: https://doi.org/10.54393/pjhs.v6i1.1970

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparison of the Side Effects of Chlorhexidine and Honey Mouthwash among Dental Patients: A Randomized Controlled Trial

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ARTICLE INFO

Keywords:
Gingivitis, Chlorhexidine Gluconate, Honey Mouthwash, Oral Hygiene

How to Cite:
Abid, M., Rauf, R., Siddiq, A., Mazhar, S., Zaidi, H. A., & Zafar, U. (2025). Comparison of the Side Effects of Chlorhexidine and Honey Mouthwash among Dental Patients: A Randomized Controlled Trial: Side Effects of Chlorhexidine and Honey. Pakistan Journal of Health Sciences, 6(1),75-79. https://doi.org/10. 54393/ pjhs.v6i1.1970

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Received Date: 17th August, 2024
Acceptance Date: 21st January, 2025
Published Date: 31st January, 2025

ABSTRACT

Gingivitis, primarily caused by bacterial plaque buildup, was managed through mechanical removal, though this requires consistency. Chemical agents like chlorhexidine mouthwash were effective but have notable side effects. Honey, with its antibacterial properties, offers a potential alternative with fewer adverse effects. **Objective:** To compare the side effects of 0.12% chlorhexidine gluconate and 10% honey mouthwash to determine which offers a safer and more comfortable option for oral hygiene in young adults. **Methods:** This randomized controlled trial was conducted from June 2020 to December 2020 to compare the side effects of two oral care solutions, 0.12% chlorhexidine gluconate and 10% honey mouthwash, among young adults. Sixty subjects were recruited from the Department of Periodontology at a tertiary care hospital in Karachi. The primary focus of the study was to observe and document any side effects associated with each mouthwash during and after three weeks of usage for plaque removal and gingival health. **Results:** The study revealed that participants in Group A (chlorhexidine) reported a higher incidence of adverse effects, including a pronounced bad taste, numbness in the mouth, and noticeable tooth discoloration. In contrast, Group B (honey) participants generally reported a pleasant taste, with significantly fewer and milder side effects. **Conclusions:** Honey mouthwash offers a more comfortable user experience with fewer negative side effects, including a pleasant taste. This makes it a promising alternative for individuals seeking an effective and gentle approach to maintaining oral health.

INTRODUCTION

The progression of gingivitis has been long thought to be triggered and/or exacerbated by natural accumulation of dental plaque, consisting of relatively high loads of endogenous oral bacteria. Accumulating metabolites and byproducts from endogenous oral organisms could lead to inflammation [1]. The most successful approach to treating and preventing dental plaque and gingivitis is still the removal of the bacterial biofilm [2, 3]. It has been shown that the application of mechanical agents is an easy and affordable way to effectively reduce gingivitis [4]. Consequently, a chemical method for plaque control using mouthwashes is seen to be preferred to make up for potential shortcomings in maintaining regular dental hygiene. Mouth rinses are frequently utilized as adjuncts to oral care and in delivering active substances to the teeth and gums [3]. Chlorhexidine, commonly known as (CHX), is a biguanide that has a positive effect against bacteria, fungi, and hydrophobic viruses [5]. Investigators recommends CHX in the context of both the prevention and treatment of periodontal disorders due to its plaque

DOI: https://doi.org/10.54393/pjhs.v6i1.1970

inhibitory action [3, 6, 7]. Apart of its demonstrated initial bactericidal activity, chlorhexidine binds to the oral mucosa and progressively releases it, continuing its antibacterial impact [8]. Chlorhexidine mouthwash, is regarded the "gold standard," although it has side effects such as teeth discoloration and taste alteration, thus it is not a miracle cure [9]. But its use has been linked to a number of localized side effects, including discoloration of teeth caused by precipitation of anions from food chromogens, temporary shedding of the oral epithelium, taste disturbances, and enhanced accumulation of deposits, especially in the subgingival area [10]. Honey, a natural product, has long been used for both nourishment and medicinal purposes. It has shown broad-spectrum antibacterial activity with few adverse effects. The majority of investigations on honey antimicrobial properties have been undertaken in vitro. It has also been investigated for the ability to reduce dental plaque production [11]. The study was designed to compare the side effects of 0.12% chlorhexidine gluconate and 10% honey mouthwash among young adults.

The aim was to determine which mouthwash offers a more comfortable and safer option for oral hygiene.

METHODS

A clinical trial (ClinicalTrials.gov ID NCT05258955) through randomization was directed to compare the side effects of mouthwashes containing natural honey and chlorhexidine. This open-label study involved sixty patients in the age group 18 to 26 years, complaining of teeth discoloration and gums bleed at the Department of Periodontology, at a Tertiary care hospital of Karachi. Patients were enrolled through convenience sampling from the target population attending the department between June 2020 to December 2020. Convenience sampling was applied to effectively sample participants with an age between 18 and 26 years old, presenting gingival staining and bleeding. All patients gave their consent before they were enrolled into the study. In order to maintain confidentiality and prevent bias in the study, a sealed-envelope randomization procedure was implemented. Participants were asked to randomly select an envelope containing their group assignment, ensuring they were unaware of their assigned group. The envelopes were prepared in advance by independent individuals who were not involved in the study. These individuals sealed the envelopes properly and signed the back of each one to confirm that they had not been opened or tampered with. This process ensured the integrity of the randomization and preserved the confidentiality of the group assignment, minimizing any potential bias in the study results. The participants with 28 teeth (excluding wisdom teeth) and practicing oral hygiene through the modified Bass technique were included. Exclusion criteria included patients with numerous extractions; overhanging restorations; dental prostheses, periodontal pockets exceeding 3 mm, medication use within one month prior to study enrollment, non-compliance with oral hygiene instructions, smoking, habits like betel chewing, and any systemic health conditions causing dental issues, such as Diabetes and Sjögren's syndrome. The randomization process employed an opaque sealed envelope technique to maintain participant anonymity. Envelopes were prepared and securely sealed by individuals unassociated with the study, with stamps applied to ensure tamper-proofing. The study protocol was approved by the Ethical Review Committee of Liaquat College of Medicine and Dentistry on February 5, 2020 (Reference Number: EC/11/20). Each participant provided handwritten informed consent prior to inclusion. The sample size was determined via the OpenEpi, based on the mean and standard deviation of plaque levels in the honey and chlorhexidine groups at day 15, which were 2.85 ± 0.44 and 2.40 ± 0.51, respectively. To account for potential dropouts, at least 27 participants were calculated for each group, with an additional 10% added, bringing the total to 30 participants per group. The study was designed with a 95% confidence interval and 95% statistical power. Partakers were assigned amongst two groups in which Group A was given chlorhexidine Mouthwash while the Group B was given natural honey mouthwash. Natural sidr honey and 0.12% chlorhexidine gluconate mouthwashes were used in the study. Sidr honey, sourced from the Islamic Shehad Centre, was formulated in collaboration with Liaquat College of Medicine and Dentistry. Each 450 ml dark bottle contained 45 ml of honey mixed with 405 ml of lukewarm water to create a 10% honey-based mouthwash. The solution was prepared by diluting 10 ml of honey in 90 ml of lukewarm water. The chlorhexidine mouthwash (0.12%) used in the study was Protect® chlorhexidine gluconate solution, a commercially available brand. Bottles containing the assigned mouthwash were provided to the participants and they were instructed to practice 10 mL two times a day for 60 seconds. They were instructed to brush using the modified Bass technique and were not allowed to use any other mouthwashes during the study period. After 21 days, patients were assessed for the presence of the common side effects: bad taste, good taste, loss of taste, numbness in the tongue and mouth, soreness or burning in the tongue/mouth, dryness, and discoloration. SPSS version 21.0 was used for data analysis, considering mean values, standard deviations, frequencies, and percentages. Descriptive statistics were applied to continuous variables (e.g., age, represented by mean and SD), while categorical variables (e.g., gender, education level, and side effects) were analyzed through frequencies. The chi-square test was used to compare side effects

DOI: https://doi.org/10.54393/pjhs.v6i1.1970

between groups, with a significance level set at $p < 0.05$ for all statistical comparisons.

RESULTS

Sixty patients visited the Outpatient Department (OPD) at the Department of Periodontology, at a tertiary care hospital in Karachi. The participants were divided into two groups: Group A, treated with chlorhexidine, and Group B, treated with honey. The mean age in Group A was 23.53 ± 2.60 years, with 66.7% of participants being male and 33.3% female. Group B had a mean age of 24.0 ± 3.76 years, comprising 73.33% males and 26.67% females. The education level distribution was as follows: in Group A, 23% completed matriculation, 30% intermediate, 33.3% undergraduate, and 13.3% were graduates. In Group B, 30% completed matriculation, 26.6% intermediate, 20% undergraduate, and 23% were graduates, as detailed in Table 1.

Table 1: Population Statistics and Level of Education of the Study Participants in Group A and B

Participant Data	Group A Mean ± SD/N (%)	Group B Mean ± SD/N (%)
Age in Years	23.53 ± 2.60	24.0 ± 3.76
Gender		
Male	20 (66.7%)	22 (73.33%)
Female	10 (33.3%)	8 (26.67%)
Level of Education		
Matriculation	7 (23%)	9 (30%)
Intermediate	9 (30%)	8 (26.6%)
Undergraduate	10 (33.3%)	6 (20%)
Graduate	4 (13.3%)	7 (23%)

Group A: Participants receiving Chlorhexidine Mouthwash
Group B: Participants receiving Natural Honey Mouthwash
Age and Level of Education: Mean ± Standard Deviation
Gender: Frequency and Percentage

Table 2 showed that participants in Group A experienced a range of side effects, including a bad taste, which was reported by 15 individuals, and loss of taste, noted by 16 participants. Additionally, 9 participants in Group A reported numbness in the tongue and mouth, while 7 experienced soreness or burning sensations. Discoloration was also reported by 9 participants in Group A. In contrast, Group B, which used honey mouthwash, did not report these side effects. Notably, Group B participants reported a good taste in 15 cases, whereas only 5 participants in Group A reported a pleasant taste. The statistical analysis showed significant differences between the two groups for bad taste, good taste, loss of taste, numbness, soreness/burning, and discoloration (p-values <0.001 for most comparisons), with no significant difference in dryness (p=0.659).

Table 2: Side Effects Experienced by Participants in Groups A and B (n=60)

Side Effects	Number of Participants Group A N (%)	Number of Participants Group A N (%)	p-Value
Bad Taste	15 (50%)	0 (0%)	<0.001
Taste Satisfaction	5 (16.7%)	15 (50%)	<0.001
Loss of Taste	16 (53.3%)	0 (0%)	<0.001
Numbness in the Tongue and Mouth	9 (30%)	0 (0%)	<0.001
Soreness / Burning in Tongue/Mouth	7 (23.3%)	1 (3.3%)	0.004
Dryness	1 (3.3%)	2 (6.7%)	0.659
Discoloration	9 (30%)	0 (0%)	<0.001

Group A received the standard treatment.
Group B received the experimental treatment.
The number of participants indicates those who reported experiencing the specific side effect.
Chi-square test was applied

DISCUSSION

Chlorhexidine (CHX) mouthwash can cause adverse drug reactions (ADRs), with tooth staining being the most commonly reported effect. These ADRs are often underreported, as many studies rely on subjective patient reports rather than objective assessments [13]. According to studies, some self-reported adverse effects were associated with 21 days of CHX mouthwash use included taste change, numbness in the mouth and tongue, oral pain, a dry mouth, and discoloration. "Loss of taste" and "numbness" were much more common at higher concentrations (0.12% and 0.2%) than at 0.06%. However, no severe side effects such as erosion or ulceration of the oral mucosa were noted [14]. Some of the most common side effects of CHX mouthwash were xerostomia, hypogeusia, tongue discoloration, calculus buildup, and extrinsic tooth staining. The most prevalent side effect that prevents people from using chlorhexidine was tooth discoloration [15]. In the study by Guerra F et al., the chlorhexidine + cetylpyridinium Chloride group showed significant improvements in bleeding perception and burning sensations compared to the chlorhexidine alone group. The chlorhexidine alone group had higher reports of burning sensations and altered taste, and was less favored for mouthwash taste compared to the other groups. The chlorhexidine + anti-discoloration System group had better results in taste alteration but more reports of dryness [16]. A seven-day study compared two chlorhexidine concentrations, 0.2% and 0.12%. Both groups experienced no burning sensations on the first and third days, with a few incidences of mild burning recorded on the seventh day. The 0.2% chlorhexidine group had a higher rate of taste disturbances than the 0.12% chlorhexidine group, which had fewer mild taste disturbances [17]. This study assesses

DOI: https://doi.org/10.54393/pjhs.v6i1.1970

common complications from using chlorhexidine mouthwashes among 41 dentists in North Macedonia, revealing that 85.4% noted taste disturbance, 78.1% observed xerostomia, and 58.6% reported tooth discoloration. Most dentists (87.8%) recommend these mouthwashes, primarily for mouth odor and periodontal diseases, and 80.5% believe side effects correlate with usage duration [18]. In a study comparing different concentrations of chlorhexidine, the most prevalent reported side-effects were "loss of taste" and "numbness" [19]. Honey has been documented to exhibit broad-spectrum antibacterial properties, effectively targeting a wide range of bacterial strains. Its minimal side effects further enhance its appeal as an oral care solution. This efficacy was attributed to honey's natural components, such as hydrogen peroxide, which was known for its antimicrobial action, and its high sugar content, which creates an environment less conducive to bacterial growth [20]. Another study found that honey mouthwash was superior to chlorhexidine in terms of antibacterial efficacy [21]. Although chlorhexidine was widely used in medicine for a variety of oral treatments, it was also a common contact allergen with undesirable side effects.

CONCLUSIONS

Based on the study findings, honey proved to be a promising natural alternative for oral health care. It demonstrated significant benefits in reducing plaque and gingival bleeding, with fewer or no side effects compared to chlorhexidine. While chlorhexidine had been effective in oral care, it was frequently associated with adverse effects such as taste disturbances, dry mouth, and tooth discoloration. In contrast, honey's antimicrobial properties, along with its positive patient acceptance, positioned it as a viable option for maintaining oral health, making it a strong candidate for further consideration in dental care practices.

Authors Contribution

Conceptualization: MA
Methodology: MA, RR
Formal analysis: AS, SM
Writing, review and editing: AS, HAZ, UZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2246

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparative Study on Histochemical Expression of CD34 in Different Variants of Ameloblastoma

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ARTICLE INFO

Keywords:

Ameloblastoma, CD34 Expression, Mean Vascular Density, Histological Variants

How to Cite:

Bashir, N., Obaid, M., Iqbal, F., Maryam, H., Naushin, T., & Khan, A. S. (2025). Comparative Study on Histochemical Expression of CD34 in Different Variants of Ameloblastoma: CD34 Expression in Ameloblastoma Variants. Pakistan Journal of Health Sciences, 6(1), 80–86. https://doi.o rg/10.54393/pjhs .v6i1.2246

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Received Date: 14th September, 2024
Acceptance Date: 22nd January, 2025
Published Date: 31st January, 2025

ABSTRACT

Ameloblastoma is a benign, locally aggressive, tumor of the oral cavity having a high propensity for recurrence. The growth potential of the tumor is linked to the proliferation of preexisting vasculature and is reflected in CD34 expression. has been rephrased as "Mean Vascular Density (MVD) which measures CD34 expression, aids in predicting this proliferation. **Objectives:** To evaluate the biological behavior of different variants of Ameloblastoma according to expression of CD34 and to correlate it with age and gender. **Methods:** The present study was analytical, cross-sectional study composed of total 40, already diagnosed cases of ameloblastoma. Immuno-histochemical expression of CD34 was analyzed. **Results:** Follicular variant has more growth potential in females 21(62%) and males reveal more vascular growth in plexiform 19(80%) acanthomatous (50%) and unicystic variant (50%). More endothelial proliferation in age group of > 40 years was seen in follicular variant, whereas, in age group of < 40 years, plexiform type was more dominant. However, relationship between the age groups and MVD scores were found to be insignificant ($p > 0.05$). Relationship between CD34 expression in ameloblastoma and its histological variants were also found to be statistically non-significant (p=0.9). **Conclusions:** All variants display highest Mean Vascular Density (MVD) score in posterior mandible. Follicular variant has more growth potential in females while in males it is found more in plexiform, acanthomatous and unicystic variants. More epithelial proliferation in the follicular variety is observed in the age group over 40, whereas more plexiform type was shown in the age group below 40.

INTRODUCTION

Ameloblastoma (AM) is recognized as a benign oral cavity tumor and has a strong propensity for local invasion. It is ranked second among tumors of odontogenic origin accounting for <1% of the tumors arising in the head and neck area [1, 2]. Ameloblastoma is of epithelial origin having mature, fibrous stroma [1]. Mostly the tumor arises in the third to fifth decades of life and is equally common in both genders, with 80% occurrence in mandible and 20% in maxilla [3, 4]. Global estimation of the incidence is 0.5 cases per million populations, however slightly higher incidence has been reported in South Africa [5]. Asians and Africans are more commonly affected as compared to Latin Americans and Europeans [6]. The aggressive nature of its behavior has compelled the researchers to seek more deepened knowledge about the mechanism that could help prevent its progression [2]. Proliferating vessels have an important role to play in predicting the biological behavior of different pathologies including tumors of odontogenic origin, as well as a therapeutic guide for the said conditions. The connective tissue stroma facilitates epithelial changes by providing the environment that is needed for the fibroblasts and blood vessels to become active resulting in neoplastic growth [7]. A cascade of events is involved in angiogenesis resulting in the proliferation of already existing vessels. The most searched mechanisms include multiplication and degradation of extracellular matrix, endothelial cell migration, and capillary formation [8]. The process is controlled by inhibitory biomarkers and growth factors [7]. It was initially discovered that CD34 was expressed as antigen on the surface of 1% to 2% of normal

DOI: https://doi.org/10.54393/pjhs.v6i1.2246

bone marrow and in the myeloblastic cell line [9]. It marks cells that act as precursors for a wide range of cells and tissues like vascular endothelial lining, connective tissue stroma, dermal epithelium, and keratinocytes [10]. The increased growth potential of ameloblastoma reflects higher expression of CD34 in this odontogenic tumor. Mean Vascular Density (MVD) is estimated to help predict the behavior of the lesions that express CD34 [11]. Depending on its accessibility and ease of use, CD34 can be employed as a specific marker that can reveal proliferating vessels in a variety of lesions. Immunohistochemical labeling is used to identify this antigen [12]. Ameloblastoma is known for its aggressive nature having variable recurrence for histologically different patterns [13-15]. Therefore, the current study was designed to assess the proliferative potential of histological variants of ameloblastoma to see if they may provide a clue for a difference in the organic behavior of these variants.

Hence, the aim of this study was to compare the expression of CD34 in histological variants of ameloblastoma and to correlate the mean vascular density with age and gender in different variants of ameloblastoma.

METHODS

This analytical cross-sectional study consisted of 40 diagnosed cases of ameloblastoma of different ages and gender groups. Sample size calculation was done using Epi-tool with the estimated true proportion of 0.01(1% prevalence), confidence interval of 95%, and precision of 0.05 about a study carried out by Nazir H and Usman I [16]. A non-probability purposive sampling technique was applied. Formalin-fixed paraffin-embedded (FFPE) blocks were recruited from the archives of the histopathology Department of Peshawar Medical College (PMC) and Pakistan Institute of Medical Sciences (PIMS). Blocks with insufficient tissue and excessive hemorrhage were excluded from the study. Before the study started, ethical approval was obtained (Prime/IRB/2022-420) from the review board of the Prime Foundation Peshawar. Already prepared slides of selected cases of ameloblastoma were examined. Following confirmation of the diagnosis,blocks with adequate tissue were chosen for immunohistochemistry.Six slides (3+3) from representative blocks, each of 4-5 microns' thin sections were made. For each case Hematoxylin and Eosin (H and E) stain was applied on one slide, one was utilized for Immunohistochemistry (IHC), and one of each case was kept aside for future use. Tonsillar tissue was taken as a positive control. One slide of positive control was used for each batch. The procedure of IHC was carried out using Mouse Anti-Human CD 34 Monoclonal Antibody (DAKO, Denmark). Scoring was carried out following the method proposed by Hosseini S *et al.*, [17]. MVD was then measured by evaluating the IHC-stained slides under the microscope. Under low magnification, four hot spots or regions with the greatest degree of vascularization were chosen. At (×40) magnification number of the vessels showing staining was counted. The mean of stained blood vessels in the four selected hot spots was taken as MVD. Cases having MVD scores of 0-19.9 were categorized as low, scores of 20-29.9 as moderate, and scores more than 40 as high. The statistical analysis was carried out using the Statistical Program for Social Sciences (SPSS) version 20. Continuous variable like age was presented as mean and standard deviation. Categorical variables like the site, gender, age group, and MVD were presented as percentages, and a chi-square test was applied to age groups and variants of ameloblastoma to find its relationship with MVD. A p-value of less than 0.05 was deemed statistically significant.

RESULTS

The study consisted of a total 40 cases of ameloblastoma. Among all cases 19/40 (47.5%) were found in males and 20/40 (50%) in females with a ratio of 0.95:1. Ameloblastoma patients ranged in age from 12 to 80 years, with a mean age of 36.13 ± 12.8. The age group under 40 years had the highest number of instances. The posterior mandible was found to be the most preferred site followed by the anterior mandible, posterior maxilla, anterior maxilla, and maxillary sinus comprising 72%, 15%, 5%, 2.5%, and 2.5% of cases respectively. Histologically, the follicular variant was most common, making 72.5% of ameloblastomas, followed by plexiform ameloblastoma 12.5%, acathomatous ameloblastoma 10% and unicystic ameloblastoma 05%. In posterior mandible maximum number of follicular variant presented with moderate MVD score 50% followed by low 35% and high score 15%. In anterior mandible follicular variant presented 60% high MVD score and 40% moderate score. In posterior and anterior maxilla, only follicular variant showed moderate 100% MVD score as seen in Figure 1.

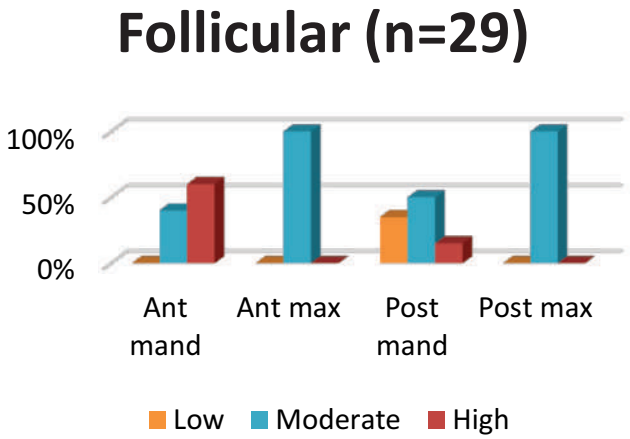

Figure 1: MVD Score of Follicular Variant with Respect to Site

DOI: https://doi.org/10.54393/pjhs.v6i1.2246

In posterior mandible Plexiform variant presented with 50% each of high and low score. Only plexiform variant presented with 100% moderate MVD score in maxillary sinus shown in Figure 2.

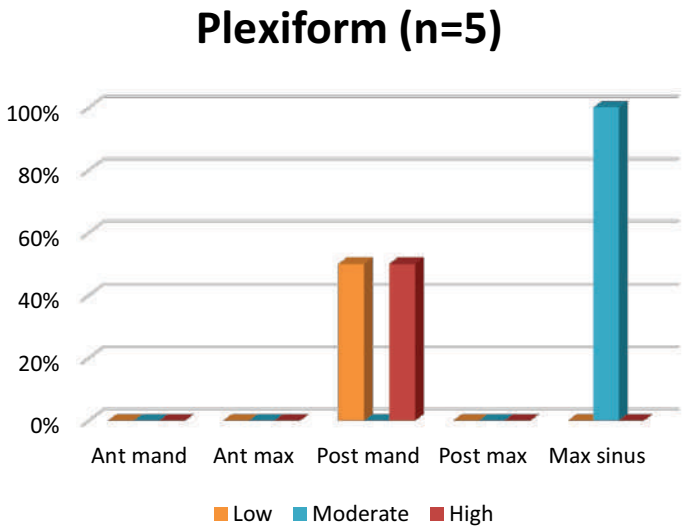

Figure 2: MVD Score of Plexiform Variant with Respect to Site

In posterior mandible acanthomatous variant presented with moderate MVD score 50% followed by 25% each of low and high score as seen in Figure 3.

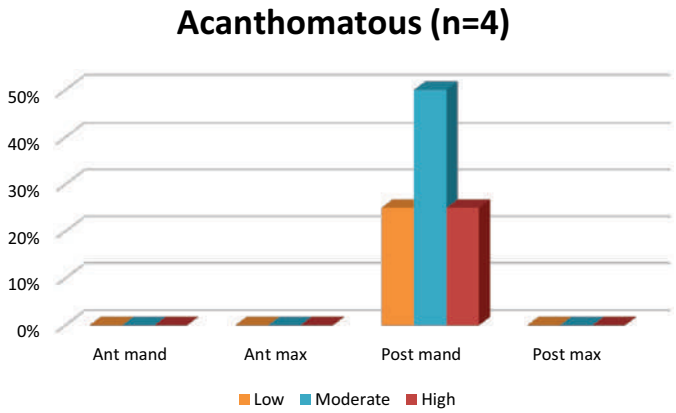

Figure 3: MVD Score of Acanthomatous Variant with Respect to Site

In posterior mandible acanthomatous variant presented with moderate MVD score 50% followed by 25% each of low and high score as seen in Figure 3.

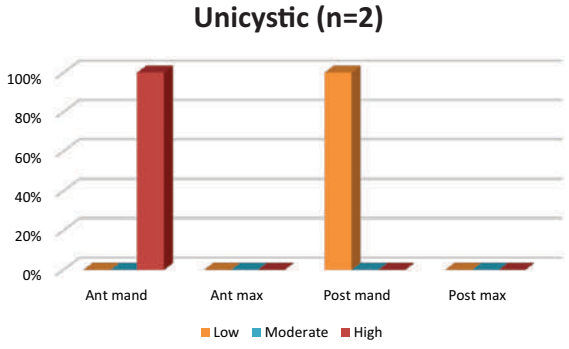

Figure 4: MVD Score of Unicystic Variant with Respect to Site

Out of 29 cases of follicular variant 11 (37.9%) of cases were present in males and 18 (62%) in females. In male patients, maximum number of follicular variant presented with moderate MVD score 63.6% followed by 27.2% of low and 9.1% of high MVD score. In female's maximum number of follicular variants showed moderate MVD score 44.4% followed by high 33.3% and low 22.2% score. Out of 5 cases of plexiform variant 4 (80%) of cases were present in males and 1 (20%) in females. In males, 50% of plexiform variant presented with high MVD score and 25% each of low and moderate score. In females only one case of plexiform variant was present showing low MVD score 100%. Among 4 cases of acanthomatous ameloblastoma equal distribution 50% was found in both genders. Males presented with 50% each of low and high MVD score while in females both the cases 100% were of moderate MVD score. Unicystic ameloblastoma in male presented with 50% each of low and high score. Whereas in female there was no case of unicystic variant as shown in the following Table 1.

Table 1: MVD Score of Ameloblastoma Variants in both the Genders (n=69)

MVD Score	Gender	
	Male n (%) (n=19)	Female n (%) (n=21)
Follicuar (n=21)	11 (37.9%)	18 (62%)
Low	3 (27.2%)	4 (22.2%)
Moderate	7 (63.6%)	8 (44.4%)
High	1 (9.1%)	6 (33.3%)
Plexiform (n=5)	4 (80%)	1 (20%)
Low	1 (25%)	1 (100%)
Moderate	1 (25%)	-
High	2 (50%)	-
Acanthomatus (n=4)	2 (50%)	2 (50%)
Low	1 (50%)	-
Moderate	-	2 (100%)
High	1 (50%)	-
Unicystic (n= 2)	2 (100%)	-
Low	1 (50%)	-
Moderate	-	-
High	1 (50%)	-
Total (n=40)	19	21

Regarding age, cases with maximum number 51.7% of follicular variant with 53.3% of the patients above 40 years of age presented with moderate MVD score followed by low 33.3% and high 13.3% score. In cases below 40 years of age, follicular variant presented with maximum number of moderate MVD score 50% followed by high 35.7% and low 14.2% score. In patients above 40 years of age, the only plexiform 100% variant presented with moderate MVD score while in patients below 40 years it presented with 50% each of low and high score. Acanthomatous presented with 50% each of low and moderate score in the patients

DOI: https://doi.org/10.54393/pjhs.v6i1.2246

above 40 years and 50% each of moderate and high MVD score in cases below 40 years. One case each of unicystic ameloblastoma was present in both the groups showing high MVD in age group above 40 and low MVD in below 40 years as seen in Table 2.

Table 2: MVD Score of Ameloblastoma Variants in both Age Groups

MVD Score	Age (Years) n (%)		p-value
	>40 (n=19)	<40 (n=21)	
Follicuar (n=29)	15 (51.7%)	14 (48.2%)	0.27
Low	5 (33.3%)	2 (14.2%)	-
Moderate	8 (53.3%)	7 (50%)	
High	2 (13.3%)	5 (35.7%)	
Plexiform (n=5)	1 (20%)	4 (80%)	0.08
Low	-	2 (50%)	-
Moderate	1 (100%)	-	
High	-	2 (50%)	
Acanthomatus (n=4)	2 (50%)	2 (50%)	0.36
Low	1 (50%)	-	-
Moderate	1 (50%)	1 (50%)	
High	-	1 (50%)	
Unicystic (n=2)	1 (50%)	1 (50%)	0.36
Low	-	1 (100%)	-
Moderate	-	-	
High	1 (100%)	-	
Total (n=40)	19	21	-

The follicular variant showed 24.1% cases of low, 51.7% cases of moderate and 24.1% cases of high MVD. The plexiform variant showed 40 % cases of low, 20% cases of moderate and 40 % cases of high MVD. The acanthomatous variant had 25% cases of low, 50% cases of moderate and 25% cases of high MVD. In unicystic variant 50% of cases presented with low and 50% with high MVD while there was no case with moderate MVD. Relationship between CD34 expression in ameloblastoma and its histological variants were found to be statistically non-significant (p-value 0.74) Table 3.

Table 3: Expression of CD34 in Different Variants of Ameloblastoma

Variants	MVD Score n (%)			Total n (%)	p-value
	Low	Moderate	High		
Follicular	7 (24.1%)	15 (51.7%)	7 (24.1%)	29 (72.5%)	0.74
Plexiform	2 (40%)	1 (20%)	2 (40%)	5 (12.5%)	
Acanthomatous	1 (25%)	2 (50%)	1 (25%)	4 (10%)	
Unicystic	1 (50%)	-	1 (50%)	2 (05%)	
Total	11 (27.5%)	18 (45%)	11 (27.5%)	40 (100%)	

Photomicrographs of Ameloblastoma showing hematoxylin and eosin (H & E) staining (A, C, and E) and immunohistochemical staining for CD34 (B, D, and F) at low, moderate, and high microvascular density (MVD) in blood vessels, respectively. Arrowheads indicate CD34-stained blood vessel as shown in Figure 5.

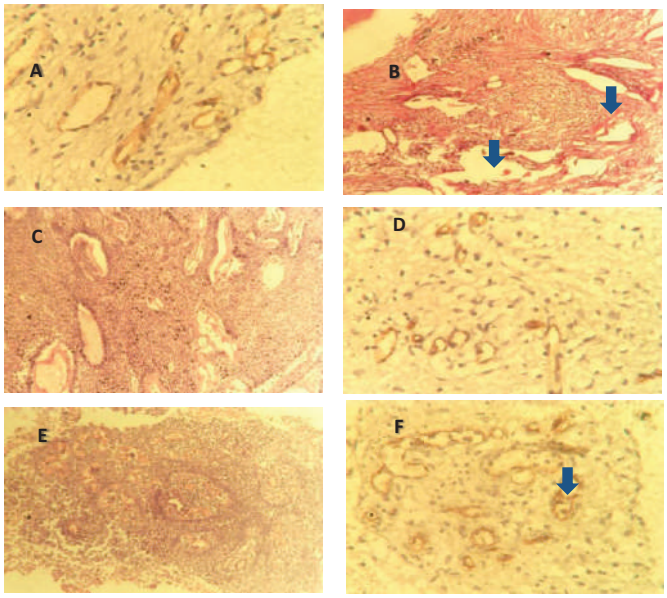

Figure 5: Photomicrograph of Ameloblastoma with H & E staining (A, C and E) and immunohistochemical staining (B, D and F) with CD 34 of low, moderate and high MVD in blood vessels respectively. Arrow heads showing CD 34 stained blood vessels.

DISCUSSION

A total of 40 cases of ameloblastoma were evaluated in the present study. The most common age group was the second and third decades of life with a mean age of 36.13 ± 12.8. The findings are similar to the previously reported studies conducted in Pakistan but different from the findings of Stefan Vila S *et al* [18, 19]. This variation may be explained based on the differences observed between different ethnic groups. Almost equal predilection was found for both the genders which is consistent with other studies [20, 21]. However, some national and international studies have demonstrated slight male predilection [18, 19]. A Pakistani study has also observed female predominance [22]. This minor discrepancy in ratio might be due to the difference in sample size. In this study, the mandible was found to be the commonest 82.5% site for ameloblastoma which is similar to Egyptian and Iranian studies and the posterior region to be the favorite site as compared to the anterior region in both the mandible and maxilla [21, 22]. The maxillary sinus was the least affected site. The results are similar to that of a Pakistani study but in contrast to study of Treville Pereira, who demonstrated the anterior region to be the commonest affected site [23, 13]. Follicular ameloblastoma was found to be the most common type. Plexiform was the second followed by acanthomatous and unicystic ameloblastoma. These results are in agreement with already existing data in the literature [24-26]. However, plexiform and unicystic ameloblastoma have been reported to be the most frequently occurring variants in studies conducted in Thailand and India [27-29]. The possibility for this contrast

DOI: https://doi.org/10.54393/pjhs.v6i1.2246

might be the variability in geographic locations, genetics, differences in cultural habits, and sample size. The importance of angiogenesis as a major player in increased neoplastic changes, invasion and aggressive behavior in multicystic ameloblastoma has been demonstrated in the literature. MVD score determines the tumor's aggressiveness which validates the angiogenesis as an important prognosticator that can assist clinicians in designing more effective treatment strategies [30]. CD 34 expression has already been identified as an effective tool to quantify vascular proliferation in a tumor [31]. Regarding CD34 expression in histological variants, the current study found that the follicular type has the highest MVD score in the posterior mandible. Anterior mandible, posterior maxilla, and anterior maxilla are then affected respectively. The maxillary sinus and posterior jaw had the highest MVD scores for the Plexiform variety. Similarly, acanthomatous and unicystic variants also expressed maximum MVD score in the posterior mandible. Based on these findings it is revealed that in the posterior mandible, all variants of ameloblastoma exhibit maximum vascular proliferation in comparison to other sites. Different researchers discovered that Solid Multicystic Ameloblastoma (SMA) had higher MVD scores than desmoplastic and unicystic types based on which they suggested its behavior to be more aggressive than the other two [30, 32, 33]. Hande AH *et al.*, also concluded the same increased angiogenesis in SMA while doing a comparison between the three and reported unicystic and desmoplastic ameloblastoma as second and third in the list [34]. In contrast, Jamshedi S *et al.*, reported the same aggressive nature for both solid multicystic and unicystic ameloblastoma [22]. All the above-mentioned studies did not compare MVD in variants of ameloblastoma with respect to sites as is done in the present study. While comparing CD34 expression status in both genders, it was discovered that the follicular variant has more growth potential in females while plexiform, acanthomatous and unicystic type proliferate violently in males. Due to scant available data in the literature investigating endothelial proliferation in ameloblastoma variants for site and gender, comparison with other studies is hampered. The present study evaluated endothelial proliferation in two age groups i.e. above and below 40 years. Follicular ameloblastoma was found to have a higher MVD score in the group of more than 40 years. In contrast plexiform variant showed more vascular growth in the group of less than 40 years whereas acanthomatus and unicystic type were equally proliferative in both age groups. These findings are in line with a Pakistani study [7]. According to Koizumi *et al.*, plexiform type is common among the younger population and the follicular type is among older people. This led to the suggestion that in addition to affecting tumor growth pattern, angiogenesis is also modulated by the patient's age. [35]. However current study could not find significant relationship with age groups ($p>0.05$). Since vasculogenesis is important for the tumor to grow and metastasize, measurement of MVD can help in its prediction together with treatment outcome [22]. Although ameloblastoma is known for its aggressive behavior, this study is the first one to correlate different variants of ameloblastoma with age, gender, and site on basis of CD34 expression or vascular proliferation. This might provide a help in further stratification of the patients having differential growth potentials in accordance with clinicopathological features. Relationship of CD 34 expression with histological variants of ameloblastoma revealed insignificant relationship which is in contrast to studies carried out in India and Iran [13, 22]. Large sample size of their study might be responsible for this difference. Although present study pointed towards insignificant relationship between variants and angiogenesis but report of high MVD score in females, in specific age group and in mandible suggest evaluation of endothelial proliferation while planning treatment specifically for the groups just mentioned.

CONCLUSIONS

All variants displayed the highest MVD score in the posterior mandible. The follicular variant has more growth potential in females while in males it is found more in plexiform, acanthomatous and unicystic variants. More epithelial proliferation in the follicular variety is observed in the age group over 40, whereas more plexiform type was shown in the age group below 40. Further investigations regarding angiogenesis in variants of ameloblastoma are needed. Stratification according to different variants, each strata containing a large number of patients is recommended. Additionally, follow-up of the patients is recommended for further exploration of MVD as a predictive factor in ameloblastoma cases.

Authors Contribution

Conceptualization: NB, FI
Methodology: MO, HM
Formal analysis: MO
Writing, review and editing: HM, TN, ASK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v6i1.2246

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DOI: https://doi.org/10.54393/pjhs.v6i1.2628

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Clinical Pattern of Limb Loss in Electrical Burn Injuries

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ARTICLE INFO

Keywords:
Electrical Burn Injuries, Amputations, High-Voltage Burns, Total Body Surface Area

How to Cite:
Sanober, A., Siddique, A. S., Shaikh, S., Irshad, S., Ahsan Qureshi, P. N. A., Sangrasi, H., & Memon, R. (2025). Clinical Pattern of Limb Loss in Electrical Burn Injuries: Limb Loss in Electrical Burn Injuries. Pakistan Journal of Health Sciences, 6(1), 87-91. https://doi.org/10.54393/pjhs.v6i1.2628

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Received Date: 3rd December, 2024
Acceptance Date: 23rd January, 2025
Published Date: 31st January, 2025

ABSTRACT

Electrical burn injuries are severe and often lead to significant morbidity, including amputations, especially in high-voltage cases. These injuries commonly occur in occupational settings and can result in prolonged hospitalization and complications. Studying clinical patterns in electrical burn injuries is crucial to identifying risk factors, improving early interventions, and guiding effective treatment plans. **Objective:** To analyze the clinical pattern of amputation in electric burn patients at Burns Unit, Liaquat University Hospital, Hyderabad. **Methods:** This prospective observational study was conducted at Liaquat University Hospital, Hyderabad, from Nov 2023 to May 2024. A total of 84 patients, of all ages and both genders who presented with electrical burn injuries were included. While those with scald burns, dry flame burns, contact burns, thermal burns, or uncontrolled diabetes mellitus were excluded. Data collection involved recording demographic details and clinical parameters like the type of burn, total body surface area affected, cause and place of burn, duration of hospital stay, mortality rate and surgical intervention. **Results:** Among all, 54.8% (n=46) required amputations, with 35.7% involving a single limb and 19% multiple limbs. Upper limb amputations were more common (60.9%) compared to lower limb amputations (39.1%), with an 11.9% mortality rate. High-voltage burns were significantly associated with severe total body surface area involvement, prolonged hospitalization, fasciotomies, and multiple limb amputations. **Conclusion:** It was concluded that the study reported a high frequency of limb loss (due to amputation) i.e. 54.8% (n=46) among patients with electric burn.

INTRODUCTION

Electrical burn injuries are among the most severe forms of trauma, with significant physical, psychological, and socioeconomic consequences [1]. These injuries result from direct contact with electrical currents, arc flashes, or thermal burns caused by electrical equipment. The clinical outcomes of electrical burns, particularly limb loss, are devastating, often leading to lifelong disability and impaired quality of life. In Pakistan, the prevalence of electrical burn injuries is rising due to industrialization, unsafe working conditions, and inadequate enforcement of safety standards [2]. Electrical burn injuries are categorized based on the voltage of the electrical current: high-voltage (>1000 volts) and low-voltage (<1000 volts) burns [3]. High-voltage injuries are more likely to cause extensive tissue damage, leading to severe complications such as compartment syndrome, tissue necrosis, and amputations [4]. The mechanism of injury involves the conversion of electrical energy into thermal energy, resulting in deep tissue damage that is often disproportionate to the visible surface injury. Furthermore, these burns may disrupt neurovascular structures, contributing to a higher likelihood of limb loss [5]. Studies from other developing countries with similar socio-economic profiles have shown that high-voltage injuries are predominantly occupational, affecting young male workers in construction and electrical industries [6].

DOI: https://doi.org/10.54393/pjhs.v6i1.2628

However, domestic accidents involving children and women also constitute a significant proportion of cases [7]. The decision to perform an amputation in patients with electrical burns is complex and influenced by multiple factors, including the severity of the burn, vascular compromise, infection, and the risk of systemic complications such as sepsis [8]. However, in resource-limited settings like Pakistan, these diagnostic modalities are not readily available, often leading to delayed interventions and a higher rate of amputations. A study in Taxes - US reported amputation rates as high as 25% among patients with electrical burns, underscoring the urgency of timely management [9]. Despite the significant burden of electrical burn injuries in Pakistan, there is a paucity of data on the clinical patterns of limb loss in these patients. Most studies are single-center reports with small sample sizes, limiting the generalizability of their findings. This study aims to analyze the clinical pattern of amputation in electric burn patients at the Burns Unit of Liaquat University Hospital, Hyderabad.

METHODS

This prospective observational study was conducted at the Department of Plastic and Reconstructive Surgery and Burns Unit, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro/Hyderabad, from Nov 2023 to May 2024. Consecutive purposive sampling was used for patient selection. A total of 84 patients of all ages and genders who presented with electrical burn injuries were included. Meanwhile, those with scald burns, dry flame burns, contact burns, thermal burns, or uncontrolled diabetes mellitus were excluded. Following ethical approval from the ERC (NO. LUMHS/REC/-199), all eligible patients were enrolled in the study after obtaining informed written consent. The sample size was calculated via the Open Epi sample size calculator, taking a percentage of limb loss in electrical burns as 31.7% [10]. The margin of error was 10% and CI was 95%. Data collection involved recording demographic details (age, gender, level of education) and clinical parameters like the type of burn, total body surface area (TBSA) affected, cause and place of burn, duration of hospital stay, infection rate and surgical intervention. Primary outcomes were assessed in terms of fasciotomies and types of amputations. Limb amputation was performed based on critical factors such as the depth of tissue damage involving muscles, bones, and tendons, progressive necrosis despite treatment, severe ischemia causing non-viable tissue and compartment syndrome resulting in increased pressure and irreversible damage. The extent of amputation was classified into minor and major amputations. Minor amputations referred to the amputation of digits while major amputations were defined as amputations below-knee/elbow- or above-knee/elbow joints. Patients were followed up for 3 months' post-discharge to assess their recovery and rehabilitation outcomes. Follow-up evaluations were conducted monthly at the Outpatient Department (OPD). Data were recorded for complications such as delayed healing and infection recurrence. Data were analyzed using SPSS version 22.0. Continuous variables were presented as mean ± standard deviation, while categorical variables such as gender, injury types, and clinical outcomes were expressed as frequencies and percentages. The chi-square test was used to determine the strength of association between different factors with high and low voltage. p-value<0.05 was considered as statistically significant and p<0.01 was considered as highly statistically significant.

RESULTS

The study included 84 patients with electrical burn injuries, predominantly male (73.8%) and aged 18–40 years (61.9%). Most patients were of low socioeconomic status (57.1%) and had high-voltage burns (61.9%). TBSA involvement was moderate (10–20%) in 45.2% of cases. Workplace injuries (54.8%) were the leading cause of burns. Hospitalization ranged from <10 days (42.9%) to >20 days (9.5%) (Table 1).

Table 1: Demographic and Clinical Characteristics of Patients (n=84)

Variables	Frequency (%)
Gender	
Male	62 (73.8%)
Female	22 (26.2%)
Age Groups (Years)	
<18	12 (14.3%)
18-40	52 (61.9%)
>40	20 (23.8%)
Education Level	
Illiterate	36 (42.9%)
Primary	28 (33.3%)
Secondary and Above	20 (23.8%)
Socioeconomic Status	
Low	48 (57.1%)
Middle	30 (35.7%)
High	6 (7.1%)
Type of Electrical Burn	
Low Voltage (<1000 kV)	32 (38.1%)
High Voltage (>1000 kV)	52 (61.9%)
TBSA Affected	
<10% (Minor)	28 (33.3%)
10–20% (Moderate)	38 (45.2%)
>20% (Severe)	18 (21.4%)
Place of Injury	
Workplace	46 (54.8%)
Home	38 (45.2%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2628

Duration of Hospital Stay	
<10 Days	36 (42.9%)
10–20 Days	40 (47.6%)
>20 Days	8 (9.5%)

Among 84 patients with electrical burn injuries, 54.8% (n=46) required amputations, with 35.7% (n=30) involving a single limb and 19% (n=16) multiple limbs. Upper limb amputations were more common (60.9%, n=28) compared to lower limb amputations (39.1%, n=18). Infection was noted in 35.7% of patients, with an 11.9% mortality rate (Table 2).

Table 2: Surgical Interventions and Outcomes (n=84)

Variables	Frequency (%)
Fasciotomies Performed	
Yes	46 (54.8%)
No	38 (45.2%)
Amputations	
None	38 (45.2%)
Single Limb	30 (35.7%)
Multiple Limbs	16 (19.0%)
Type of Amputation	
Upper Limb	28 (60.9%)
Lower Limb	18 (39.1%)
Infection Rate during Hospitalization	
Yes	30 (35.7%)
No	54 (64.3%)
Mortality	
Yes	10 (11.9%)
No	74 (88.1%)

High-voltage burns were significantly associated with severe TBSA involvement (>20%, 26.9%, p=0.002), prolonged hospitalization (>20 days, 15.4%, p=0.008), fasciotomies (69.2%, p=0.001), and multiple limb amputations (23.1%, p=0.026). No significant association was found between burn type and gender, type and extent of amputation, or mortality (Table 3).

Table 3: Association of Type of Electrical Burn with Different Factors

Variables	Low Voltage	High Voltage	p-value
Gender			
Male	22 (68.8%)	40 (76.9%)	0.401
Female	10 (31.3%)	12 (23.1%)	
TBSA Affected			
<10% (Minor)	18 (56.3%)	10 (19.2%)	0.002*
10–20% (Moderate)	10 (31.3%)	28 (53.8%)	
>20% (Severe)	4 (12.5%)	8 (15.4%)	
Duration of Hospital Stay			
<10 Days	20 (62.5%)	16 (30.8%)	0.008*
10–20 Days	12 (37.5%)	28 (53.8%)	
>20 Days	0 (0%)	8 (15.4%)	
Fasciotomies Performed			
Yes	10 (31.3%)	36 (69.2%)	0.001**
No	22 (68.8%)	16 (30.8%)	
Amputations			
None	18 (56.3%)	20 (38.5%)	0.026*
Single Limb	10 (31.3%)	20 (38.5%)	
Multiple Limbs	4 (12.5%)	12 (23.1%)	
Type of Amputation			
Upper Limb	8 (66.7%)	20 (60.6%)	0.721
Lower Limb	4 (33.3%)	12 (39.4%)	
Extent of Amputation			
Minor	20 (83.3%)	12 (54.5%)	0.13
Major	4 (16.7%)	10 (45.5%)	
Mortality			
Yes	2 (6.3%)	8 (15.4%)	0.287
No	30 (93.8%)	44 (84.6%)	

*p<0.05 significant, **p<0.01 highly significant

DISCUSSION

Electrical burns are a major cause of severe injuries requiring surgical intervention, often leading to amputations and long-term morbidity. The current study observed that males (73.8%) aged 18–40 years (61.9%) were predominantly affected, consistent with a study conducted in South China by Ding H *et al.*, which reported 76% male dominance in similar age groups [11]. This trend reflects the higher involvement of males in outdoor, high-risk occupations. International studies, such as one from India by Khor D *et al.*, also found comparable gender ratios [12]. Most patients in this study belonged to low socioeconomic backgrounds (57.1%), aligning with findings by Schaap Re *et al.*, emphasizing the link between poverty and limited workplace safety measures in low-income settings [13]. High-voltage burns accounted for 61.9% of cases, significantly associated with severe TBSA involvement (>20%, 26.9%, p=0.002) and multiple limb amputations (23.1%, p=0.026). These findings are corroborated by a study by Kim E *et al.*, which reported higher TBSA involvement and amputations in high-voltage injuries [9]. Workplace injuries (54.8%) were predominant, similar to findings from Iran, where industrial burns were a leading cause [14]. The average hospital stay was 10–20 days (47.6%), with high-voltage burns significantly prolonging hospitalization (>20 days, 15.4%, p=0.008). These findings align with Tolouie M and Farzan R, which highlighted longer hospitalization in patients with extensive injuries [15]. The findings highlight that high-voltage burns are strongly associated with severe total body surface area (TBSA) involvement, leading to more extensive tissue damage. This results in prolonged hospitalization due to the need for intensive care, multiple surgeries, and extended rehabilitation, emphasizing the need for timely intervention and specialized care for these patients.

DOI: https://doi.org/10.54393/pjhs.v6i1.2628

Mortality in this study was 11.9%, lower than rates reported in an Ethiopian study by Alemayehu S *et al.*, which found 18% mortality, possibly due to differences in healthcare facilities and early intervention [16]. Amputations were required in 54.8% of cases, with single-limb amputations (35.7%) being more frequent than multiple-limb amputations (19%). Upper limb amputations (60.9%) were more common than lower limb (39.1%), which is consistent with studies by Pedrazzi et al., in Switzerland and Kamran M *et al.*, in Pakistan, reporting 58% and 64% upper limb amputations, respectively [17, 18]. High-voltage burns necessitated more fasciotomies (69.2%, p=0.001) and multiple limb amputations (23.1%, p=0.026), in agreement with international data [19]. High-voltage burns are more likely to require fasciotomies due to the severity of tissue damage and compromised blood flow. This finding highlights the need for careful monitoring and prompt surgical management to prevent complications such as compartment syndrome, which could otherwise result in further tissue loss or amputation [20]. While regional studies report similar patterns in demographics and clinical outcomes, developed countries demonstrate lower amputation and mortality rates due to advancements in electrical safety regulations, early rehabilitation, and multidisciplinary approaches[21].

CONCLUSIONS

It was concluded that the study reported a high frequency of limb loss (due to amputation) among patients with electric burns. High-voltage burns were the predominant cause of severe injuries leading to a significantly higher rate of fasciotomies and multiple limb amputations. Upper limb amputations were more common than lower limb amputations. Severe TBSA involvement, longer hospital stays, and infections were significant contributors to the need for surgical intervention. These findings emphasize the importance of early intervention, proper management strategies, and preventive measures to mitigate the devastating outcomes of electrical burn injuries.

Authors Contribution

Conceptualization: AS
Methodology: AS, ASS, SS, SI, PNAAQ, HS, RM
Formal analysis: PNAAQ
Writing review and editing: ASS, SS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2603

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparative Analysis of Host and Virus-Driven Variables Affecting Response to Ribavirin and Interferon Therapy in Hepatitis C Patients

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ARTICLE INFO

Keywords:
Interferon Therapy, Ribavirin, Hepatitis C Host Factors, Hepatitis C Virus Factors.

How to Cite:
Jamal, I., Aslam Rind, M., Nazir, M., Saleem, M., Shah, M., & Rajput, A. (2025). Comparative Analysis of Host and Virus-Driven Variables Affecting Response to Ribavirin and Interferon Therapy in Hepatitis C Patients : Host and Virus-Driven Variables Affecting Ribavirin and Interferon Therapy in HCV. Pakistan Journal of Health Sciences, 6(1), 92-96. https://doi.org/10.54393/pjhs.v6i1.2603

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Received Date: 25th November, 2024
Acceptance Date: 17th January, 2025
Published Date: 31st January, 2025

ABSTRACT

Current guidelines advocate for individualized treatment approaches for the management of Hepatitis C, that incorporate baseline assessments of viral genotype, host comorbidities, and socioeconomic factors to maximize therapeutic success. **Objectives:** To analyze the impact of host and virus-driven variables on treatment response in patients receiving ribavirin and interferon therapy. **Methods:** This prospective cohort study was conducted on 138 patients aged 18–65 with confirmed chronic HCV infection who were eligible for interferon and ribavirin therapy. The patients were followed up to a 24-week post-treatment to assess recovery measured in terms of sustained virological response (SVR). The host-driven factors included age, gender, BMI, and the presence of IL28B polymorphism while virus-driven factors included HCV genotype and baseline viral load. **Results:** The study sample predominantly consisted of male (55.1%), and genotype 3 virus accounted for 68.1% of participants. A high proportion (76.1%) of participants achieved SVR. Factors associated with better treatment outcomes included younger age (90.7% in the 31–45 age group), gender (89.5% of male), normal BMI (91.2% of those with a BMI of 18.5–24.9), and the favorable IL28B polymorphism CC genotype (91.8%). Low baseline viral load was observed in 60.1% of patients, and those with genotype 3 had better SVR rates. **Conclusions:** It was concluded that younger age, male gender, normal BMI, favorable IL28B polymorphism along with low baseline viral load, and genotype 3 were positively associated with achieving SVR.

INTRODUCTION

Hepatitis C virus (HCV) remains a pressing global health concern, affecting an estimated 58 million individuals worldwide as of 2024, with approximately 1.5 million new infections occurring annually [1, 2]. The virus is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC). The burden of the epidemic is particularly felt by low- and middle-income countries with limited access to diagnostic and therapeutic resources. The prevalence of HCV in Pakistan is 4.9%, which is dangerously high, even compared with other countries, mainly attributed to low public knowledge, unsafe medical practices, and unscreened blood transfusion [2, 3]. Especially in rural areas, the lack of healthcare infrastructure makes them more susceptible. HCV risk factors are behavioral or systemic, creating a paradigm of risk. Transmission usually occurs through the sharing of needles among intravenous drug users, unsafe medical procedures that involve the reuse of syringes, and transfusions of unscreened blood products. Sociodemographic factors like poverty, less education, and less access to health services amplify the virus's spread. Patients demonstrating a high baseline activation of interferon-stimulated genes (ISGs), termed interferon refractoriness, are less likely to mount a strong antiviral

DOI: https://doi.org/10.54393/pjhs.v6i1.2603

response and achieve viral clearance when placed on treatment. In addition, comorbid conditions like diabetes and obesity have also been linked to less effective treatment responses [4, 5]. Host genetic variation is a critical determinant of treatment success [6]. For instance, the IL28B polymorphism (rs12979860) is an independent favorable predictor of the SVR rates, as demonstrated in specific variants of the gene IL28B polymorphism is a genetic variation in the IL28B gene, which encodes interferon lambda-3. These variations significantly influence the immune response to the Hepatitis C Virus (HCV) and predict treatment response, especially to interferon-based therapies, with certain variants (e.g., CC genotype) associated with higher cure rates [6]. There are six major genotypes because of a variation of the virus genome. This heterogeneity impacts treatment response and disease course. While genotype 1 is the most prevalent globally, genotype 3 is the predominant genotype in Pakistan. Genotypes 2 and 3 tend to be more responsive to interferon (IFN)-based therapies, whereas genotype 1 correlates with low SVR rates [7]. Treatment approaches have evolved considerably over time. Direct-acting antivirals (DAAs) were the first truly new class of drugs to be developed in over fifty years and have revolutionized HCV therapy with cure rates ≥ 95% in most patient populations within eight weeks and with few adverse effects [8]. However, in resource-limited settings like Pakistan, where access to DAAs is constrained, ribavirin and pegylated interferon remain integral components of treatment. These regimens achieve SVR rates of 50-80% depending on the patient's genotype, viral load, and baseline characteristics [9]. Predictors of SVR include both host and virus-driven factors. Host factors such as age, sex, BMI, insulin resistance, and fibrosis stage play crucial roles. Virus-driven factors include genotype, baseline viral load, and mutations within the viral genome [10]. Despite therapeutic advancements, challenges remain, particularly in low-income settings. Affordability and accessibility of DAAs remain significant barriers, underscoring the need for optimized use of traditional therapies based on predictive factors. Current guidelines advocate for individualized treatment approaches that incorporate baseline assessments of viral genotype, host comorbidities, and socioeconomic factors to maximize therapeutic success [8, 11].

This study aimed to analyze the impact of host and virus-driven variables on treatment response in patients receiving ribavirin and interferon therapy in high-prevalence regions like Pakistan.

METHODS

This prospective cohort study was conducted on 138 HCV patients, at Liaquat University Hospital, Jamshoro, Pakistan from January 2021 to June 2022. Adults patients aged 18–65 years with confirmed chronic HCV infection (anti-HCV positive and detectable HCV RNA) who were eligible for interferon and ribavirin therapy were included. Patients with co-infections (e.g., HBV or HIV), severe comorbidities, or prior HCV treatment were not included. The sample size was calculated using the Open Epi sample size calculator, with the proportion of sustained virological response (SVR) among HCV patients treated with interferon estimated at 52%, a margin of error of 7%, and a 90% confidence interval [12]. The study was approved by the Research Ethics Committee of Liaquat University of Medical & Health Sciences, Jamshoro, Pakistan. (Reference No. LUMHS/REC/-037). After taking informed written consent, eligible participants were enrolled in the study and were provided with standardized treatment. Pegylated interferon-alpha (Peg-IFN-α) was given subcutaneously at a dose of 180 µg weekly and ribavirin, administered orally based on body weight (<75 kg: 1000 mg/day; ≥75 kg: 1200 mg/day) [13]. The treatment duration was 48 weeks for genotypes 1 and 4 and 24 weeks for genotypes 3. The patients were followed at weeks 4, 12, 24, and the end of treatment, and a post-treatment follow-up at week 72 to assess recovery measured in terms of sustained virological response (SVR) which was defined as undetectable HCV RNA 24 weeks after treatment. The host-driven factors included age, gender, BMI, and presence of IL28B polymorphism. The IL28B polymorphism (rs12979860) was detected by PCR amplification followed by restriction fragment length polymorphism (RFLP) analysis. Virus-driven factors were HCV genotype (1, 3 & 4) and baseline viral load, categorized as low (<600,000 IU/mL) or high (≥600,000 IU/mL), quantified through real-time PCR [13]. Data were analyzed using SPSS version 22.0. Descriptive statistics were used to summarize patient characteristics and the chi-square test was used to assess the association of factors with SVR.

RESULTS

The study population had a mean age of 42.5 ± 10.3 years, with most participants falling in the 31 to 45 years of age (39.1%). The male-to-female percentage was 55.1% to 44.9%. The mean BMI was 25.4 ± 3.1 kg/m^2, with nearly half of the participants (49.3%) having a normal BMI. Baseline viral load analysis showed that (60.1%) of participants had a low viral load (<600,000 IU/mL), and genotype distribution was dominated by genotype 3 (68.1%) (Table 1).

Table 1: Descriptive Statistics of Participants

Characteristic	Mean ± S.D / Frequency (%)
Age (Years)	42.5 ± 10.3
18 to 30	38 (27.5%)
31 to 45	54 (39.1%)
46 to 65	46 (33.3%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2603

Gender	
Male	76 (55.1%)
Female	62 (44.9%)
BMI (kg/m^2)	25.4 ± 3.1
<18.5 (Underweight)	4 (2.9%)
18.5-24.9 (Normal)	68 (49.3%)
25-29.9 (Overweight)	44 (31.9%)
≥30 (Obese)	22 (16.0%)
Baseline Viral Load	
Low (<600,000 IU/mL)	83 (60.1%)
High (≥600,000 IU/mL)	55 (39.9%)
Genotype	
Genotype 3	94 (68.1%)
Genotype 1 & 4	44 (31.9%)

76.1% of participants achieved sustained virological response (SVR), whereas 23.9% did not achieve SVR (Figure 1).

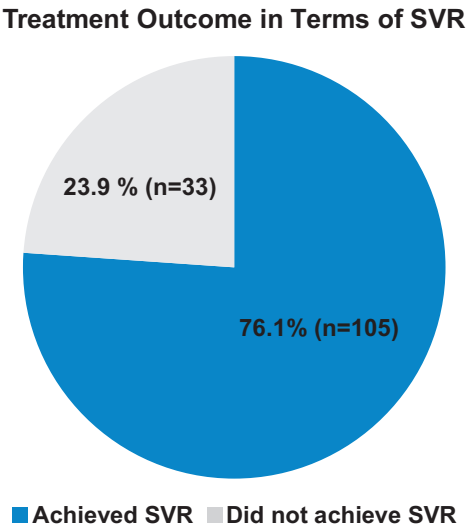

Figure 1: Treatment Outcomes of The Patients in Terms of Sustained Virological Response

Participants aged 18 to 45 years showed the highest SVR rates, while those aged 46 to 65 years had significantly lower SVR rates (47.8%, p=0.23). Male exhibited significantly higher SVR rates (89.5% vs. 59.7%, p=0.01). Regarding BMI, participants with normal BMI had the highest SVR rates (91.2%), while obese individuals had significantly lower success (36.4%, p=0.08). The presence of the CC genotype for the IL28B polymorphism was a strong predictor of SVR (91.8% vs. 49.2%, p<0.001) (Table 2).

Table 2: Association of Host Factors with SVR

Host Factor	SVR Achieved	SVR Not Achieved	p-value
Age (Years)			
18 to 30	34 (89.5%)	4 (10.5%)	0.23
31 to 45	49 (90.7%)	5 (9.3%)	
46 to 65	22 (47.8%)	24 (52.2%)	
Gender			
Male	68 (89.5%)	8 (10.5%)	0.01*
Female	37 (59.7%)	25 (40.3%)	
BMI (kg/m^2)			
<18.5 (Underweight)	3 (75.0%)	1 (25.0%)	0.08
18.5-24.9 (Normal)	62 (91.2%)	6 (8.8%)	
25-29.9 (Overweight)	32 (72.7%)	12 (27.3%)	
≥30 (Obese)	8 (36.4%)	14 (63.6%)	
Presence of IL28B Polymorphism (rs12979860)			
CC (Favorable)	67 (91.8%)	6 (8.2%)	<0.001**
CT/TT (Unfavorable)	18 (49.2%)	19 (50.8%)	

* Statistically significant
** Highly statistically significant

Participants with a low baseline viral load were significantly more likely to achieve SVR (95.2% vs. 47.3%, p<0.001). Regarding genotype, those with genotype 3 had higher SVR rates (86.2%) compared to genotypes 1 & 4 (25.0%, p<0.03) (Table 3).

Table 3: Association of Viral Factors with SVR

Viral Factor	SVR Achieved	SVR Not Achieved	p-value
Baseline Viral Load			
Low (<600,000 IU/mL)	79 (95.2%)	4 (4.8%)	<0.001**
High (≥600,000 IU/mL)	26 (47.3%)	29 (52.7%)	
Genotype			
Genotype 3	94 (86.2%)	15 (13.8%)	<0.03*
Genotype 1 & 4	11 (25.0%)	33 (75.0%)	

* Statistically significant
** Highly statistically significant

DISCUSSION

This study explored the host and virus-driven factors among patients of hepatitis C about the treatment success with ribavirin and interferon therapy. The overall sustained virological response (SVR) rate of 76.1% observed in this study aligns with global data on genotype-specific responses to interferon-based therapy. A meta-analysis reported an average SVR rate of approximately 70-80% for patients with genotype 3, similar to the 86.2% seen in our cohort [14]. However, the response rates for genotypes 1 and 4 in our study (25.0%) were lower than the global average of 40-50% for these genotypes, potentially reflecting regional differences in patient adherence, baseline health conditions, or genetic predispositions. The lower responsiveness to antiviral therapies is due to genetic resistance and slower viral clearance. Moreover, additional factors like regional differences in adherence, baseline health conditions, and genetic predispositions likely further reduced the sustained virologic response (SVR) compared to genotype 3, which generally responds more favorably to treatment [15]. Age was a major factor correlating with treatment response in this study, with younger participants (18 to 45 years) achieving significantly higher SVR rates than older participants. Such a univocal tendency has been reported by some studies among younger patients, who respond more durable to therapy [16]. Markedly, this could be due to the immune-

DOI: https://doi.org/10.54393/pjhs.v6i1.2603

senescence and co-morbidities found in the geriatric age group. Male gender was strongly associated with higher SVR rates (89.5%) than female (59.7%), which has been earlier reported. For example, a study from Croatia reported similar results, highlighting hormonal and metabolic differences that may influence therapy outcomes [17]. In this study, body mass index (BMI) was important in determining the treatment outcomes. It was found that patients with a normal BMI had the highest rates of SVR (91. 2%) whereas obese participants had relatively lower response rates (36. 4%). Obesity has been repeatedly found to be associated with a poor response to treatment, most likely because of added inflammation, insulin resistance, and changes in the pharmacokinetics of the drug [18]. A review supported these results, where lower rates of SVR were reported in obese patients receiving interferon therapy [19]. This cohort did show significantly higher figures (91.8%) when treated with interferon, especially those with the favorable IL28B polymorphism (CC genotype). This goes hand in hand with the findings of other studies which claim that the IL28B CC genotype provides superior immune responsiveness to interferon therapy [20]. A study in Myanmar also reported similar findings where SVR rates of this polymorphism were reported over 90%. This reinforces the predictive power of this polymorphism [21]. Baseline viral load and genotype significantly influenced outcomes in this study. Patients with a low baseline viral load (<600,000 IU/mL) had markedly higher SVR rates (95.2%) compared to those with high viral loads. This observation is consistent with global studies that have identified baseline viral load as a crucial determinant of treatment success [22]. Furthermore, the predominance of genotype 3 in this study reflects the regional epidemiology of hepatitis C, contrasting with genotype 1 dominance in the Middle East and North African countries [23]. The study adds value to the understanding of tailoring treatment strategies based on patient-specific and viral factors, which may result in better treatment outcomes.

CONCLUSIONS

The study revealed that both host and viral factors significantly influence treatment outcomes in patients receiving ribavirin and interferon therapy in high-prevalence regions like Pakistan. Younger age, male gender, normal BMI, favorable IL28B polymorphism along with low baseline viral load, and genotype 3 were positively associated with achieving SVR.

Authors Contribution

Conceptualization: IJ
Methodology: MAR, MN, MS[1], AR
Formal analysis: IJ, MAR, MN, MS[1], MS[2], AR
Writing review and editing: MAR, MN
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2208

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Diagnostic Accuracy of Fine Needle Aspiration Cytology in Salivary Gland Lesions: A Comparative Study with Histopathology as the Reference Standard at Bahawal Victoria Hospital, Bahawalpur, Pakistan

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ARTICLE INFO

Keywords:
Fine Needle Aspiration Cytology, Salivary Gland Neoplasm, Histopathology, Cytology

How to Cite:
Afzal, A., Shaheen, U., Khalid, F., Iqbal, F., & Akhtar, A. (2025). Diagnostic Accuracy of Fine Needle Aspiration Cytology in Salivary Gland Lesions: A Comparative Study with Histopathology as the Reference Standard at Bahawal Victoria Hospital, Bahawalpur, Pakistan: Fine Needle Aspiration Cytology for Diagnosing Salivary Gland Lesions. Pakistan Journal of Health Sciences, 6(1), 98-101. https://doi.org/10.54393/pjhs.v6i1.2208

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Received Date: 5th October, 2024
Acceptance Date: 22nd January, 2025
Published Date: 31st January, 2025

ABSTRACT

Fine-needle aspiration cytology (FNAC) is one of the most widely used diagnostic tools for evaluating salivary gland lesions. However, its diagnostic accuracy is uncertain due to certain factors. **Objective:** To analyze the diagnostic accuracy of FNAC in salivary gland lesions compared to histopathological examination in a clinical setting. **Methods:** This cross-sectional study was conducted from October 2021 to June 2022 at Bahawal Victoria Hospital, Bahawalpur, Pakistan. A total of 75 patients, aged 18 to 75 years, were included in the study who were previously clinically diagnosed with salivary gland lesions. Every patient included in the study underwent the FNAC, and the outcomes were compared to the histopathological analysis of the excised biopsies. The results are analyzed in terms of sensitivity, specificity, NPV, PPV, and diagnostic accuracy. **Results:** Among the 75 patients, the mean age was 42.5 ± 14.3 years, with a male-to-female ratio of 1:1.08. FNAC results showed 7 non-neoplastic lesions (9.3%), 61 benign (81.3%), and 7 malignant neoplasms (9.3%). A histopathological analysis identified 63 benign, 5 malignant, and 7 non-neoplastic neoplasms. FNAC showed a 96.0% overall diagnostic accuracy, with sensitivity, specificity, Positive predictive value (PPV), and Negative Predictive Value (NPV) of 97.0%, 88.9%,98.5%, and 80.0% respectively. Two false-negative instances (2.7%) and one false-positive case (1.3%) were found in the study. **Conclusion:** FNAC is an extremely sensitive and accurate diagnostic tool especially when it is required to distinguish between benign and malignant neoplasms. However, its low specificity increases the risk of false-negative results where histopathological confirmation becomes an integral part of the diagnosis especially the cases where clinical suspicions are high.

INTRODUCTION

Salivary gland lesions involve a wide spectrum of conditions which range from inflammatory processes to benign and malignant tumors which necessitate a reliable and accurate diagnostic tool for efficient treatment planning [1]. Fine Needle Aspiration Cytology (FNAC) is a globally preferred diagnostic method for the evaluation of salivary gland lesions as it quick, cost-effective, and minimally invasive approach [2]. In addition, FNAC is particularly useful in distinguishing non-neoplastic lesions from benign and malignant tumors. Such versatility and effectiveness of FNAC are supported by multiple studies conducted in different clinical settings [3]. The FNAC procedure is straightforward and includes aspiration of cells from the lesion through a fine-gauge needle that are then microscopically examined after some preprocessing and staining [4]. FNAC is used the most when the cytological findings are definitive enough to eliminate the need for any further invasive diagnostic procedures such

DOI: https://doi.org/10.54393/pjhs.v6i1.2208

as incisional biopsy [5]. Despite the widespread use of FNAC, there are certain limitations and the most significant is accuracy. The accuracy of FNAC can be influenced by several factors and the most significant are the experience and competency of the clinician performing the procedure, and microscopically examining the aspirate after required processing steps. The quality/ quantity of the aspiration and the inherent cytological features of the lesion also contribute to the level of accuracy [6]. Apart from the factors affecting the accuracy of the FNAC accuracy, some of the salivary gland tumors are challenging in FNAC based diagnosis due to their similarities of cytological features with benign lesions like in low-grade mucoepidermoid or acinic cell carcinoma [7]. Similarly, cystic lesions and tumors with extensive necrosis or hemorrhage may also yield insufficient or misleading cytological material which results in inaccurate results [8, 9]. The accuracy of FNAC findings can only be evaluated by comparing its results with histopathological examination results, which is an established standard for definitive diagnosis. The statistical analysis of FNAC sensitivity and specificity varies in the literature [10].

This study aimed to analyze the diagnostic accuracy of FNAC in comparison to histopathology of excision biopsies of salivary gland lesions.

METHODS

This cross-sectional study was conducted at a tertiary care hospital, Bahawal Victoria Hospital, Bahawalpur, Pakistan, from October 2021 to June 2022 after approval from IRB vide letter No. 1226/DME/QAMC Bahawalpur. A total of 75 patients were included in the study who were presented with clinically diagnosed salivary gland lesions. The inclusion criteria were patients aged 18 years and above, presenting with a well-palpable swelling in the salivary glands, suspected to be either neoplastic or non-neoplastic, who consented to undergo both FNAC and subsequent histopathological examination. On the other hand, the exclusion criteria were patients with non-palpable salivary gland lesions, with recurrent salivary gland lesions with previous diagnostic interventions and patients who were unwilling to undergo either FNAC or histopathological examination. A non-probability consecutive sampling method was employed which ensured the inclusion of all eligible patients. The sample size was calculated based on the method designed for cross-sectional studies with a prevalence of 5% (0.05) [11-13]. The sample size and prevalence are also in line with other reported studies [14, 15]. The calculated sample size is more than twice the similar study done at the Liaqat National Hospital, Karachi [16]. Given the sample size calculation, 75 patients ensured adequate power for detecting statistically significant differences between FNAC and histopathological results. FNAC was conducted on all patients using a 22-gauge needle attached to a 05 mL syringe. A written consent was taken, and vitals were measured. The needle, after creating negative pressure was inserted into the palpable lesion taking care of proper sterilization. Sufficient cellular material was aspirated by making one to two attempts at different angles. Adequacy was confirmed on-site by microscopy. Vitals were again recorded at the end of the procedure to ensure patient stability. Smears were prepared by spreading aspirated material on glass slides. Half of the slides were air dried for Diff Quik stain and the rest were fixed in 95% ethanol for Papanicolaou stain. After FNAC reporting all patients underwent surgical intervention of the lesion. The excised tissue specimens were processed, embedded in paraffin, and sectioned for histopathological examination using Hematoxylin and Eosin (H&E) staining. A histopathologist, blinded by the FNAC results, evaluated the specimens. The cytological diagnosis from FNAC was categorized into non-neoplastic, benign, and malignant neoplasms with probable differentials and further explanations in the comments. These results were then compared with the histopathological diagnosis to evaluate FNAC's accuracy. Data on patient demographics, lesion site, cytological and histopathological diagnoses, and FNAC outcomes (true positive, true negative, false positive, false negative) were meticulously recorded. Analysis of the collected data were performed using a statistical analysis tool SPSS version 26.0. The demographic characteristics of the patients were obtained based on the descriptive statistics which include mean age, gender distribution, and lesion location. In the comparison of the diagnostic results using FNAC and histopathology, the chi-square test was employed with a p-value < 0.05 considered statistically significant.

RESULTS

A total of 75 patients of age 18 to 75 years with clinically diagnosed salivary gland lesions were included in the study where the mean age of the patients was 42.5 ±14.3 years. The male-to-female ratio of the sample population was 1:1.08. The submandibular gland (n=12, 16.0%) and parotid gland (n=63, 84.0%) included the bulk of lesions among the 75 individuals. There were no cases involving sublingual or minor salivary glands. The distribution of lesions by gland location is shown in Table 1.

Table 1: Distribution of Location of Salivary Gland Lesions

Gland	Number of Cases Frequency (%)
Parotid Gland	63 (84.0%)
Submandibular Gland	12 (16.0%)
Total	75 (100%)

FNAC results categorized the lesions into three groups: non-neoplastic, benign neoplasm, and malignant

DOI: https://doi.org/10.54393/pjhs.v6i1.2208

neoplasms. Table 2 provides a comparative distribution of lesions based on FNAC and histopathological diagnoses.

Table 2: Distribution of FNAC and Histopathological Diagnosis

Diagnosis	FNAC Diagnosis (n, %)	Histopathological Diagnosis (n, %)
Non-Neoplastic	7 (9.3%)	7 (9.3%)
Benign Neoplasm	61 (81.3%)	63 (84.0%)
Malignant Neoplasm	7 (9.3%)	5 (6.7%)
Total	75 (100%)	75 (100%)

The diagnostic accuracy of FNAC in diagnosing salivary gland lesions was evaluated by comparing FNAC results with histopathological findings. The following measures were calculated:

True Positives (TP): 64 cases (85.3%) were correctly identified by FNAC as neoplastic (benign or malignant).

True Negatives (TN): 8 cases (10.7%) were correctly identified as non-neoplastic.

False Positives (FP): 1 case (1.3%) was incorrectly classified as neoplastic by FNAC.

False Negatives (FN): 2 cases (2.7%) were incorrectly classified as non-neoplastic or benign by FNAC, which were later identified as malignant by histopathology. Based on these results, the following diagnostic parameters were calculated:

Sensitivity : $\frac{64}{64+2} \times 100 = 97.0\%$

Specificity : $\frac{8}{8+1} \times 100 = 88.9\%$

Positive Predictive Value (PPV): $\frac{64}{64+1} \times 100 = 98.5\%$

Negative Predictive Value (NPV): $\frac{8}{8+2} \times 100 = 80.0\%$

Overall Diagnostic Accuracy : $\frac{64+8}{75} \times 100 = 96.0\%$

These results indicate that FNAC is highly sensitive with a sensitivity of 97.0% in the diagnosis of salivary gland lesions, with specificity of 88.9% and an overall diagnostic accuracy of 96.0%. The high PPV reflects the strong ability of FNAC to accurately identify neoplastic lesions, while the NPV suggests a moderate ability to exclude malignancy. A comparison of FNAC and histopathological findings showed a high degree of concordance between the two diagnostic methods, especially in the diagnosis of neoplastic lesions. Table 3 gives a detailed comparison of FNAC and histopathological diagnoses.

Table 3: Diagnostic Comparison of Cytology and Histopathology

FNAC Diagnosis	Histopathological Diagnosis	Concordant Cases n (%)	Discordant Cases n (%)
Non-Neoplastic	Non-Neoplastic	7 (9.3%)	1 (1.3%)
Benign Neoplasm	Benign Neoplasm	59 (78.7%)	2 (2.7%)
Malignant Neoplasm	Malignant Neoplasm	6 (8.0%)	N/A
Total	Total	72 (96.0%)	3 (4.0%)

The study identified 2 false-negative cases (2.7%) where FNAC failed to identify malignancy but later on confirmed by histopathology. Similarly, there was also a single false-positive case (1.3%), where FNAC incorrectly identified a non-neoplastic lesion as malignant. Table 4 summarizes the characteristics of the false-negative cases.

Table 4: Summary of False-Negative Cases

Case	Age (Years)	Gender	FNAC Diagnosis	Histopathological Diagnosis
1	47	Female	Benign Neoplasm	Malignant Neoplasm
2	60	Male	Non-Neoplastic	Malignant Neoplasm

DISCUSSION

This study tries to compare the diagnostic accuracy of FNAC against the histopathological diagnosis, where salivary gland lesions are under study for FNAC evaluation. As it is an inexpensive procedure that can be done in the laboratory and minimally invasive, being the primary mode of analysis, the usage of FNAC in evaluating salivary gland lesions has become widespread across all geographic boundaries. The statistical analysis of the results shows that the overall diagnostic accuracy of FNAC was 96.0%, which is highly consistent with FNAC accuracy rates reported in other similar studies. Many studies have reported diagnostic accuracy ranging from 80.0% to 95.0% [17-19]. The high sensitivity observed in this study is 97.0%, which supports the use of FNAC as a reliable diagnostic tool. The sensitivity of this study is marginally higher than the range reported in the literature, which typically falls between 87.0% and 94.0% [17-19]. Similarly, the high PPV of 98.5% indicates a strong likelihood of the correct diagnosis. The specificity of 88.9% in this study reflects its capability to correctly identify non-neoplastic lesions. Although this figure is commendable, however, is slightly lower than the specificities reported in other studies typically ranging from 85.0% to 95.0% [17-19]. The false-positive case underscores the inherent limitations of FNAC, where overlapping cytological features between benign and malignant lesions may lead to diagnostic errors. Moreover, the study identified two false-negative cases (2.7%), where FNAC failed to detect malignancies that were later confirmed by histopathology. These findings are clinically significant, as they highlight the potential risk of underdiagnosis, particularly in cases where malignant lesions present with benign-appearing cytological features and have the potential to metastasize. In situations when clinical suspicion is still high despite benign FNAC results, such false-negative results highlight the significance of keeping a high index of suspicion and the possible need for repeat FNAC or straight progression to incisional biopsy and histological investigation. Comparing current findings with those of other studies, the

DOI: https://doi.org/10.54393/pjhs.v6i1.2208

diagnostic parameters in present research are within the range of previously reported values. For example, a study reported sensitivity, specificity, and overall accuracy of 89.0%, 92.0%, and 91.0%, respectively, which are closely aligned with current results [17-19]. Other studies [20, 21] also showed high sensitivity and specificity, though slightly lower than ours, highlighting the variability across different studies due to factors such as sample size, technique, and operator expertise. In current study, the concordance rate between FNAC and histopathology was 96%, which indicates a high degree of agreement between these two diagnostic modalities in distinguishing benign from malignant lesions. This high concordance is important for clinical decision-making because it ensures the reliability of FNAC in the preoperative assessment of salivary gland lesions. The excellent sensitivity and diagnostic accuracy of FNAC shown in this work supports its use as a useful diagnostic tool for the preliminary assessment of salivary gland abnormalities [18-20]. FNAC offers a rapid and reliable method for distinguishing between neoplastic and non-neoplastic lesions, aiding in clinical management decisions, especially in the region with limited resources and a population that is not aware. However, the specificity, while high, was not perfect, indicating that FNAC should be used in conjunction with other diagnostic modalities, particularly in cases with inconclusive or suspicious results. The identification of false-negative cases highlights the importance of a cautious approach in interpreting FNAC results, especially in cases where clinical and radiological findings suggest a higher likelihood of malignancy. In such cases, a multidisciplinary approach involving repeat FNAC, imaging studies, or direct histopathological examination may be warranted to avoid diagnostic errors. While present study provides valuable insights into the diagnostic utility of FNAC in salivary gland lesions, it has its unavoidable limitations. Although the sample size is sufficient for preliminary analysis but may not fully cover the broad spectrum of salivary gland pathology due to regional and time-bound study. Furthermore, the human errors in sampling, processing, and diagnostic nature of FNAC could influence the results. Future studies with larger sample sizes and broader regional collaboration could provide more comprehensive data and further validate the findings.

CONCLUSIONS

This study effectively demonstrates FNAC as an effective diagnostic tool for the evaluation of salivary gland lesions with high sensitivity and overall diagnostic accuracy of 97.0% and 96.0% respectively. FNAC successfully identifies neoplastic lesions, particularly benign ones. The high PPV of 98.5% further supports the reliability of the FNAC's in diagnosing neoplastic conditions. A specificity of 88.9% indicates that FNAC is generally reliable, however, there is a risk of false-positive results. There were two false-negative cases, 2.7%, where malignancies were missed by FNAC but detected by histopathology evaluation.

Authors Contribution

Conceptualization: AA[1], US
Methodology: AA[1], AA, FK
Formal analysis: US, FI, AA
Writing, review and editing: FI, FK, AA,

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2274

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Evaluating the Impact of Site of Oral Cancer on Quality of Life of Patients

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ARTICLE INFO

Keywords:

Mouth Neoplasms, Oral cavity, Chemotherapy, Quality of life

How to Cite:

Shah, S. G. S., Shah, S. L. S., Hameed, A., Khalil, Z. U. R., Masood, A., & Shah, F. J. (2025). Evaluating the Impact of Site of Oral Cancer on Quality of Life of Patients: Impact of Oral Cancer on the Quality of Life of Patients. Pakistan Journal of Health Sciences, 6(1), 102-106. https://doi.org/10.54393/pjhs.v6i1.2274

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Received date: 30th November, 2024
Acceptance date: 21st January, 2025
Published date: 31st January, 2025

ABSTRACT

The Oral Health Impact Profile-14 was created to evaluate how oral health disorders affect the life of the patient, though it is widely utilized in patients with cancer, still, there is limited information regarding its measurement specifically related to the impact of cancer sites in a patient. **Objectives:** To evaluate the site of oral cancer and its impact on patients' oral Health-related quality of life. **Methods:** Diagnosed oral cancer patients were employed from the dental college of Peshawar, and 134 individuals were recruited. Patients of oral cancer, aged 20-59 of both genders were interviewed by using a convenience sampling technique. The Patients were asked about age gender, dental visit, site of cancer, treatment modalities, and various questions related to oral health impact profile. Data analysis was performed using SPSS version 26.0. **Results:** The study revealed that the majority of patients were aged 20-29 and predominantly male (67.9%), and most frequently occurs in the buccal mucosa (35.1%). The results revealed significant challenges among participants, with 30.6% experiencing difficulties in speech and 28.4% with a reduced sense of taste. Physical pain was reported by 38.8%, with 54.5% having eating uncomfortably. **Conclusions:** It was concluded that the study emphasized how patients' quality of life regarding oral health is greatly impacted by the location of cancer.

INTRODUCTION

Oral cancer is the general term for any cancer of the mucosa of the lip, palate, gums, floor of the oral cavity, and tongue [1]. Globally, 9.6 million people died due to cancer, and 18.1 million newly reported worldwide [2]. Pakistan is one of the top nations with the highest incidence of mouth cancer. It is the second most common cause of death, which accounted for 11.27% of deaths in 2020 [3]. Research highlights that cancer has become the leading cause of death in 91 out of 172 countries worldwide [4]. Oral cancer affects the tongue, floor of the mouth, buccal mucosa, gingiva, lips, retromolar trigone, and hard palate. Oropharyngeal cancer involves the base of the tongue, soft palate, tonsils, and pharyngeal wall. [5], Human papillomavirus (HPV), socioeconomic factors, tobacco use, and genetics significantly increase the risk of cancer [1]. Furthermore, risky behaviours include the use of betel nuts, tobacco, alcohol, and exposure to viral infections [6]. There are several treatment options for oral cavity cancers including pharmacologic cancer therapy, radiation therapy (RT), and surgery, either used separately or in combination. Early-stage cancers have high cure rates with surgery or radiation therapy, although radiation therapy better maintains function [7]. In the past decade, greater attention has been given to patients' quality of life (QoL) following cancer treatment. Assessing a patient's QoL provides valuable insights into the wide range of health

DOI: https://doi.org/10.54393/pjhs.v6i1.2274

challenges faced by the patient [8]. The oral health impact profile (OHIP), initially 49 items, was shortened to Oral Health Impact Profile-14 (OHIP-14), this updated version is a reliable tool for assessing how patients' lives are affected by their oral health since it preserves accuracy, sensitivity, and cross-cultural reliability [9]. Head and neck cancer (HNC) affects various regions of the head and neck, leading to significant physical changes such as alterations in appearance and pain, as well as functional impairments, including difficulties with chewing, swallowing, and speaking. Beyond these physical and functional challenges, HNC also has profound psychosocial consequences, such as anxiety, depression, and reduced social functioning. Treatments like surgery, chemotherapy, and radiotherapy often result in additional adverse effects and long-term complications [10]. Despite the substantial burden of oral cancer in the population, there is limited data on the prevalence of oral cancers at specific sites and their association with patients' overall well-being.

This study aims to assess the location of oral cancer and its effect on patients' oral health-related quality of life (OHRQoL) by using OHIP-14 as a measurement tool.

METHODS

The cross-sectional study was performed from August, 2023 to March, 2024, at the Khyber College of Dentistry in the Oral Maxillofacial Department. The Gandhara University's Ethical Review Board granted ethical permission (No. GU/Ethical Committee/2023/198) for the study. The study population comprised 134 diagnosed oral cancer patients. The inclusion criteria for this study required that participants be diagnosed and treated for oral cancer. Participants needed to be aged 20-59, of any gender and must have provided written consent at the time of data collection. Those who did not fit the requirements for inclusion were eliminated from the research. Utilizing the Open Epi calculator (version 3.01), the sample size was estimated to be 110 individuals, based on a 95% confidence level, 5% precision, and 7.7 % prevalence rate of oral cancer [11]. However, it was increased to 134 to account for the possible absence of answers and dropouts. Convenience sampling was used to recruit patients. The goals, methods, and confidentiality of the study were fully disclosed to the participants. They were encouraged to ask questions for clarification. Data were collected through patient interviews, where questions related to age, gender, dental visits, types of treatment, and sites of oral cancers were asked. The questionnaire assesses seven aspects of quality of life functional limitation, physical pain, psychological discomfort, physical disability, psychological disability, social disability, and handicap using a 5-point Likert scale (0=never, 4=always). The total score, calculated using the additive method, indicates that higher scores reflect a poorer oral health-related quality of life, which was administered in person by the researcher to ensure accuracy. The scoring system classified impact into three categories based on the score. A score between 0 and 9 indicated a poor impact, suggesting a minimal or negligible effect on health. Scores ranging from 10 to 18 represented as average impact and a score greater than 18 denoted as strong impact, highlighting a pronounced effect on health. Interviews were conducted privately to guarantee participant comfort and confidentiality. A pre-validated questionnaire was used and Cronbach's value was 0.98 and corrected item-total correlations ranged from 0.77-0.93 [10]. For data analysis, SPSS version 26.0 was used. Descriptive statistics summarized the data, and the Kolmogorov-Smirnov test assessed normality. The Kruskal-Wallis test was applied to examine the relationship between OHIP-14 scores and oral cancer site, with a p-value of 0.05 or less indicating statistical significance.

RESULTS

Most respondents were aged 20-29 years and were predominantly male (67.9%). The buccal mucosa comprised 35.1% of cases, followed by the floor of the mouth at 21.6% and the hard palate at 17.9%. The majority of patients received surgery, radiation therapy, and chemotherapy, accounting for 26.9% of the treatments (Table 1).

Table 1: Detailed Overview of Patient Demographics

Variables	Categories	Frequency (%)
Age	20-29 Years	49 (36.6%)
	30-39 Years	19 (14.2%)
	40-49 Years	42 (31.3%)
	50-59 Years	24 (17.9%)
Gender	Male	91 (67.9%)
	Female	43 (32.1%)
Site of Oral Cancer	Tongue	21 (15.7%)
	Hard Palate	24 (17.9%)
	Buccal Mucosa	47 (35.1%)
	Floor of Mouth	29 (21.6%)
	Lip	13 (9.7%)
Treatment of the Patient	Chemotherapy	27 (20.1%)
	Surgery	24 (17.9%)
	Surgery+ RT	23 (17.2%)
	Surgery+ RT+ Chemo	36 (26.9%)
	RT + Chemo	24 (17.9%)
Dental Visit	Within 6 Months	11 (8.2%)
	Once in A Year	44 (32.8%)
	Never	79 (59.0%)

The results indicated significant challenges across multiple domains like the participants faced functional limitations, with 30.6% having trouble pronouncing words and 28.4% reporting a worsened sense of taste (Table 2).

DOI: https://doi.org/10.54393/pjhs.v6i1.2274

Table 2: Frequency of Responses to the OHIP-14 Scale

Characteristics	0 = never	1 = Rarely	2 = Occasionally	3 = Often	4=Very Often
Functional Limitations					
Trouble Pronouncing Any Words	36 (26.9%)	12 (9.0%)	41 (30.6%)	22 (16.4%)	23 (17.2%)
Felt A Sense of Taste Worsened	38 (28.4%)	31 (23.1%)	25 (18.7%)	22 (16.4%)	18 (13.4%)
Physical Pain					
Had A Painful Aching	17 (12.7%)	19 (14.2%)	33 (24.6%)	13 (9.7%)	52 (38.8%)
Uncomfortable to Eat	7 (5.2%)	9 (6.7%)	32 (23.9%)	13 (9.7%)	73 (54.5%)
Psychological Discomfort					
Have Been Self-Conscious	22 (16.4%)	17 (12.7%)	17 (12.7%)	39 (29.1%)	39 (29.1%)
Felt Tense	22 (16.4%)	15 (11.2%)	7 (5.2%)	46 (34.3%)	44 (32.8%)
Physical Disability					
Unsatisfactory to Diet	5 (3.7%)	13 (9.7%)	12 (9.0%)	29 (21.6%)	75 (56.0%)
Had to Interrupt Meals	46 (34.3%)	30 (22.4%)	28 (20.9%)	16 (11.9%)	14 (10.4%)
Psychological Disability					
Difficult to Relax	81 (60.4%)	15 (11.2%)	10 (7.5%)	17 (12.7%)	11 (8.2%)
Embarrassed	86 (64.2%)	28 (20.9%)	9 (6.7%)	3 (2.2%)	8 (6.0%)
Social Disability					
Irritable with Other People	65 (48.5%)	24 (17.9%)	11 (8.2%)	18 (13.4%)	16 (11.9%)
Difficulty Doing Usual Jobs	64 (47.8%)	23 (17.2%)	13 (9.7%)	22 (16.4%)	12 (9.0%)
Handicap					
Life Was Less Satisfying	96 (71.6%)	19 14.2%)	8 (6.0%)	4 (3.0%)	7 (5.2%)
Unable to Function	59 (44.0%)	27 (20.1%)	17 (12.7%)	16 (11.9%)	15 (11.2%)

The findings showed a significant association ($p<0.001$) between the cancer site and OHIP-14 scores. Poor OHIP impact was prevalent in tongue and hard palate cancers, while strong impact was most common in the buccal mucosa (52.9%) and floor of mouth (30.6%) cancers (Table 3).

Table 3: Association Between the Site of Cancer and OHIP-14

OHIP-14	Site of Oral Cancer					
	Tongue	Hard Palate	Buccal Mucosa	Floor of Mouth	LIP	p-value
Poor Impact: 0≤ to≤9	7 (50.0%)	6 (42.9%)	0	0	1 (7.1%)	<0.001*
Average Impact: 10≤ to ≤18	7 (20.0%)	11 (31.4%)	2 (5.7%)	3 (8.6%)	12 (34.3%)	
Strong Impact: score>18	7 (8.2%)	7 (8.2%)	45 (52.9%)	26 (30.6%)	0	

*Fishers Exact Value: <0.001 Shows Significant Associations

DISCUSSION

A study on oral cancer reported that age or sex variations were not significantly different at any of the sites and the most common tumors were located on the anterior tongue, followed by the buccal mucosa [12]. Based on other research, the tongue was the place most frequently afflicted, then the gingiva [13]. In another study, the head and neck cancer group had a mean age of 49.75 ± 13.44 years and the most common cancer cases were aged 35-64 years. Males predominated in both groups (66% in the cancer group, and 70% in controls). Cancer was most common on the tongue (36%) [14]. The OHIP-14 responses showed that most patients reported difficulty with daily tasks (21%), tension (21%), irritability (22%), worry about dental issues (32%), discomfort while eating (33%), and unsatisfactory diet (35%). After treatment, these responses improved, except for tension [15]. A study conducted on oral cancer revealed the mean index value was 4.64 before treatment which then declined to 4.25 post-treatment, highlighting the impact of treatment on patients' well-being [16]. A cross-sectional study with 133 oral cancer patients using OHIP-14 found over 95% reporting negative impacts on oral health-related quality of life. The highest impacts were on eating (83.5%), speaking (77.4%), and emotional status (64.7%), with physical pain, functional limitations, and disability being the most affected dimensions [17]. The findings of the current study showed a significant association ($p<0.001$) between cancer sites and OHIP-14 scores. Poor OHIP impact was observed in tongue and hard palate cancers, while the strong impact was most frequent in the buccal mucosa (52.9%) and floor of mouth (30.6%) cancers. Studies that were previously conducted reported the mean OHIP-14 scores for various tumor sites. Patients with mandibular tumors had the highest mean score (31.60 ± 15.73), indicating the greatest oral health impact, followed by those with loco-regional metastasis (30.33 ± 10.70) while the lip cancers had the

DOI: https://doi.org/10.54393/pjhs.v6i1.2274

lowest mean score (16.00 ± 14.99), suggesting a lesser impact [18]. According to a study conducted, the OHIP scores for various cancers consistently indicated worse outcomes, reflecting significant disturbances in oral health. These disturbances adversely affected patients' quality of life, highlighting the widespread impact of oral complications across different cancer types [19]. Patients with buccal mucosa cancer exhibited a lower quality of life, highlighting the need for regular follow-ups and supportive therapy. Preoperative psychological reassurance was essential for enhancing postoperative adaptation to psychosocial challenges [20].

CONCLUSIONS

It was concluded that the location of oral cancer significantly impacts patients' quality of life. Policymakers should enhance outcomes by improving access to specialized dental care, and psychosocial support, and integrating routine quality-of-life assessments into cancer care protocols.

Authors Contribution

Conceptualization: SGSS
Methodology: SGSS, SLSS, AH, ZURK, AM, FJS
Formal analysis: SLSS
Writing review and editing: ZURK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2274

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DOI: https://doi.org/10.54393/pjhs.v6i1.2109

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Adverse Perinatal Outcomes: Their Association with Maternal Anemia

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ARTICLE INFO

Keywords:
Anemia, Pregnancy, Perinatal outcomes, Hemoglobin, Iron supplementation

How to Cite:
Aziz, A., Parveen, S., Khan, B., Sultana, H., Akhtar, A., & Raza, K. (2025). Adverse Perinatal Outcomes: Their Association with Maternal Anemia : Perinatal Outcomes with Maternal Anemia. Pakistan Journal of Health Sciences, 6(1), 107-111. https://doi.org/10.54393/pjhs. v6i1.2109

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Received Date: 27th September, 2024
Acceptance Date: 19th January, 2025
Published Date: 31st January, 2025

ABSTRACT

The incidence of anemia during the third trimester of pregnancy correlates with a heightened risk of negative postnatal outcomes. **Objective:** To access the relationship between hemoglobin levels in laboring women and perinatal outcome. **Methods:** A prospective cohort study was done at Department of Obstetrics and Gynecology, Nishtar Hospital, Multan from September 2020 to December 2021 using non-probability purposive sampling technique. A total of 135 anemic pregnant women (Group A) fulfilling inclusion and exclusion criteria was recruited for the study from labour room plus 135 non-anemic women were also recruited as control group (Group B). The data was recorded and explored. **Results:** 135 anemic laboring pregnant ladies were taken in this study having mean age 25.63 ± 4.53 years (range; 19-37 years) and 85.2% had ages less than 30 years. Cesarean section deliveries were noted to be in 50.4% in group A (anemic women) versus 48.1% in group B (non-anemic women). Preterm birth was noted to be 29.6% in group A versus 6.7% in group B. Small for gestational age was 53.3% in group A versus 12.6% in group B. Low birth weight was 54.8% in group A versus 16.3% in group B. Still birth was 7.4% only in anemic women while it was not observed in control group. **Conclusions:** The results of this study supported strong relationship of low haemoglobin in mothers with untoward perinatal outcome; growth retarded babies, preterm, Low birth weight and cesarean section rate. Strong media awareness campaigns should be launched for awareness for iron supplementation among targeted population.

INTRODUCTION

The World Health Organization (WHO) has estimated that around 2 billion world population or approximately one third of the people are affected with anemia and recent estimated have shown great variation in its burden among pregnant women. Maternal anemia is more prevalent in developing countries particularly Africa and Southeast Asia, where it can be encountered in as many as 35-75% of total pregnancies while it is less than 20% in developed nations [1, 2]. The sustainable development goals take very clear steps towards nutritional status that incudes the World Health Assembly targets for scaling down anemia in reproductive age groups (15-49 years) to half by 2025 [3, 4]. The threshold up to which anemia in pregnant women can affect perinatal outcomes still inconclusive due to certain issues such as; insufficient biological factors, social and economic conditions, different environmental conditions and changes in lifestyle modifications as well as prior to or during pregnancy may be implicated in high burdens of low birth weight [5]. Various dietary habits, such as taking low nutritional diets and lower weight gains in pregnancy, are contributing factors towards low intake of the nutrients required which are measured as necessary for the growth of the fetus for example vitamin B and iron. Ionic iron is the essential mineral which may promote the synthesis of new hemoglobin molecules as well as it is the major basis for energy and required in transporting the oxygen to various organs of the body [6, 7]. Lower concentrations of hemoglobin (Hb%) may promote various changes in angiogenesis of placenta which may restrict supply of oxygen thus limiting fetal growth. This may consequently

DOI: https://doi.org/10.54393/pjhs.v6i1.2109

lead to certain adverse events such as intrauterine growth restriction and may lead to low birth weight [8, 9]. Recent studies have demonstrated that anemia in pregnancy i.e. Hb levels less than 11g/dl is noticeably associated with birth weight less than gestational age in babies in comparison with those ladies having normal hemoglobin levels during pregnancy [10, 11].

Hence, this study has been done to explore the role of maternal hemoglobin levels with adverse perinatal outcomes in the anemic new moms of Southern Punjab, Pakistan to ascertain role of hemoglobin levels with such adverse outcomes.

METHODS

It was a prospective cohort study, carried out at Department of Obstetrics and Gynecology, Nishtar Hospital, Multan from September 2020 to December 2021 using non-probability purposive sampling technique. The study was approved by the Institutional Ethical Review Board of Nishtar Medical University; Multan vide Reference No. 14417-27/NMU. Iron deficiency anemia in third trimester was defined as Hemoglobin <11g/dl and serum ferritin < 30 microgram/liter according to WHO. Inclusion criteria were laboring mothers with maternal age 18-45 years, primigravida or multi gravida (up to 3) and singleton pregnancy accessed by ultrasound. All women selected were otherwise having uncomplicated pregnancies with body mass index of 18.5-24.9kg/m^2. Exclusion criteria were laboring mothers with multiple pregnancies, medical disorders like diabetes, hypothyroidism, hyperthyroidism, Hypertension, Ischemic heart disease, valvular heart disease, previous history of preterm births and malignancy were precluded from the study. Babies born with neonatal sepsis, birth asphyxia and meconium aspiration were excluded. Sample size was 270 pregnant women calculated by following formula. $n = z^2\ pq/d^2$, where, p = 75% (hypothesized frequency of need of NICU admission in newborn of anemic women), q = 100 - p, d = 5.2% margin of error), z = 1.96 (95% confidence) [12]. Sample was divided into two equal groups of anemic (Group A) and non-anemic women (Group B). Women were recruited for the study from labour room after informed consent and was assured of their confidentiality. Detail history was taken from laboring mothers regarding number of children before current pregnancy, inter birth interval, menstrual irregularities, pregnancy termination. Small for Gestational Age (SGA), Low Birth Weight (LBW), and stillbirths, were measured by comparing the frequency of these outcomes in the anemic group (Group A) with the non-anemic group (Group B). The reference values for SGA and LBW were based on the World Health Organization's criteria for gestational age-specific growth percentiles and weight thresholds, respectively. Stillbirths were recorded based on the absence of signs of life at birth, as per the hospital's standard clinical definitions. The data were recorded and explored by using SPSS version 27.0. Descriptive statistics was used to summarize data. Maternal outcomes such as mode of delivery and preterm labour was analyzed in both groups. Fetal outcomes like small for gestational age, low birth weight, still birth, and NICU admission were studied in the anemic and non-anemic group. The Hb% levels of women during labour and birth weights were extracted from the labour room record. Mean or median with respective measures of dispersion was calculated for quantitative variables like age, gestational age of patient. Frequencies and percentages were calculated for categorical variables like maternal anemia and birth weight of baby. Effect modifiers like age, gestational age and parity was controlled by stratification. Post stratification chi-square test was applied to see their effect on outcome. All tests were two sided and judged statistically significant at $p<0.05$.

RESULTS

A total of 135 anemic laboring pregnant ladies were taken in this study having mean age 25.63 ± 4.53 years (range; 19-37 years) and 115 (85.2%) had ages less than 30 years. Of these 135 laboring anemic women, 53 (39.3%) belonged to rural areas and 82 (60.7%) belonged to urban areas. Majority of these women were poor 90 (66.7%) and 45 (33.3%) were middle income. Similarly, 97 (71.9%) were illiterate while 117 (86.7%) were house-wives and 79 (58.5%) were living in joint family system. Only 26 (19.3%) were having regular antenatal monthly visits to the hospital. Overall Hb level was 10.04 ± 0.46 g/dl in anemic women and 11.57 ± 0.54 g/dl in non-anemic women. Maternal outcome like cesarean section deliveries were noted to be in 50.4% in group A versus 48.1% in group B (P = 0.715). Preterm labour resulting in preterm delivery was noted to be 29.6% in group A versus 6.7% in group B (P = 0.001). Small for gestational age was 53.3% in group A versus 12.6% in group B (P = 0.001). Low birth weight was 54.8% in group A versus 16.3% in group B (P = 0.001). Still birth was 7.4% only in anemic women while it was not observed in control group. NICU admission was 67% among anemic women. Early neonatal deaths were never reported in any group.

Table 1: Association of Maternal Hemoglobin Levels with Maternal Outcomes

Maternal Outcomes	Hemoglobin Levels (gm/dL)		p-Value
	Group A Mean ± SD	Group B Mean ± SD	
Mode of Delivery (Cesarean Deliveries)			
Yes	9.64 ± 0.36	11.23 ± 0.77	0.001
No	10.97 ± 0.88	11.84 ± 0.23	
Preterm Labour			
Yes	9.32 ± 0.42	11.51 ± 0.32	0.001
No	10.98 ± 0.97	11.91 ± 0.63	

DOI: https://doi.org/10.54393/pjhs.v6i1.2109

The association between maternal hemoglobin levels and neonatal outcomes is presented in Table 2. For neonates classified as Small for Gestational Age (SGA), the mean hemoglobin level was significantly lower in anemic mothers (Group A: 9.64 ± 0.41) compared to non-anemic mothers (Group B: 11.31 ± 0.42, p = 0.001). Among non-SGA neonates, the hemoglobin levels were higher in both groups, with Group A at 10.77 ± 0.88 and Group B at 11.88 ± 0.71. Similarly, Low Birth Weight (LBW) neonates were more prevalent in Group A, with a mean hemoglobin level of 9.74 ± 0.46 compared to 11.51 ± 0.49 in Group B (p = 0.001). For non-LBW neonates, hemoglobin levels in Group A and Group B were 10.90 ± 0.70 and 11.71 ± 0.67, respectively. Stillbirths were reported exclusively in Group A, with a mean hemoglobin level of 9.52 ± 0.37 (p = 0.001), while no cases were observed in Group B. These findings underscore the significant impact of maternal anemia on adverse neonatal outcomes, including SGA, LBW, and stillbirths.

Table 2: Association of Maternal Hemoglobin Levels with Neonatal Outcomes

Neonatal Outcome	Group A Mean ± SD	Group B Mean ± SD	p-Value
Small For Gestational Age			
Yes	9.64 ± 0.41	11.31 ± 0.42	0.001
No	10.77 ± 0.88	11.88 ± 0.71	
Low Birth Weight			
Yes	9.74 ± 0.46	11.51 ± 0.49	0.001
No	10.90 ± 0.70	11.71 ± 0.67	
Still Births			
Yes	9.52 ± 0.37	NA	0.001
No	10.85 ± 0.89	NA	

DISCUSSION

Maternal anemia still remains global health issue with most of the burden falls among developing countries such as Africa, Southeast Asia and in this country, Pakistan [13]. Recent estimates have demonstrated that these countries harbor maternal anemia as much as double high in comparison with developed countries. Data have shown maternal anemia may affect 35-75% of pregnancies developing countries while this figure drops to be 19% for developed countries. It was well narrated that maternal anemia was a powerful predictor for poor perinatal outcomes (both maternal and neonatal) such as low birth weight, preterm deliveries, NICU admissions, small for gestational age and still births [14]. Furthermore, recent reports from developing nations have also implicated maternal mortality was two times high among severely anemic pregnant women [15]. A total of 135 anemic laboring pregnant ladies were taken in this study having mean age 25.63 ± 4.53 years (range; 19-37 years) and 115 (85.2%) had ages less than 30 years. Debella A *et al.*, from Ethiopia has also reported 26.6 ± 6.15 years mean age of the anemic pregnant women, similar to this case series [16]. Mahmood T *et al.*, from Bahawalpur has also reported 29.4 ± 12.5 years mean age of the anemic pregnant ladies, similar to these results [17]. Bone JN *et al.*, from India has reported similar findings among anemic pregnant women [18]. Kabir MA *et al.*, from Bangladesh has also described 25.71 years mean age of the anemic pregnant women, similar to these results [19]. Baig JA *et al.*, has also reported 28.85 ± 5.12 years mean age of the anemic pregnant women, similar to this study results [20]. Of these 135 laboring anemic women, 53 (39.3%) belonged to rural areas and 82 (60.7%) belonged to urban areas. Debella A *et al.*, from Ethiopia has also reported 38.8% anemic pregnant women were from rural areas, like these findings [16]. Kabir MA *et al.*, from Bangladesh has also reported 32% of the anemic pregnant women from rural areas, same as these results [19]. Majority of these women were poor 90 (66.7%) and 45 (33.3%) were middle income. Debella A *et al.*, from Ethiopia has also reported findings like this study [16]. Kabir MA *et al.*, from Bangladesh has also reported majority of the anemic pregnant women were poor, just like these results [19]. Baig JA *et al.*, has also reported same end result [20]. Similarly, 97 (71.9%) were illiterate while 117 (86.7%) were house-wives and 79 (58.5%) were living in joint family system. Only 26 (19.3%) were having regular antenatal monthly visits to the hospital. Debella A *et al.*, from Ethiopia also reported 49.2% of the anemic pregnant women were housewives and 40% were illiterate, similar to these results [16]. Kabir MA *et al.*, from Bangladesh has also reported 89% of the anemic pregnant women were housewives, similar to these results [19]. Baig JA *et al.*, has also reported 64% of anemic pregnant women were living in joint family system, similar to the study results [20]. Cesarean section deliveries were noted to be in 50.4% in group A versus 48.1% in group B (P = 0.715). Mahmood T *et al.*, from Bahawalpur has also reported 45% cesarean section rate among anemic pregnant ladies, similar to our results [17]. Preterm birth was noted to be 29.6% in group A versus 6.7% in group B (P = 0.001). Debella A *et al.*, from Ethiopia has also reported 22.2% preterm births among anemic pregnant women, similar to our results [16]. Mahmood T *et al.*, from Bahawalpur has also reported 39% preterm birth among anemic pregnant ladies versus 15% among control group (P=0.001), similar to our results [17]. Kabir MA *et al.*, from Bangladesh has also reported 40.5% preterm births among anemic pregnant women, similar to our results [19]. Baig JA *et al.*, has also reported 36% preterm births among anemic pregnant women compared with 18% in non-anemic group (P=0.001), similar to these study results [20]. Low birth weight was 54.8% in group A versus 16.3% in group B (P = 0.001). Debella A *et al.*, from Ethiopia has also reported 18.8% low birth weight among anemic pregnant women, lower than our results [16]. Mahmood T *et al.*, from Bahawalpur has also reported 59% low birth weight among

DOI: https://doi.org/10.54393/pjhs.v6i1.2109

anemic pregnant ladies versus 23% in control group (P=0.001), similar to our results [17]. Kabir MA *et al.*, from Bangladesh has reported 18.3% low birth weight among anemic pregnant women [19]. Baig JA *et al.*, has also reported 63% low birth weight among anemic pregnant women versus 18% in non-anemic group, similar to our study results [20]. Small for gestational age was 53.3% in group A versus 12.6% in group B (P = 0.001). Mahmood T *et al.*, from Bahawalpur has also reported 73% small for gestational age among anemic pregnant ladies versus 23% among control group, similar to our results [17]. Still birth was 7.4% only in anemic women while it was not observed in control group. Debella A *et al.*, from Ethiopia has also reported 4.9% still births among anemic pregnant women, just like our results [16]. Mahmood T *et al.*, from Bahawalpur has also observed 8% still births among anemic pregnant ladies versus 3% among control group, same to our results [17]. Another study by Kabir MA *et al.*, in Bangladesh has also stated 8% still births rate among anemic pregnant women, close to our outcome [19]. Baig JA *et al.*, has also mentioned same findings [20].

CONCLUSIONS

These results supported that strong relationship of maternal anemia with deleterious perinatal sequel. Low birth weight, growth retarded babies, cesarean section rate and preterm births were the major adverse outcomes observed in our study. Mean hemoglobin level was significantly lower among anemic pregnant women with adverse events as compared with those having normal pregnancy outcomes. Strong media awareness campaigns should be launched at national level for awareness for iron supplementation among targeted population to overcome these adverse events.

Authors Contribution

Conceptualization: AA[1]
Methodology: BK, HS, AA[2], KR
Formal analysis: BK, HS
Writing, review and editing: AA[1], SP

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2595

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Knowledge and Practices of Breast Self-Examination among Female Students of Bahria University of Health Sciences Karachi

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ARTICLE INFO

Keywords:
Breast Self-Examination, Awareness, Knowledge, Practice, Cancer Detection, Health Education

How to Cite:
Tanwir, F., Razzaq, A., Ijaz, B., Bibi, T., Hafeez, N., Gulzada, M., & Fahim, M. F. (2025). Knowledge and Practices of Breast Self-Examination among Female Students of Bahria University of Health Sciences Karachi: Breast Self-Examination Knowledge and Practices. Pakistan Journal of Health Sciences, 6(1), 112-118. https://doi.org/10.54393/pjhs.v6i1.2595

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Received date: 5th November, 2024
Acceptance date:23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

Breast Self-Examination is an efficient approach for investigating physical and visual abnormalities in breast tissue. **Objective:** To evaluate the awareness, knowledge, practice of breast self-examination among female university students in five colleges of Bahria University Health Sciences Karachi. **Methods:** A cross-sectional study at Bahria University Health Sciences Campus Karachi with random sampling among female students from the Dental, Medical, Doctor of Physical Therapy, Nursing sections and Medical Laboratory Technicians. The data were collected using a self-administered google questionnaire form distributed online via WhatsApp. The questionnaire encompassed sections on the socio-demographic characteristics of the participants, as well as their awareness, knowledge, attitude, and practice towards BSE. For data analysis SPSS Software version 25.0 was used. **Results:** 240 female participants were enrolled in study, 77.5% knew the meaning of BSE, while 31.7% had complete knowledge. 5.4% BDS students did it in routine practice, 63% believed, it helps in cancer monitoring, 22.8% performed to detect nodules and 8.7% carried out because of family history. Out of 110 participants from nursing section, 7.3% followed BSE in routine practice, 65.5% believed it's beneficial in the detection of cancer. However, the main reason for performing was detection of cancer 62.9%. Several barriers were encountered such as time constraint, lack of knowledge 46.7%, uncomfortable 6.7%, fear 30.4% and misconception. **Conclusions:** Participants had understanding of BSE but they lacked complete knowledge of breast self-examination due to limited access to health care resources and insufficient understanding about the technique also encounter significant barriers during practicing.

INTRODUCTION

Breast cancers hold a significant global health concern, standing as an important cause of mortality affecting women worldwide. It is characterized by abnormal cell growth forming undifferentiated masses. Symptoms include breast lump, change in shape, size and skin, redness and nipple discharge from it. If left untreated the tumor can metastasize. International prevalence data shown by WHO is 2.3 million cases annually, with 685,000 deaths. Over five years, 7.8 million women have been diagnosed, marking it as the most prevalent global cancer [1, 2]. At national level, breast cancer affects one in four women, with an incidence 4.5 times higher than other cancers [3]. Annually, 1.38 million new cases arise globally, with 0.46 million fatalities. Early detection can render 99% of cases treatable [4]. Moreover, according to the age distribution, 25-49 year was the range in which it was observed with the highest rate of 34.2% in contrast with other age groups. Risk factors such as oral contraceptive usage, cigarette smoking, obesity, high body mass, increasing age, high intake of dairy products and poor nutrition such as vitamin D deficiency are most commonly found in latest literature [5-8]. Additionally, familial history

DOI: https://doi.org/10.54393/pjhs.v6i1.2595

of breast cancer imparts a major role in the development of the disease. Also reproductive factors like menopause, early menarche and hormonal therapies contribute to risk [9, 10]. Screening methods recommended by health professionals for breast cancer investigation includes Breast Self-Examination (BSE), clinical breast examination and mammography. BSE is most cost effective and easy procedure for the woman as it ensures breast lump at earliest. It is a basic and efficient approach for investigating any physical and visual abnormalities in the breast tissues [11-13]. Early diagnosis is important for successful treatment and can notably reduce morbidity and mortality associated with breast cancer; particularly in areas where identification of cancer and management is limited. Hence, BSE appears as a more reachable preference for detecting abnormalities [14, 15].

Therefore, this research aimed to evaluate the awareness, knowledge, and practice of BSE among female university students in various health disciplines at Bahria University Health Sciences Karachi, while also assessing barriers to BSE to provide insights for curriculum integration and targeted educational initiatives.

METHODS

A cross-sectional study was carried out at Bahria University Health Sciences Karachi, from June to December 2023. Ethical approval was obtained from Committee of the PNS SHIFA (ERC/2023/DENTAL/67). The study focused on female students from the Dental, Medical, Doctorate of Physical Therapy, Nursing sections and Medical Laboratory Technicians. Inclusion criteria involved, females who were 17 years of age and older, who were studying in Bahria University Health Sciences and those who gave consent, whereas exclusion criteria focused on those females who were not agree to participate. Questionnaire was utilized as the primary data collection method, with a total of 240 female students. It was a self-administrative questionnaire; validity of questionnaire was checked using Cronbach's alpha test via SPSS. Alpha value was observed to be 0.81(good). Participants were selected through simple random sampling and the data were collected using a self-administered google questionnaire form distributed online via WhatsApp. The questionnaire encompassed sections on the socio-demographic characteristics of the participants, as well as their awareness, knowledge, attitude and practice towards BSE [16]. Calculation of the sample size was done using OpenEpi software. Sample size was determined at a 95% confidence level to achieve a balance between precision and confidence in estimating the proportion of interest. The assumed prevalence for larger sample was considered as 50%. The required sample was found to be 218 ± 10%. However, we considered 240 subjects as sample. For data collection, the collected data were entered into Microsoft Excel for organization and further analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 25.0. Continuous variables were analyzed using mean and standard deviation, while categorical variables were presented as frequency and percentages. Further data variables were showed using stacked bar chart.

RESULTS

The study involved 240 females, 113 (47%) were aged between 17-20 years, while 111(46%) were aged between 21-24 years. In terms of discipline, 92(38.3%) were from Dental section, 110 (45.8%) were from Nursing Department, 26 (10.8%) from Doctor of Physical Therapy (DPT), 3(1.3%) from Medical Laboratory Technician (MLT) and 9 (3.8%) participants from MBBS. In addition, 78(32.5%) were in first year, 44 (18.3%) were in second year, 48 (20%) from third year, 40 (16.7%) from fourth year and 30 (12.5%) from final year. Sources of information of participants regarding BSE: such as books 8.3%, social media/ print media 35.4%, from hospital 10% and 40.8% from class/workplace. Data revealed that 10.8% subjects were aware of the maternal predilection of breast cancer in their family. However, only 5% expressed paternal familial history. But a major percentage of 82.5% participants were completely unaware (Table 1).

Table 1: Base Line Characteristics of Participants (N=240)

Variables	Responses	N (%) / Mean ± SD
Age Group	17-20	113 (47.1%)
	21-24	111 (46.3%)
	> = 25	16 (6.7%)
Discipline	MBBS	9 (3.8%)
	BDS	92 (38.3%)
	Nursing	110 (45.8%)
	DPT	26 (10.8%)
	MLT	3 (1.3%)
Academic Year	1st Year	78 (32.5%)
	2nd Year	44 (18.3%)
	3rd Year	48 (20%)
	4th Year	40 (16.7%)
	5th Year	30 (12.5%)
Source of Information	Books	20 (8.3%)
	Social/Print Media	85 (35.4%)
	Hospital	24 (10.0%)
	Friends	13 (5.4%)
	Class/Workplace	98 (40.8%)
Familial Breast Cancer History	Maternal Side	26 (10.8%)
	Paternal Side	12 (5.0%)
	None	202 (84.6%)
Do you know at what age it's important to start BSE?		
Mean ± SD (Years)		21.39 ± 8.11
Range		(12-50 Years)

DOI: https://doi.org/10.54393/pjhs.v6i1.2595

Awareness of participants regarding Breast Self-Examination (BSE) is documented in table 2. Participants were asked about the awareness and their responses were recorded as "Yes ", "No" and "Don't Know. Following questions were asked as written in table. Out of 240 participants, 77.5% knew what BSE stands for whereas 54.2% were able to perform BSE, 28.7% had answered no regarding the performance. Moreover 31.7% had complete knowledge about breast self-examination and majority 47.5% lacked complete knowledge. Additionally, majority participants 96.7% consider BSE as an essential practice. Whereas only 16.3% practiced BSE routinely however during practicing only 7.9% found a mass during self-examination. Likewise, 77.1% consider it essential and 62.5 % responders had been taught about BSE in their medical school(Table 2).

Table 2: Describe the Awareness of Breast Self-Examination (BSE)among Participants(N=240)

Awareness of Participants	Yes N(%)	No N(%)	Don't Know N(%)
Do you know what BSE stands for?	186(77.5%)	39(16.3%)	15(6.3%)
Are you able to perform BSE?	130(54.2%)	69(28.7%)	41(17.1%)
Do you have complete knowledge about BSE?	76(31.7%)	114(47.5%)	50(20.8%)
Do you think BSE is important?	232(96.7%)	3(1.3%)	5(2.1%)
Is Breast Self-Examination in your routine practice?	39(16.3%)	182(75.8%)	19(7.9%)
Did you ever Found a mass or lump while performing BSE?	19(7.9%)	197(82.1%)	24(10%)
Is it appropriate to perform BSE?	185(77.1%)	30(12.5%)	25(10.4%)
Have you heard or been taught in university about BSE?	150(62.5%)	83(34.6%)	7(2.9%)

Figure 1 depicted the correlation of participants enrolled in different discipline and the barriers encountered while practicing BSE. Majority participants lacked information and anxious about the results. Among 92 participants who were enrolled in BDS: 46(50%) lacked basic knowledge, 7 (7.6%) were uncomfortable with the process where as 26 (28.3%)apprehended about the results and 13(14.1%)took it as a misconception. Out of 110 from Nursing: 44(40%) had insufficient knowledge about BSE, 8 (7.3%) were uncomfortable, 38(34.5%)were frightened by the outcome and 20(18.2%)had misconception about it.

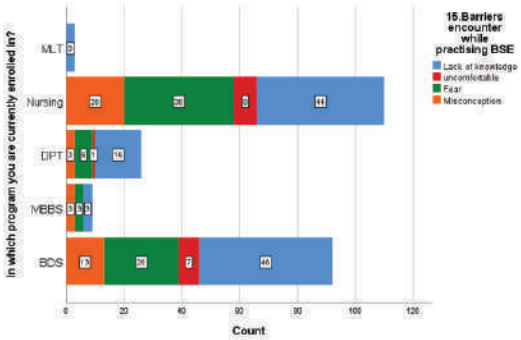

Figure 1: Correlation of Participants and Barriers Encounter during Practicing BSE

Table 3 illustrated knowledge and practice of participants regarding BSE. This section inquired about knowledge related to BSE through the following questions. Out of 240 participants, the majority 83.8% self-monitored themselves while 24% reported to the doctor for the BSE evaluation, 5.8% reported to the trained nurses, and 4% sought advice from their mother. Besides, 89.6% participants were renowned that it could be done manually, 3.3% responders familiar that it could be done through CT scan, 2.5% via ultrasound and 2.5% using specialized instruments. Concerning how BSE is performed 77% participants mentioned it could be done by palpating or feeling the breast manually, 15.8% individuals supposed by observing oneself in the mirror. As far as significance of BSE is concerned 82.5% participants considered that it helps in detection of early breast cancer, only 12.5% believed an important part of routine. After finding a mass/lump 95.4% participants had knowledge that they would report it to physician. The vast majority 94.2% were familiar that it could transform into cancer. However, 5.8% were heedless to fact. Also 69.6% responders assumed that the best time to carry out BSE is after menstruation, 2.9% after post pregnancy, 3.8% during first trimester, and 7.1% during lactation. Almost two thirds of the participants 69.8% agreed that BSE is a time taking procedure. Furthermore, the best age to start BSE as a routine practice, half of the responders 70% believed it should be initiated as soon as puberty starts. Only 35.7% deem that they had sufficient knowledge about BSE. This section inquired about practice related to BSE as mentioned in table. Almost half of the participants 49.6% examined their breasts for any abnormalities. 69% considered that it's a prolonged procedure. Barriers encountered while performing BSE includes the following: 46.7% lacked basic Knowledge of BSE, 6.7% were uncomfortable with the procedure and 16.3% considered it a misconception and 30.4% feared about the results.

Table 3: Knowledge and Practice routine of participant regarding Breast Self-Examination(BSE)(N=240)

Variables	Responses	N(%)
BSE is performed by?	Doctor	24(10%)
	Trained Nurse	14(5.8%)
	Mother	1(.4%)
	Yourself	201(83.8%)
BSE is performed with?	CT Scan	8(3.3%)
	Ultrasound	6(2.5%)
	Manually	215(89.6%)
	Specialized Instrument	6(2.5%)
	None	5(2.1%)
BSE is Performed as?	Observing the radiograph	8(3.3%)
	Palpating/Feeling the Breast Manually	185(77.1%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2595

	Observing Yourself in Front of Mirror	38 (15.8%)
	Inspection by a nurse	2 (.8%)
	Don't know	7 (2.9%)
What is Significance of BSE?	Diagnostic Criteria by Doctors	8 (3.3%)
	Helps in Detection of Early Breast Cancer	198 (82.5%)
	Important Part of Routine Medical Checkup	30 (12.5%)
	Don't know	4 (1.7%)
What Action You'll Take After Finding a Mass/Lump During BSE?	Visit a Doctor	229 (95.4%)
	Go to a Laboratory	4 (1.7%)
	Do Home Remedies	3 (1.3%)
	Nothing	4 (1.7%)
Can a Mass/Lump have Transformed into Cancer?	Yes	226 (94.2%)
	No	14 (5.8%)
What is the Best Time to Perform BSE?	After Menstruation	167 (69.6%)
	Post Pregnancy	7 (2.9%)
	During First Trimester	9 (3.8%)
	During Lactation	17 (7.1%)
	Don't Know	40 (16.7%)
What is the Best Age to Start BSE as a Routine?	Beginning of Puberty	169 (70.4%)
	From 25 Years	33 (13.8%)
	From 35 Years	9 (3.8%)
	In late 40s after Menopause	3 (1.3%)
	Don't Know	26 (10.8%)
Do you Think you have Appropriate Knowledge about BSE	Yes	85 (35.4%)
	No	86 (35.8%)
	Don't Know	69 (28.7%)
Practicing Breast Self-Examination		
Do you examine Breast for any Abnormalities?	Yes	119 (49.6%)
	No	121 (50.4%)
BSE is time Taking Procedure?	Agree	165 (69.8%)
	Disagree	75 (31.3%)
Reason for Practice BSE	Routine Practice	13 (5.4%)
	Early Detection of Cancer	151 (62.9%)
	Presence of Nodule	42 (17.5%)
	Family History	34 (14.2%)
Barrier Encounter while Performing BSE	Lack of Knowledge	112 (46.7%)
	Uncomfortable	16 (6.7%)
	Fear	73 (30.4%)
	Misconception	39 (16.3%)

Figure 2 depicted the correlation between participants enrolled in different discipline and their reason for practicing BSE. The majority performed BSE as it would help in early detection of cancer and nearly half did due to presence of a nodule. Among 92 participants who were enrolled in BDS: 5 (5.4%) considered it a routine practice, 58 (63%) believed it would help in monitoring of cancer whereas 21 (22.8%) performed to detect nodules and 8 (8.7%) supposed it would be carried out because of family history. Out of 110 participants from Nursing section 8 (7.3 %) considered it should be implemented it in practice routine, 72 (65.5%) believed it would be beneficial in the detection of cancer whereas 13 (11.8%) deemed it should be executed to find out nodules and 17 (15.5%) supposed it should be performed of because of familial history as shown in figure 2.

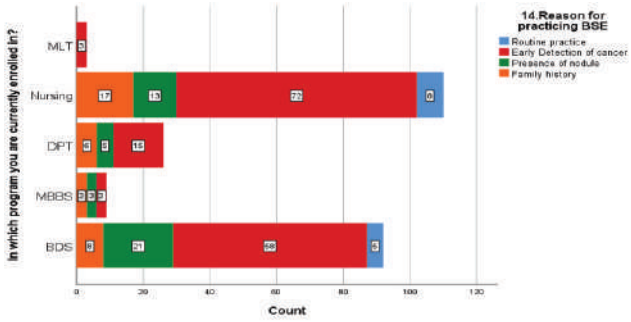

Figure 2: Correlation of Participants and Reason for practicing Breast Self-Examination

DISCUSSION

Breast Cancer is second leading cause of death. Early detection through routine screening can significantly reduce mortality and morbidity rates. Breast Self-Examination is a convenient approach for identifying breast abnormalities. According to Workineh et al., BSE is recommended for women aged of 20 and above, preferred monthly for 20 minutes, between the 7th and 10th days of the menstrual cycle (2–3 days' post-menses) [12, 17]. On the contrary, Ferdowsy, highlighted that women are still unmindful to the term BSE. It concludes that there is a substantial lack in comprehensive knowledge about BSE. Besides, some participants understood the definition and technique however they lacked comprehension of its significance, clinical relevance, and outcomes, leading to scarce execution of routine BSE [19]. Approximately 75.8% of women did not perform BSE due to insufficient understanding, inadequate guidance and not prioritizing it and considering themselves at low risk of cancer. Similar findings were observed in studies conducted in Nigeria, Ethiopia and Cameroon [20-24]. In comparison to this, study conducted by Ogunkayode and Ajuwon found only 9.5% females had good knowledge and practice of BSE [25]. In this study, (50%) BDS and (40%) Nursing women's had insufficient BSE knowledge. Despite being in healthcare fields, their curriculum may lack emphasis on breast health education, indicating barriers to effective health promotion training. Most of the participants of this study stated that time constraints and fear were common barriers to performing BSE. This Fear can notably discourage women in executing BSE regularly; may be because the participants were young and had insufficient knowledge and experience of BSE. This study highlighted the sources of knowledge about BSE among participants, the most familiar being social/print media and university (40%). This aligns with a study conducted in Baghdad that highlighted significant role of mass media's in

DOI: https://doi.org/10.54393/pjhs.v6i1.2595

disseminating BSE knowledge by using diverse medium such as social media (Instagram, Facebook and YouTube) print media (Newspaper, magazines, brochures). Whereas, this study showed that the best source of information observed in the data were found primarily to be the curriculum followed by the health campaigns organized by University management in campus. Despite this, a significant knowledge gap persists regarding risk factors, particularly familial predisposition, which needs more emphasis. On the contrary literature has shown studies where participant had substantial knowledge about family history regarding breast cancer [26]. Attitude regarding BSE adoption in routine is not much appreciable, significantly observed attributes to this pattern includes knowledge gap among females regarding its prevalence and alarmingly increasing ratio, neither they are internally motivated to follow BSE until pain or mass is felt in mammary glands [19]. Regarding maneuvers to execute BSE, this study participant was aware that it could be done by palpating or feeling breast manually, consistent with the female Ethiopian study. A surprise finding was participants were aware that BSE should be done after menstrual cycle, breast show abnormal change and a study by KSU students showed similar results which could be due to different source of information and education level of participants [27]. Early Detection of cancer was the main reason reported by participants for performing BSE. This aligns with the research done by Hijrah H *et al.*, resulted as only 22% understood breast self-examination helps in early detection [23]. Hence organization should incorporate detail awareness programs into dental, nursing, medical and allied health programs. This will increase significance of early detection and emphasize self-examination as a preventive tool. Practice of BSE was found difficult by the participants due to anxiety of detecting abnormalities is a common barrier often associated with low health literacy and fear about cancer [28]. Addressing these barriers through counseling, emotional support, and hands-on training as part of the curriculum could improve outcomes. Practicing BSE was limited also due to discomfort and misconception, this finding of the study was found coherent with latest literature [29]. Health care professionals should provide accurate guideline during hands-on practice which might ease discomfort and anxiety. Regarding misconception that BSE is ineffective it could be due to uncertainty and ambiguity about its purpose. Accurate guidance during health campaigns can alleviate these issues, improve compliance, and promote early breast cancer detection. Similar barriers such as lack of knowledge, fear, time management and privacy issue were identified in studies conducted in Malaysia, Emirati students and Jordanian female university students [30]. Interestingly studies, found that participants had information that breast masses are self-detected by women. Obvious identification of breast cancer signs is significant for early prognosis and intervention though few respondents seek advice from health professionals as they are efficient in self-examination or they inadequate access to health services. Regarding BSE examination 89.6% individuals of this study had understanding that it could be done manually while the rest had no proper information regarding imaging such as CT and Ultrasound. These results points out insufficient information could lead to ineffective BSE practice. However, according to Alomair AN *et al.*, they reported that BSE approach has insufficient efficacy[30].

CONCLUSIONS

In this study participants had understanding of BSE and their primary reason for performing BSE is cancer detection but they lacked complete knowledge and inconsistent practice due to limited access to health care resources and insufficient understanding about the technique also encounter significant barriers while practicing.

Authors Contribution

Conceptualization: FT
Methodology: TB, MG
Formal analysis: AR
Writing, review and editing: FT, AR, BI, NH, MG, MFF

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.1526

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Evaluation of Use of Intensive Care Unit (ICU) Scoring Systems among Healthcare Professionals

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ARTICLE INFO

Keywords:
ICU Scoring Systems, Critical Care Prognosis, Severity Assessment, Pakistan Healthcare Evaluation

How to Cite:
Jahangir, A., Saba, N.-U.-., Raza, M., Hyder, F., & Sultan, S. F. (2025). Evaluation of Use of Intensive Care Unit (ICU) Scoring Systems among Healthcare Professionals: Intensive Care Unit Scoring Systems Evaluation. Pakistan Journal of Health Sciences, 6(1), 119-123. https://doi.org/10.54393/pjhs.v6i1.1526

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Received date: 15th April, 2024
Acceptance date: 6th January,2025
Published date: 31st January, 2025

ABSTRACT

The prognosis of patients in the Intensive Care Unit (ICU) is a matter of worry for critically ill patients, their families, and healthcare personnel. However, predicting the chances of recovery in the ICU can be challenging. Scoring systems serve as standardized instruments utilized in critical care research to determine which patients should be included in a study and to establish the comparability of different patient groups. **Objective:** To determine the frequency of use of Scoring Systems to predict the outcome of critically ill patients in the intensive care units of Pakistan. **Methods:** This cross-sectional study was conducted in all the healthcare institutions of Pakistan that are recognized by CPSP for fellowship in ICU training, from 10th April 2018 till 10th October 2018. Forty-one ICU physicians were included. Pre-designed questionnaires were sent to these physicians. **Results:** Out of 41 physicians, 33 (80.5%) of them used and 8 (19.5%) did not use ICU scoring systems. Only 3 consultants reported the use of Anatomical scoring systems. GCS was the most used Disease Specific Scoring System (97.5%), followed by Child Pugh's Score (80%) and Ranson's Criteria (70%). 50% reported the use of Sequential Organ Failure Assessment (SOFA) and 42% used Multiple Organ Dysfunction Score (MODS). 63% used Acute Physiology and Chronic Health Evaluation (APACHE). 93% did not use any Therapeutic Weighted Score. 77.5% used Richmond Agitation-Sedation Scale (RASS) and 25% used Ramsey's. **Conclusion:** It was found that 80.5% physicians used ICU scoring systems to assess mortality and severity of illness.

INTRODUCTION

Critical illness scoring systems are useful for guiding therapy and evaluating the degree of disease and organ failure [1]. Their usage allows one to forecast the overall performance of an intensive care unit, as well as the patient's clinical results and in-hospital mortality [2]. When making important clinical decisions, these rating systems might be helpful. Consequently, hospital resources may be utilized to their full potential, resulting in a decrease in total cost [3]. One such purpose for them is to sort really sick patients into different groups for clinical studies [4]. Although there isn't a universally accepted way to classify the several ICU scoring systems, they can be grouped according to the system in question, the illness at play, the organ in question, the degree of physiological disturbance, or the therapeutic procedures that have taken place. In addition to this, there are ratings that evaluate more routine aspects of intensive care unit treatment, such as pain management and sedative depth [5]. Early evaluations of outcome prediction relied on doctors' subjective assessments, which Florence Nightingale initiated in 1863 [2]. The fast evolution of intensive care units necessitated the subsequent establishment of scoring systems. Scores have been utilized extensively to evaluate results in intensive care units on a global scale. Additionally, several scoring methods have been contrasted to ascertain whether one produces superior outcomes. Sixty patients in

DOI: https://doi.org/10.54393/pjhs.v6i1.1526

critical care were the subjects of a prospective research by Sekulic AD et al [6]. Each patient was given an assessment of APACHE II, SAPS II, and MPM II when they were admitted to the intensive care unit. Multiple time periods following admission were assessed for the SOFA and MPM II: 24 hours, 48 hours, 72 hours, and 7 days later. Consequences were strongly predicted by APACHE II and SAPS II scores. The results of this study led to the introduction of consistent use of APACHE II and SAPS II scores upon ICU admission, as well as MPM II and SOFA scores for the duration of the patient's stay in the ICU. Researchers Hosseini M *et al.*, studied 300 critically sick patients to see how well APACHE II and SOFA predicted outcomes in intensive care units [7]. Those patients who did not make it out of the ICU had far higher APACHE II scores than those who did. Data was collected during the first twenty-four hours of admission for the purpose of comparing LODS and APACHE II in a different study that was conducted on 521 patients who were admitted to the neurological intensive care unit [8]. The death rate that was observed was 10.0%, which is much higher than the mortality rates that were anticipated by LODS and APACHE II, which were 7.2% and 4.8%, respectively. In order to determine whether critically sick patients need sedatives or analgesics, the PAD guidelines advocate using delirium, pain, and sedation score systems in the intensive care unit [9]. Patients on mechanical ventilation are less likely to need ventilator support and spend less time in the Intensive Care Unit (ICU) when pain evaluation is performed, according to research by Haniffa R *et al* [10]. Various metrics have also been used in Pakistani intensive care units to forecast patient outcomes. Patients in critical illness who had higher initial SOFA scores had a greater death rate, according to research by Akbar A et al [11]. Both Lo ML *et al.*, and Hashmi M *et al.*, came to the same conclusion: a high APACHE-II score was inversely related to the duration of stay and increased death risks [12, 13]. Researchers Naqvi IH *et al.*, found that APACHE II, SOFA, and SAP II scores were greater in the non-survivor group compared to the survivor group [14].]. In another study, three scoring systems including Child-Pugh, APACHE II and III were compared to evaluate their prognostic accuracy for predicting short term mortality in patients diagnosed with liver cirrhosis. Among compared scoring systems, Child-Pugh is found to be most reliable one and APACHE scores were found to be less reliable in hospital settings [15]. Several international surveys have found out how frequently these ICU scoring systems are being used. A UK National Survey conducted by Raffa JD *et al.*, found out that 88% of the ICUs used a sedation scoring system [16]. A European survey published in 2001 also showed that sedation scores are most commonly used in the ICUs of UK and Ireland (the Ramsay scale in 74% of cases) So far, no such survey has been conducted in Pakistan [17]. Keeping in mind the numerous benefits of these scoring systems, their use should be common in the ICU settings. However, insufficient data exists regarding their use in this country.

The purpose of this study was to ascertain the frequency with which scoring systems are utilized in Pakistan's intensive care units for the purpose of predicting the outcomes of critically ill patients.

METHODS

This cross-sectional study was conducted in all healthcare institutions of Pakistan that are recognized by CPSP for fellowship in ICU training from 10th April 2020 till 10th October 2020 and 41 physicians were enrolled. Before data collection, CPSP letter approved on 23rd of December 2019 with reference number CPSP/REU/ANS-2016-218-1605 was taken. In order to collect the data, Purposive sampling technique was used as study targeted respondents of specific expertise. Sample size was calculated by using following formula

$$n=\frac{\frac{z.p(1-p)}{e^2}}{1+\frac{z.p(1-p)}{e^2}}$$

Online questionnaire was used to collect date from each hospital which included severity, scoring systems, critically ill, intensive care, risk prediction, APACHE, MODS, RASS, SOFA. Consultants of each ICU in the above-mentioned setting having an ICU working experience of more than 1 year, age greater than 30-70 years, qualification FCPS or any other equivalent foreign degree and either gender were included. Those consultants with an MCPS degree and consultants responding after 6 months were excluded. Pre-designed questionnaires were sent via email to the ICU physicians in Pakistan who are working in institutions recognized for fellowship in ICU training by CPSP. A monthly reminder was sent to the non-responders regularly for 6 months. If they failed to respond within 6 months, they were labeled as "non- responders" in the results. Frequency and percentage were used as categorical variables, whereas Standard Deviation (SD) and mean were utilized as quantitative variables. Data were entered and analyzed using SPSS version 21.0. Descriptive analysis was conducted.

RESULTS

The mean age was 41.25±9.3 years whereas the mean duration of practice was 12.05±9.69 years respectively (table 1).

Table 1: Descriptive Statistics of the Patients (n=41)

Variables	Minimum - Maximum	Mean ± SD
Age (Years)	30 – 63	41.25 ± 9.3
Duration of Practice (Years)	1- 40	12.05 ± 9.69

DOI: https://doi.org/10.54393/pjhs.v6i1.1526

Out of the total, 33 physicians (80.5%) utilized the ICU scoring system, while 8 (19.5%) did not, with a statistically significant p-value of <0.005. Among the participants, 33 (80.5%) were male, and 8 (19.5%) were female. Additionally, 24 physicians (58.5%) were under 40 years of age, whereas 17 (41.5%) were over 40. Regarding the duration of practice, 25 physicians (61%) had less than 10 years of experience, while 16 (39%) had more than 10 years. Moreover, 38 participants (92.7%) held an FCPS qualification, and 3 (7.3%) had other qualifications (Table 2).

Table 2: Demographic Information of the Patients (n=41)

Variable	N (%)
Yes	33 (80.49%)
No	8 (19.51%)
Male	33 (80.49%)
Female	8 (19.51%)
Age < 40	24 (58.54%)
Age > 40	17 (41.46%)
Practice Duration < 10	25 (60.98%)
Practice Duration > 10	16 (39.02%)
FCPS	38 (92.68%)
Other	3 (7.32%)

GCS was the most used Disease Specific Scoring System (97.5%), followed by Child Pugh's Score (80%) and Ranson's Criteria (70%) (Figure 1).

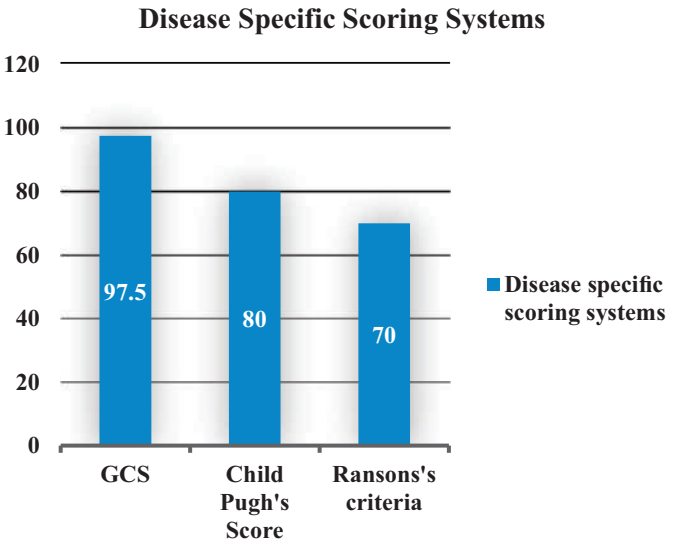

Figure 1: Use of different Scoring Techniques for Disease Diagnosis

50% reported the use of SOFA and 42% used MODS. 63% used APACHE. 93% did not use any Therapeutic Weighted Score. 77.5% used RASS and 25% used Ramsey's. Most commonly used Pain Scale was Visual Analogue Scale (VAS) (60%) followed by Numeric Rating Scale (NRS) (50%), 35% used Confusion Assessment Method for Intensive Care Unit (CAM-ICU) (Table 3).

Table 3: Use of Prediction Scoring Systems

Variables	%
Prediction Scoring Systems	
SOFA	50%
MODS	42%
APACHE	93%
RASS	77.5%
Ramsey's	25%
Therapeutic Weighted Score	
Yes	7%
No	93%
Use of Pain Scale	
VAS	60%
NRS	50%
CAM ICU	
VAS	35%
NRS	65%

DISCUSSION

Common applications of general sickness severity ratings in the intensive care unit include outcome prediction, characterization of disease severity and degree of organ dysfunction, and assessment of resource consumption. The many types of scoring are complementary, not mutually exclusive or competitive. The accuracy of indicators for disease severity and prognosis may be enhanced by their potential synergistic effects. It will be required to update all of these scoring systems when new diagnostic, therapeutic, and prognostic techniques become available and as Intensive Care Unit (ICU) demographics change. While some grading systems are more general and used to all patients in the Intensive Care Unit (ICU), others are more disease-or organ-specific, such as the Glasgow Coma Scale (GCS). Modern critical care, patient demographics, and disease frequency have all undergone dramatic changes, and statistical and computational approaches have also come a long way. In the present study, thirty-three (80.5%) and 08 (19.5%) used and did not use any ICU scoring system. Only 3 consultants reported the use of Anatomical scoring systems. GCS was the most used Disease Specific Scoring System (97.5%), followed by Child Pugh's Score (80%) and Ranson's Criteria (70%). 50% reported the use of SOFA and 42% used MODS. 63% used APACHE. 93% did not use any Therapeutic Weighted Score. 77.5% used RASS and 25% used Ramsey's. Most commonly used Pain Scale was VAS (60%) followed by NRS (50%). 35% used CAM-ICU. In a study, APACHE III and Child-Pugh scores were assessed for all 282 patients. Upper gastrointestinal hemorrhage (38%), liver failure (21%), hepatorenal syndrome (19%), hepatocellular cancer (4%), and spontaneous bacterial peritonitis (6%), were the prominent reasons of death. Survivors had lower Child-Pugh and APACHE III scores (8.6 ± 2.3 and 58.9 ± 35.1)

DOI: https://doi.org/10.54393/pjhs.v6i1.1526

compared to non-survivors (10.9 ± 2.7 and 87.4 ± 30.3) with a p-value less than 0.001. While Child-Pugh properly identified 67% of cases using discriminant analysis, APACHE III accurately recognized 75% of cases ($p < 0.05$) [18]. Every intensive care unit in the United Kingdom took part in a separate postal survey that was conducted across the entire country. There were 192 answers obtained, which is 63.5% of the total number of 302 units that were contacted. A sedative scoring approach was utilized by responding critical care units at a rate of 88%, with the Ramsey sedative Scale being utilized by 66.4% of those centers. In addition to the fact that the majority of units have recorded sedation standards, an astounding 78% of those units also provide evidence that sedation holding is performed on a daily basis. The length of action, rather than the cost, is the major consideration that should be taken into account while selecting a sedative from among the various available options. In intensive care facilities in the United Kingdom, it is routine practice to adhere to sedation guidelines and to use a sedation score tool [19-21]. Another research surveyed 647 critical care doctors from 16 western European nations. Only 35% of those who took the survey reported ever using propofol, while 63% reported ever using midazolam. Midazolam was chosen over propofol in several countries, including France, Germany, the Netherlands, Norway, and Austria, among others. Opioids such as morphine (33%), fentanyl (33%), and sufentanil (24%), were given most often for the purpose of pain treatment. Only 18% of Austrians used a sedative scale, compared to 72% of Britons and 22% of Irish. The Ramsay scale was widely regarded as the most accurate way to measure sedative levels when it was in use [17, 20].

CONCLUSIONS

General sickness severity ratings help ICUs evaluate resource utilization, predict prognosis, and characterize disease and organ failure. Disease-specific grading methods are needed because all grades were established for mixed ICU patient groups, reducing subgroup accuracy. ICU populations fluctuate as new diagnostic, therapeutic, and prognostic methods are developed, thus scoring systems must be updated. Since the scoring systems measure diverse things, we think they should complement one other rather than compete. Despite their purpose, organ dysfunction scores predict outcomes. APACHE and SAPS ratings should predict outcomes. These tools assist doctors and management allocate resources and evaluate performance by accurately evaluating illness severity and prognosis.

Authors Contribution

Conceptualization: AJ
Methodology: NUS, MR, FH
Formal analysis: FH
Writing, review and editing: NUS, MR, FH, SFS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2611

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Prospective Study on the Incidence of Hospital Acquired Infections in Intensive Care Unit

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ARTICLE INFO

Keywords:
Hospital-Acquired Infections, Intensive Care Unit, Ventilator-Associated Pneumonia, Infection Control Practices

How to Cite:
Hayee Phulpoto, A., Aziz, A., Memon, A. Q., Channa, M. A., Pervez, S. A., & Ramani, R. K. (2025). Prospective Study on the Incidence of Hospital Acquired Infections in Intensive Care Unit: Incidence of Hospital Acquired Infections. Pakistan Journal of Health Sciences, 6(1), 124-129. https://doi .org/10.54393/ pjhs. v6i1.2611

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Received Date: 29th November, 2024
Acceptance Date: 20th January, 2025
Pubished Date: 31st January, 2025

ABSTRACT

Hospital-Acquired Infections (HAIs) in the ICU significantly impact patient morbidity, mortality, and length of stay. **Objective:** To determine the incidence of HAIs, identify key risk factors, and analyze their impact on clinical outcomes in ICU patients. It was prospective observational study. **Methods:** A total of 220 ICU patients were included. Data on demographics, ICU stay duration, device use (e.g., central lines, ventilators, urinary catheters), comorbidities, and infection control practices were collected. HAIs were diagnosed based on CDC definitions and categorized as Ventilator-Associated Pneumonia (VAP), Central Line-Associated Bloodstream Infection (CLABSI), Catheter-Associated Urinary Tract Infection (CAUTI), and Surgical Site Infections (SSI). Incidence rates were calculated using descriptive statistics, and risk factors were identified through multivariate logistic regression. **Results:** Results showed that 150 (68.2%) patients developed HAIs, with VAP being the most common (30%), followed by CAUTI (16.7%), CLABSI (20%), and SSI (13.3%). Independent risk factors for HAIs included ventilator use ($p<0.001$), prolonged ICU stay ($p=0.004$), and use of urinary catheters ($p=0.002$) and central lines ($p=0.003$). Patients with HAIs had higher mortality (30% vs 12%, $p=0.003$) and longer ICU stays (21 days' versus 12 days, $p<0.001$). **Conclusions:** HAIs are frequent in ICU patients, particularly VAP. They significantly increase mortality and prolong ICU stays, highlighting the need for enhanced infection control practices, especially for patients with extended ICU stays or those requiring invasive devices.

INTRODUCTION

Conversely, Healthcare-Associated Infections (HAIs) pose a considerable hazard to patients and are linked with greater morbidity, mortality as well as health care costs [1, 2]. Due to the severity of their illness, prolonged hospitalizations and frequent use of invasive devices (e.g. ventilators or central lines), intensive care units are particularly susceptible for Healthcare-Associated Infections (HAIs). Understanding the burden, types and risk factors of HAIs is important for optimizing infection prevention efforts [3, 4]. Hospital-Acquired Infections (HAIs) are a major concern in health care settings, particularly among patients undergoing standard Intensive Care Units (ICUs), where the immune response of bedridden individuals is compromised and invasive therapeutic measures may be imperative leading to vulnerability from bacteria producing pathogens characterized by rapid growth within these environments [5]. Patients who get sick while being treated in a medical facility or become ill from the ICU are admitting Hospital-Acquired Infections (HAIs) also called nosocomial Infections [6]. These infections are an emerging menace to healthcare systems around the globe because of increase in patient morbidity, mortality and health care cost [7, 8]. The intensive care unit is one setting in which HAIs can

DOI: https://doi.org/10.54393/pjhs.v6i1.2611

develop and disseminate easily, due to an increasing number of critically sick patients today as well as extensive use of invasive devices. ICUs are usually looking after dysfunctional patients [9]. Long stays in hospital, multiple comorbidities and weak immune systems make them susceptible to infections. Some of the most common types of Healthcare-Associated Infections (HAIs) in intensive care units include Ventilator-Associated Pneumonia (VAP), Catheter-Associated Urinary Tract Infections (CAUTIs), central line associated bloodstream infections (CLABSIS, and surgical site infections). Not only do these infections persist, but they also spread really fast [10]. Moreover, to develop good preventative and control methods of HAIs we need to know the frequency, risk factors etiology and outcome related with these infections. Healthcare-Associated Infections (HAIs) are a major cause of morbidity and mortality in Intensive Care Units (ICUs), driven by factors like prolonged hospital stays, invasive procedures, and antimicrobial resistance. While studies have documented HAI prevalence and risk factors, limited data exist on comparing outcomes between patients with and without HAIs, particularly in specific region or population, if applicable. This study aims to bridge these gaps by evaluating HAI incidence, identifying key risk factors, and analyzing differences in outcomes, contributing to improved prevention strategies and patient care in ICUs.

The objective of this study was to determine the incidence rate of healthcare-associated infections, key risk factors and analyze differences in clinical outcomes (HAIs) in Intensive Care Unit (ICU) patients.

METHODS

It was prospective observational study. It was conducted for six months from February 2024 to July 2024 at the department of Intensive Care Unit (ICU) of Khairpur Medical College Khairpur/KMC Civil Hospital Khairpur Mir's. Inclusion criteria: Patients' ages ranged from 18 to 55 years and included both males and females. Inclusion criteria: Patients hospitalized to the ICU for longer than 48 hours. Patients who informed consent or whose consent was gained from family members in the event that the patient was incompetent. Exclusion criteria: Patients stayed in the hospital for less than 48 hours. The ICU included patients who had active infections at the time of admission. To calculate the participant sample size formula: $n = Z2 \cdot p \cdot (1-p) / d2$, 95% confidence level with 10% margin of error is required and the predicted prevalence of HAIs is 50%. Information about demographics, length of stay, use of devices (e.g., central lines, ventilators, urine catheters), comorbidities, and infection control measures were gathered prospectively from every patient admitted to the intensive care unit. The following categories were used to classify hospital-acquired infections (HAIs): Ventilator-Associated Pneumonia (VAP), Central Line-Associated Bloodstream Infection (CLABSI), Catheter-Associated Urinary Tract Infection (CAUTI), and Surgical Site Infection (SSI), where appropriate. Infections were identified based on clinical symptoms and verified by microbiological testing. The consecutive sampling technique was used in this study. The CDC's definitions for each form of HAI were followed while making the diagnosis. Using SPSS version 23.0, statistical analysis of the gathered data was carried out. Multivariate logistic regression was used to determine the risk factors linked to HAIs, and descriptive statistics were used to determine the incidence rates of each type of HAI. This study was approved by the Institutional Review Board (IRB) reference number (KMC/RERC/100).

RESULTS

Table 1 outlined the important demographic characteristics of the ICU patient population investigated. The average age of the 220 patients was 36.5 ± 5 years, demonstrating that the participants were of various ages. The total number of HAIs patients was 68.18%. The gender shows that male patients account for 68% of the group, while females make up 31.8%. Patients stayed in the ICU for an average of 14 days, due to unique care needs. These demographics lay the groundwork for comprehending the research population's features.

Table 1: Participant's Demographics Variables

Variables	Value	% / Mean ± SD
Total Patients	220	-
Mean Age	18-55 Years	36.5 ± 5 Years
Gender Distribution	Male	68%
	Female	31.8%
Patients with HAIs	150	68.18%
Average Length of Stay	-	14 ± 7 Days

Figure 1 showed the distribution of various forms of Hospital-Acquired Infections (HAIs) among a total of 150 patients. Ventilator-Associated Pneumonia (VAP) was the most common cause, accounting for 30% of cases (45 patients), followed by Central Line-Associated Bloodstream Infections (CLABSI) at 20% (30 patients). Catheter-Associated Urinary Tract Infections (CAUTI) accounted for 16.7% (25 patients), whereas Surgical Site Infections (SSI) made up 13.3% (20 patients). Other forms of HAIs accounted for an additional 20% (30 patients). The Chi-Square Test revealed statistically significant relationships between all infection types (p-values ranged from <0.001 to 0.020). This demonstrated the enormous burden of HAIs in the study population and stresses the importance of focused therapies in the ICU setting.

DOI: https://doi.org/10.54393/pjhs.v6i1.2611

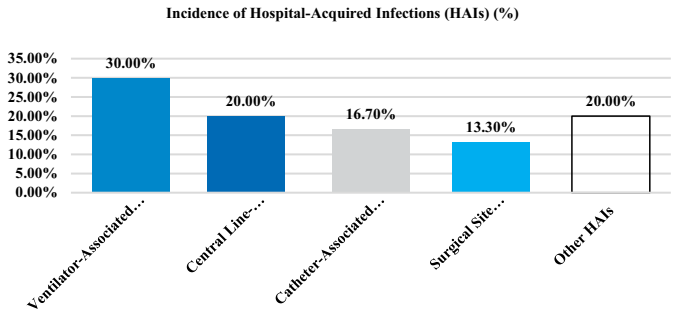

Figure 1: Incidence of Hospital-Acquired Infections(HAIs)

Table 2 showed the relationship between numerous risk variables and Hospital-Acquired Infections (HAIs), as well as the p-values. Ventilator use was identified as the most significant risk factor, with a p-value of less than 0.001 when examined using the Chi-Square Test, demonstrating a high connection with HAIs. Independent Samples t-Test showed a significant correlation with an extended ICU stay (p=0.004). In addition, diabetes and immunosuppression were significantly associated with HAIs ($P < 0.01$) by applying Logistic Regression Analysis, signifying that these comorbidities increase the risk of getting infected at most levels in an appreciable manner. Use of urinary catheter and central line was associated with HAIs, having $p = 0.02$), and ($p = 0.03$) as calculated by Chi-Square Test respectively. Taken together, these results may reflect some of the most important factors contributing to HAIs in ICUs and thus how targeted therapies may influence these risks.

Table 2: Risk Factors Associated with HAIs

Risk Factors	Association with HAIs (p-Value)
Ventilator Use	0.001
Prolonged ICU Stay	0.004
Diabetes	0.01
Immunosuppression	0.01
Urinary Catheter Use	0.02
Central Line Use	0.03

Table 3 compared outcome of 150 patients with Hospital-Acquired Infections (HAIs) to that in 70 not to have an HAI. Patients in the group developing HAIs were at a much higher risk of death (30% compared to 12%, p=0.003), which proved highly significant. Moreover the mean duration for stay in ICU was significantly higher among those patients with HAI (21 days) compared to their counterparts without one (12days), p-value > In addition, compared to community-acquired pneumonia patients, a greater proportion of HAI patients necessitated mechanical ventilation (65 versus 40%, p=0.001), and had higher rates of readmission within the study period length at least partially due to being discharged to long-term care facilities (18 versus 8%, p=0.001). These results highlight the considerable effects of HAIs on patient outcomes in ICU and, hence call for strict measures to incidence of their occurrence.

Table 3: Outcomes of Patients with and without Hospital-Acquired Infections(HAIs)(n=220)

Outcome Measure	Patients with HAIs Percentage % / Mean ± SD	Patients without HAIs Percentage %/Mean ± SD	p-value
Mortality Rate (%)	30%	12%	0.003
Average Length of ICU Stay (Days)	21 ± 8 days	12 ± 5 days	0.001
Mechanical Ventilation Use (%)	65%	40%	0.001
Readmission Rate (%)	15%	5%	0.001
Discharge to Long-Term Care (%)	18%	8%	0.001

DISCUSSION

Therefore, this study aimed to investigate the incidence and type of Hospital-Acquired Infections (HAIs) as well as its risk factors in a specific group with critical health status who are more likely to acquire infection because they need invasive procedures for treatment especially those patients who admitted at intensive care unit-ICU [11]. These results show the urgent need for effective infection control strategies in intensive care units and are consistent with findings from other investigations at different healthcare settings. Conclusions an overall HAI incidence rate of 68.18% is alarmingly high which also indicates that infection control protocols need to be further strengthened as well. The previous studies reported that shown high incidence of HAI in ICUs, and the further association between higher burden of infection to lower income settings. We suspect that the high incidence rates in the study reflect, on one hand the use of invasive devices and prolonged hospital stay; but also a very ill population with an important burden of comorbidity which, taken together increase risk for HAIs. Infection stands as an obvious target, which is corroborated by the overwhelming prevalence of certain types such as VAP and CLABSI thereby suggesting that if device-related infections are dealt effectively this may significantly reduce infection rates overall [12]. Ventilator-Associated Pneumonia (VAP) is a common and serious hospital-acquired infection in ICU patients, often linked to prolonged ventilator use. Interventions like early extubation, or minimizing the duration of mechanical ventilation, can significantly reduce the risk of VAP. Incorporating protocols like the "ventilator bundle," which includes head-of-bed elevation, daily sedation interruptions, and oral care with chlorhexidine, has been shown to reduce VAP rates. Regular monitoring for signs of infection and prompt weaning from the ventilator when appropriate can also minimize the risk. In this study, VAP was the most frequent

DOI: https://doi.org/10.54393/pjhs.v6i1.2611

HAI observed in 30% of ICU patients. The long-term artificial ventilation for critically ill patients, which impinges natural respiratory defense mechanisms may result in VAP leading to its predominance. There is a common perception that extensive intubation can help pathogenic organisms to colonize, leading delayed pneumonia. For example, mechanical ventilation has been identified as the primary risk factor for VAP in previous studies like that of Grasselli G *et al.*, in (2021) and Baccolini V *et al.*, in (2021) [13, 14]. In the ICU cohort an even larger proportion were HAIs, with CLABSI and CAUTI causing a sizeable percentage of these. This was because 20% of the CLABSI rate found is attributable to us failing to use central lines for patients requiring high frequency medications or fluids. According to Krauss DM *et al.*, in (2022), sterility breakdown during insertion or maintenance of a line, pathogens are able to enter the bloodstream. CAUTI, was also detected with the incidence rate of 16.7% in this study and it is resulted from a similar mechanism [15]. CAUTI promote bacterial colonization surface that leads to biofilm formation on the catheter. Central Line-Associated Bloodstream Infections (CLABSI) and Catheter-Associated Urinary Tract Infections (CAUTI) are closely associated with prolonged catheter use. Implementing best practices in catheter care, such as using the sterile insertion technique, ensuring proper maintenance, and removing catheters as soon as they are no longer necessary, can significantly reduce these infections. In particular, educating healthcare staff about the importance of catheter removal protocols and regular monitoring for any signs of infection can help minimize the incidence of these infections. This is in line with earlier studies, emphasized the significance of prolonged catheterization as a risk factor for CAUTI. A minority of cases were Surgical Site Infections (SSI), likely related to pre-existing infection [16]. We identified the use of ventilators, prolonged stays in ICU, comorbidities (diabetes and immunosuppression) and invasive devices like central lines or urine catheters to be among major risk factors for HAIs. To develop targeted prevention measures it is essential to be aware of all these elements as each contributes an increased infection risk for ICU patients. There was a consistent relationship between ventilator use and HAIs. This is similarly of a considerable magnitude to the effect reported by Despotovic A *et al.*, in (2020), who also identified mechanical ventilation as a major risk factor for intensive care unit acquired pneumonia Prolonged ventilation can result in complications, for instance including increased risk of ventilator-associated pneumonia and thus frequent monitoring for the possibility of weaning from a ventilator may also benefit outcomes [17]. Extended ICU stays (p=0.004) was also significantly associated with increased HAI rates in the higher group Full size table Longer hospital stays increase the risk of colonization and infection with organisms endemic to that facility for obvious reasons. This finding is in agreement with Peters L *et al.*, in (2019) who reported that hospital length of stay increases the likelihood of infection. For example, a longer ICU stay could reflect the presence of more severe underlying conditions with resultant increased risk for infection from invasive surgeries or other interventions [18]. HAIs were also associated with adverse clinical outcomes in ICU patients (with an average hospital stay of 21 days and overall mortality rate of approximately 30%) beyond the context of the investigation, as reported by us elsewhere [19]. This result is congruent with the studies of Harhay MO *et al.*, in (2019) and van Wagenberg L *et al.*, in 2020 indicated that adverse outcomes associated with HAIs include longer recovery times, increased risk of complications and higher costs. HAIs burden severely ill patients more, impacting negatively on the recovery mechanisms and increasing risk of adverse outcomes [20, 21]. Local factors contributing to the findings of Hospital-Acquired Infections (HAIs) may include healthcare infrastructure, such as staffing levels and available resources, which can affect infection prevention efforts. Infection control practices, including adherence to hand hygiene and sterilization protocols, are crucial in reducing HAIs. Additionally, local antibiotic resistance patterns may lead to more severe infections. Patient demographics, such as age and comorbidities, can increase susceptibility to infections, while ICU practices like mechanical ventilation and catheterization may raise HAI risk. Environmental factors, economic constraints, and cultural attitudes towards hygiene can also influence infection rates in a healthcare setting [22]. The findings of this study carried several implications for clinical practice. Tight infection control strategies required to lessen heavy burden of HAIs in an intensive care unit. Strategies should aim to minimize the utilization of invasive devices such as central lines, ventilators and urine catheters by standard assessment and timely removal. To focusing on strategies to reduce the incidence of HAIs in ICUs and improve patient outcomes.

CONCLUSIONS

HAIs are frequent in ICU patients, with VAP as the most common type. HAIs almost double mortality and extend ICU stay which thereby underscores the need for specific infection control measures, particularly in patients with long duration of ICU admissions or those requiring devices for vital functions.

DOI: https://doi.org/10.54393/pjhs.v6i1.2611

Authors Contribution

Conceptualization: AHP
Methodology: AA, AQM, MAC
Formal analysis: AQM, SAP
Writing, review and editing: RKR, SAP

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2565

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Corneal Endothelial Cell Loss after Cataract Extraction by Phaecoemulsification versus Conventional Extra Capsular Cataract Extraction Technique

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ARTICLE INFO

Keywords:
Cataract, Phacoemulsification, Endothelial Cell Loss, Ophthalmology

How to Cite:
Khoso, A. A., Pirzado, I. A., Bhutto, S. A., Gopang, Z., Kandhro, P. A. G., & Azam, M. (2025). Corneal Endothelial Cell Loss after Cataract Extraction by Phaecoemulsification versus Conventional Extra Capsular Cataract Extraction Technique: Phaecoemulsification Versus Conventional Cataract Extraction Technique. Pakistan Journal of Health Sciences, 6(1), 130-135. https://doi.org/10.54393/pjhs.v6i1.2565

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Received Date: 12th November, 2024
Acceptance Date: 23rd January, 2025
Published Date: 31st January, 2025

ABSTRACT

A cataract is a condition affecting the eye in which the lens, previously clear, has developed cloudiness and flexibility, obstructing the passage of light. This condition progressively deteriorates and is a significant contributor to global blindness. A cataract is identified through a thorough examination of the pupil using a torch light and a slit lamp, both in dilated and non-dilated states. In 1967, Charles Kelman introduced phacoemulsification, an innovative surgical technique for the treatment of cataracts. **Objective:** To compare the corneal endothelial cell loss after cataract extraction performed with conventional extra capsular cataract extraction versus standardized Phacoemulsification. **Methods:** Non-randomized clinical trial study was conducted at Department of Ophthalmology, Chandka Medical Hospital Shaheed Mohtrama Benazir Bhutto Medical University Larkana in time frame of six months by using probability consecutive sampling technique. Data analysis was performed by using SPSS version 24.0. The Chi-square test was utilized for cross-tabulation. **Results:** In comparison to individuals receiving ECCE, those undergoing PHACO tended to be younger and exhibited a greater proportion of females. While the PHACO group consistently exhibited a higher endothelial cell count during all post-operative intervals, both techniques led to a significant decrease in the number of endothelial cells observed post-operation. **Conclusion:** The present study supported the common understanding that phacoemulsification is linked to a significantly reduced incidence of endothelial cell loss.

INTRODUCTION

Located beneath the descemet's membrane is a singular layer of cells known as the endothelium cell [1]. The cornea is composed of several key components. The structure consists of hexagonal cells, each measuring 20 micro meters in width. The typical quantity of capillary cells observed in young individuals is approximately 3000/mm^2 [2, 3]. With advancing age, there is a reduction in the quantity of capillary cells, and the remaining cells tend to exhibit a decrease in thickness. An optical junction complex with a tighter link consists of cells that occupy the spaces left by the aqueous humour, while also exhibiting intercellular gaps [4]. The aqueous humour contains approximately 20 to 30 minute microvilli cells that extend from the optical plasma membrane. The functional endothelium maintains corneal dehydration, allowing the corneal stroma to perform its pumping action while ensuring the permeability barriers in the aqueous humour remain intact [5]. The corneal endothelium can be observed and examined using a specular photographic microscope, ensuring that no damage occurs during the process. Employing a specular microscope alongside computer-assisted morphometry to examine the dimensions, morphology, and quantity of capillary cells [6]. A beam is directed towards the eye using a specular

DOI: https://doi.org/10.54393/pjhs.v6i1.2565

microscope between the aqueous humour and the endothelium of the eye, observed through the optical interface and narrow image [7, 8]. The device analyses the reflected image and presents it as a specular photomicrograph. In clinical environments, the specular microscope represents the most precise method for examining the endothelium. The surgical procedure for cataracts alters the cellular structure of the corneal epithelium, which is significant as it has a direct impact on visual acuity following the operation [9-11]. Endothelial cells are diminished in all forms of ocular surgical procedures. This is a widely accepted fact among individuals. Nine, ten, and eleven Advancements in tools and techniques have led to cataract surgery resulting in the removal of only 6–14% of endothelial cells. This represents a significantly smaller loss compared to the substantial loss associated with phacoemulsification, the previous method employed for cataract removal [12-14].

The aim of this study was to examine corneal endothelial cell loss by two procedures of cataract surgery i.e., Extra Capsular Cataract Extraction (ECCE) versus extraction by Phacoemulsification, in this population.

METHODS

Non-randomized clinical trial study was conducted at Department of Ophthalmology, Chandka Medical Hospital at SMBBMU, Larkana in time frame of six months (from1st May to 31st October 2023) by using probability consecutive sampling technique after approval of research ethics committee of Shaheed Mohtrama Benazir Bhutto Medical University Larkana (No.SMBBMU/OFF ERC/231) on dated (20-04-2023). Inclusion criteria of patients in phacoemulsification cataract extraction technique includes poster sub capsular cataract, nuclear cataract, cortical cataract and corneal endothelial cell count more than 1000 mm2 whereas inclusion criteria in extracapsular cataract extraction technique includes hyper nature cataract, intumescent cataract, corneal endothelial cell count less than 1000 cells mm2 and pseudo exfolial syndrome. Exclusion criteria of patients with phacoemulsification cataract extraction technique involves hyper nature cataract, pseudo exfolial syndrome, corneal degeneration and corneal endothelial dystrophy were excluded and exclusion criteria of patients in extracapsular cataract extraction technique includes immature cataract, posterior sub capsular cataract, posterior polar cataract and congenital cataract were excluded from the study. Sample size was calculated through Epitools calculator.

Table 1: Epidemiological Studies Over Two Means with Equal Sample Size and Equal Variances

Variables	N
Sample Size Group 1	648
Sample Size Group 2	648
Total Sample Size	1296
Confidence Level	0.95
Power	0.8
Tails	2

Data were collected after getting the written consent from the patients. The Outpatient Department (OPD) was responsible for identifying patients with cataracts. These patients were then admitted to the Eye Ward, where a thorough medical history review and an ocular examination was conducted. A specular microscopy examination was carried out on the selected patients both prior to and during the surgical treatment. After the procedure, the prescribed protocol for follow-up assessments was adhered to on the first day, first week, first month, and three months after the treatment was completed. An analysis was performed on the data acquired using SPSS version 24.0. Descriptive results were produced for a number of variables, including age and gender. The Chi-square test was utilized for statistical association. Additionally, p-values and the customary criterion for significance, set at $p < 0.05$, were used.

RESULTS

Table 2 shows demographic parameters of the study participants. As comparing the demographic and clinical characteristics of participants undergoing two cataract surgery procedures Extracapsular Cataract Extraction (ECCE) and Phacoemulsification (PHACO) a total of 1,296 patients were divided equally between the two groups (n=648 for each). The mean age of the ECCE group was 69.15 ± 13.7 years, while the PHACO group had a significantly lower mean age of 62.6 ± 16.8 years (p<0.0001). Gender distribution also differed significantly between the groups (p<0.0001), with the ECCE group having 39% females and 61% males, compared to the PHACO group, where 55% were female and 45% were male. No significant difference was observed regarding the eye affected, with 51% of the right eyes and 49% of the left eyes being involved in the ECCE group, while 52% of the right eyes and 48% of the left eyes were affected in the PHACO group (p=0.809)(Table 2).

Table 2: Demographic Information of Study Subjects (n=1296)

Variables	ECCE Group Mean ± SD / Frequency (%)	PHACO Frequency (%)	p-value
Age	69.15 ± 13.7	62.6 ± 16.8	<0.0001
Gender			
Female	252 (39%)	360 (55%)	<0.0001
Male	396 (61%)	288 (45%)	
Eye Effected			
Right	335 (51%)	338 (52%)	0.809
Left	313 (49%)	310 (48%)	

DOI: https://doi.org/10.54393/pjhs.v6i1.2565

Table 3 demonstrated the endothelial cell count pre and post procedure in the study participants. Endothelial cell count measurements were taken pre- and post-operatively in both groups. Pre-operatively, the ECCE group had a mean cell count of 2620.69 ± 41.07 cells/mm^2, while the PHACO group had a slightly higher count of 2657.1 ± 33.6 cells/mm^2 (p<0.0001). On post-operative day 1, a reduction was seen in both groups, with the ECCE group showed a mean count of 2523.30 ± 43.1 cells/mm^2 and the PHACO group showed 2607 ± 33.7 cells/mm^2 (p<0.0001). As a result of postoperative week 1, the ECCE group had a calculation of 2473.3 ± 43.1 cells/mm^2, and the PHACO group had 2557.1 ± 33.7 cells/mm^2 (p<0.0003). After postoperative month 1, the ECCE group had 2423.3 ± 43.2 cells/mm^2 and the PHACO group had 2507 ± 33.6 cells/mm^2 (p<0.0004) and 3rd month postoperatively, the cell count in the ECCE group was 2373 ± 43.1 cells/mm^2 while in the PHACO group, it was 2457 ± 33.68 cells/mm^2 (p<0.0005).

Table 3: Pre and Post Procedure Endothelial Cell Count in Patients (n=1296)

Variables	ECCE Group Mean ± SD	PHACO Mean ± SD	p-value
Pre-operative Count (cells/mm^2)	2620.69 ± 41.07	2657.1 ± 33.6	<0.0001
Post-Operative Day 1	2523.30 ± 43.1	2607 ± 33.7	<0.0001
Post-Operative Week 1	2473.3 ± 43.1	2557.1 ± 33.7	<0.0003
Post-Operative Month 1	2423.3 ± 43.2	2507 ± 33.6	<0.0004
Post-Operative Month 3	2373 ± 43.1	2457 ± 33.68	<0.0005

Figures 1 demonstrated the variations in endothelial cell counts ahead of and behind surgery for procedures. In both groups, a significant decline in endothelial cell count up was seen post-operatively (p<0.0001), representing the impact of both procedures on endothelial cell fitness.

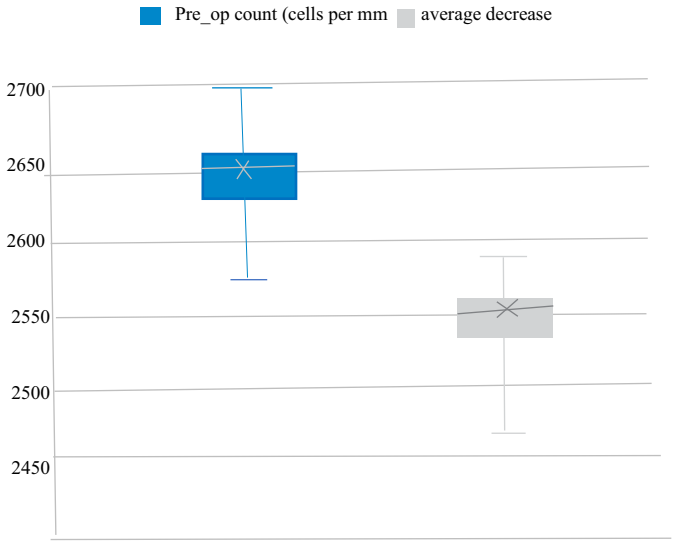

Figure 1: Differentiation in the Cell Count up before and after the Extracapsular Cataract Extraction Procedure (p-value 0.0001)

Figure 2 illustrated the significant difference in cell count before and after the phacoemulsification procedure. The p-value of less than 0.0001 indicated a highly statistically significant reduction in cell count post-procedure, suggesting that phacoemulsification has a profound impact on cellular dynamics.

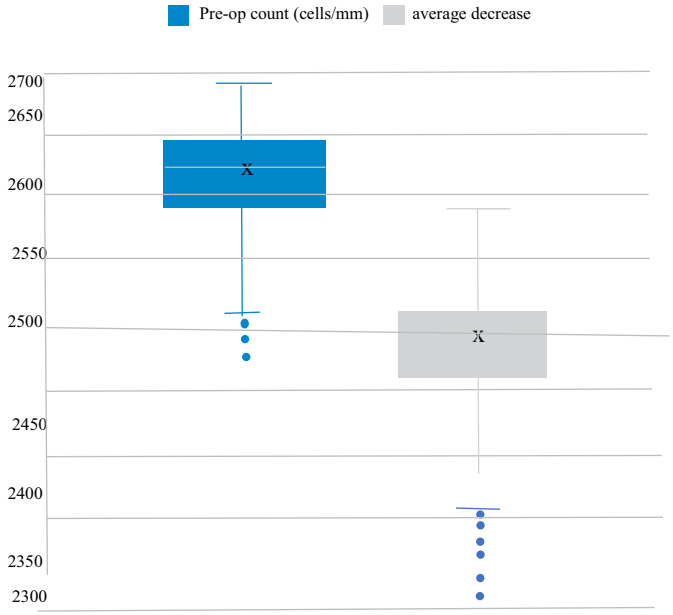

Figure 2: Difference in the Cell Count before and after the Phacoemulsification Procedure (p-value <0.0001)

DISCUSSION

The research comparing the patients of two groups who underwent Extracapsular Cataract Extraction (ECCE) and Phacoemulsification (PHACO) revealed notable differences in age, gender, and the belongings of these surgical techniques on the density of corneal endothelial cells. The preference for phacoemulsification in younger patients is likely due to its minimally invasive nature, quicker recovery, and improved outcomes [15-17]. The observed significantly lower mean age of the PHACO group, recorded at 62.6 ± 16.8 years, compared to the ECCE group, which has a mean age of 69.15 ± 13.7 years. Additionally, it was a prominent difference in gender division, as the PHACO group exhibited a highfraction of females (55%) in comparison to the ECCE group (39%). This difference in gender may be predisposed by factors like patient preferences, the recommendation by surgeons. Previous studies indicate that women have a higher likelihood of undergoing cataract surgery [18-20]. The diminution of endothelial cells indicates a considerablealarm in cataract surgery [21]. The corneal endothelium is crucial for maintaining the clarity and proper function of the cornea [22]. Upon examination of the preoperative endothelial cell counts, the PHACO group exhibited a count of 2657.1 ± 33.6 cells/mm2, while the ECCE group presented with a count of

DOI: https://doi.org/10.54393/pjhs.v6i1.2565

2620.69 ± 41.07 cells/mm^2. This indicated that the PHACO group had a marginally higher endothelial cell count. Although the difference observed was statistically significant, it holds clinical insignificance, indicating that both groups exhibited endothelial cell populations that were relatively healthy prior to the surgical intervention. Conversely, the reduction in endothelial cell density following surgery was more pronounced in the ECCE group when compared to the PHACO group throughout all follow-up intervals. On the first post-operative day, the ECCE group demonstrated a mean cell count of 2523.30 ± 43.1 cells/mm^2, whereas the PHACO group showed a higher count of 2607 ± 33.7 cells/mm^2. The observed pattern continued consistently during the follow-up period, with the ECCE group exhibiting a greater reduction in endothelial cell count at each subsequent visit. By the third month post-operation, the cell count in the ECCE group decreased to 2373 ± 43.1 cells/mm2, while the PHACO group exhibited a higher count of 2457 ± 33.68 cells/mm^2. A study by Sharma N *et al.*, exposed that average loss of endothelial cells through ECCE was about 12%, while phacoemulsification led to a cut of 7% [23]. The observed lessening in cell loss subsequent phacoemulsification may be ascribed to the smaller incision size and the less invasive character of the surgery. Such factors together donate to minimizing the mechanical stress exerted on the corneal endothelium postoperatively. Self-care and awareness contributes further momentous interventions and handling of the eye [24, 25]. The results were collaborated by a study Ali FS *et al* [26]. The study showed that phacoemulsification outperformed ECCE concerning its efficacy in managing endothelial cell density especially in older patients. The study's answer indicate that older patients display a larger susceptibility to endothelial cell harm owing to a decline in the rejuvenation of these cells linked by ageing. The condensed trauma connected to phacoemulsification plays a critical role in preserving corneal health [27]. Mencucci R *et al.*, tinted that the fluidics of phacoemulsification shows substantial reward [28]. The findings of the current study indicated that the closed system employed in phacoemulsification leads to a more stable intraocular pressure and a decrease in turbulence. Both of these aspects play a role in reducing the loss of endothelial cells. Patel SP *et al.*, conducted a systematic analysis, mentioning related patterns of endothelial cell maintenance [29]. They documented that phacoemulsification established significantly abridged cell loss at one month and three months subsequent the process while compared to ECCE. The research emphasized that the energy needed for phacoemulsification, though it may create a probable risk factor, has been condensed due to advancements in ultrasound expertise. These advancements encompass torsional and pulse modulations, which reduce the total energy delivered to the eye. The elevated endothelial outcomes observed in phacoemulsification may be linked to advancements in technology, which, when paired with reduced incision sizes, elucidate this phenomenon. The gradual decrease in endothelial cell density observed in both groups raises concerns regarding the long-term health of the cornea, with a more significant impact noted in the ECCE group. The follow-up duration of the current study, which is three months, aligns with findings from other research, including that of Yamazaki Y *et al.*, which indicated that the most considerable cell loss occurs within the first month post-surgery, with stabilization occurring thereafter [30]. It is essential to conduct extended follow-up periods to ascertain whether the loss of endothelial cells persists beyond this stage and to assess the potential for corneal decompensation in individuals identified as high risk. The reduction in endothelial cell density is observed following both treatment modalities. However, owing to the minimally invasive characteristics of phacoemulsification and the progress in surgical techniques, it has emerged as the favoured approach for cataract extraction, especially in younger patients with a diminished risk of complications. The findings of this study, along with recent research, suggest that Early Childhood Care and Education (ECCE) may still play a role in specific clinical situations; however, it is linked to an increased risk of postoperative endothelial cell loss and the associated complications.

CONCLUSIONS

This study demonstrated that both Extracapsular Cataract Extraction (ECCE) and Phacoemulsification (PHACO) significantly reduce endothelial cell counts post-operatively, though the impact is more pronounced in the ECCE group. Phacoemulsification was associated with a significantly lower reduction in endothelial cell count at all post-operative time points, suggesting it may be less traumatic to the corneal endothelium compared to ECCE. Overall, PHACO appeared to offer better preservation of endothelial cell health post-operatively, making it a preferable option for cataract surgery in suitable patients.

Authors Contribution

Conceptualization: AAK
Methodology: AAK, IAP
Formal analysis: AAK, SAB
Writing, review and editing: SAB, ZG, PAGK, MA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

DOI: https://doi.org/10.54393/pjhs.v6i1.2565

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2565

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DOI: https://doi.org/10.54393/pjhs.v6i1.1972

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparison of Perception and Academic Outcome of Final Year BDS Students Regarding Lecture-Based Learning and Problem-Based Learning

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ARTICLE INFO

Keywords:
Lecture-Based Learning, Problem-Based Learning, Students Teaching Methods

How to Cite:
Khalil, A., Afreen, A., Amjad, S., Afreen, Z., Siddiqui, M. O., & Iqbal, Q. (2025). Comparison of Perception and Academic Outcome of Final Year BDS Students Regarding Lecture-Based Learning and Problem-Based Learning : Comparison between Lecture vs. Problem-Based Learning. Pakistan Journal of Health Sciences, 6(1), 136-141. https://doi.org/10.54393/pjhs.v6i1.1972

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Received Date: 16th August, 2024
Acceptance Date: 21st January, 2025
Published Date: 31st January, 2025

ABSTRACT

This study explores the differences in student perception and academic outcomes between traditional lecture-based learning and problem-based learning methods in an educational setting. **Objective:** To find the effectiveness of Problem-Based Learning (PBL) versus Lecture-Based Learning (LBL) in enhancing academic performance and student satisfaction. **Methods:** Comparative cross-sectional study was carried out among final year BDS students at Watim Medical and Dental College Rawalpindi. The study evaluated lecture-based learning (LBL) versus problem-based learning (PBL) in Prosthodontics and Operative dentistry. LBL consisted of interactive lectures with clear objectives, while PBL involved group-based problem solving over two months. Academic outcomes were assessed via class tests, with feedback gathered through a structured questionnaire. Data were analyzed using SPSS version 21.0. **Results:** A total of 131 final year BDS students were included. Both genders were considered however majority were females (74%). Mostly participants appreciated both teaching methodologies (58%), a significant proportion favored lecture-based learning (26%) over problem-based learning (11.5%). Perceptions varied on the effectiveness of each method in fostering understanding, self-learning habits, and analytical skills. Many participants expressed dissatisfaction with resource availability and syllabus coverage in PBL sessions, despite positive views on facilitator training. Exam results showed a higher pass rate with PBL (76.3%) compared to LBL (56.5%), but satisfaction with PBL did not significantly influence exam outcomes ($p>0.05$). **Conclusions:** The study concluded that future research should focus on optimizing educational methodologies in dental education to effectively prepare students for the complex demands of healthcare through innovative and balanced approaches.

INTRODUCTION

There is always a quest for exploring the most effective learning method. This led to origination of student oriented innovative techniques like problem-based learning (PBL), case-based learning (CBL) and team-based learning (TBL) [1]. PBL is one of the most successful methods in which student should lead their own learning trail. The original idea of PBL was proposed and initiated by Barrows and Tamblyn at McMaster University (Canada) in 1969 [2]. Later the strategy was applied in Europe and other parts of the world in medical and other sciences [3]. The indigenous strategy was to present a problem or problematic scenario and then motivate the students to find the appropriate solution. The activity is usually done in small groups (8 to 10 students) along with an instructor. Identifying the problem, brain-storming ideas, researching and discussing the solutions are the various steps followed in this student-centered learning process [4,5]. Interactive lectures are one of the oldest and widely used teaching methods in medical education. The students are fond of this method because the teacher covers the entire topic. So, the student's time is saved. They take notes and prepare the topic [6]. When it comes to base wisdom, teaching methods that involve active participation of the students and enhance self-facilitated learning can be ground-

DOI: https://doi.org/10.54393/pjhs.v6i1.1972

breaking [6, 7]. Currently, conventional lectures are evolving and continuously changed by team-based learning like the introduction of problem-based learning [8]. PBL is a teaching method that not only have a positive impact on academic performance of the students but it also greatly enhances the communication skills, self-learning abilities, problem solving skills, independent working abilities as well as team work [9, 10]. As the students first experience the problem situations and then proceed with self-directed learning, it also increases students' metacognitive awareness levels as compared to the traditional teaching methods [11]. Studies show that there is increase long term knowledge retention in problem-based learning as compared to conventional lecture-based learning [12]. Despite the global shift towards more interactive and student-centered learning approaches like Problem-Based Learning (PBL), there is a paucity of research evaluating its effectiveness compared to traditional Lecture-Based Learning (LBL) within the context of dental education in Pakistan.

This study aimed to fill this gap by providing a comparative analysis of PBL and LBL, thereby contributing valuable insights that could guide future curriculum development and pedagogical strategies in Pakistan's dental schools.

METHODS

A comparative cross-sectional study was conducted among final year BDS students at Watim medical and dental college Rawalpindi. Study was conducted in the lectures of Prosthodontics and Operative dentistry after approval granted by the hospital ethical review board under letter no:WM&DCR/R&D(ERB)/2023/85. Convenience method was used for sampling. Sample size was 131 calculated by WHO calculator. Level of significance was 5%, power of the test was 95%, test value of population mean was 3.32, anticipated population mean was 3.81, population standard deviation was 1.205, n=131[13]. The duration of study was 4 months from November 2023 to March 2024. A questionnaire was constructed with 19 questions. It recorded the demographic details in first portion and the feedback about the teaching method in later questions. Students were taught for two months by conventional lecture-based learning (LBL) and feedback was recorded using questionnaire. Then they were taught by problem-based learning (PBL) for next two months and feedback was recorded. In this study LBL refers to the interactive lectures. The lectures were delivered through power point presentations with clear learning objectives and students were involved in summarizing the lecture at the end. In PBL method, 2 lectures were utilized to cover one topic. In first lecture, students were divided in small groups (8-10 students). Then a problem based clinical scenario or question was presented to students and they were instructed to work together to solve it in class and also at home using books, articles and other sources from internet. In the next lecture the teacher facilitated open discussion among groups. At the end feedback was recorded using the questionnaire. Students were also asked about their contentment with either of the teaching methods and their overall satisfaction with the resources and facilities available for each. Assessment was done at the end of two months to record and compare the academic outcome of each method. Subjects scoring at least 50% in the assessment were declared as passed, while those scoring less than 50% were declared as failed. For this purpose, class tests were conducted on completion of topics done by both teaching methods and percentages were calculated and compared. Data were collected and analyzed by using SPSS version 21.0. Responses of the participants were presented as frequency and percentage for categorical variables. To determine the association between PBL and LBL with the exam results, the Chi-square test for association was applied, with a confidence level of 95% and a significance level of 5%.

RESULTS

The study population comprised on 131 participants with the mean age of 23.27±1.27 years, out of which 97 (74%) females and 34 (26%) male participants. Amongst the study population, majority (69; 52.3%) were day scholars. All of the participants attended both of the sessions and were assessed after the completion of the sessions. All of the participants attended both of the sessions and were assessed after the completion of the sessions. 76 (58%) of the participants liked both of the methodologies, though 34(26%) liked lecture-based learning (LBL) and 15 (11.5%) liked problem-based learning (PBL). 66 (50.4%) of the study participants were of the view that both of the strategies lead to better understanding. 56 (42.7%) of the participants were of the view that the habit of self-learning is inculcated by PBL method, while 47 (35.9%) claims that both of the methods inculcate self-learning. 56 (42.7%) said that both of the methods lead to better analytical approach towards a problem. 72 (55%) of the participants said that both of the methods lead to more clarification of concepts (Table 1).

Table 1: Responses of Study Population (n=131)

Variables		Frequency (%)
Gender	Female	97 (74%)
	Male	34 (26%)
Housing	Day Scholar	69 (52.7%)
	Hostelite	62 (47.3%)
Age (in years)	21	9 (6.9%)
	22	28 (21.4%)
	23	37 (28.2%)

DOI: https://doi.org/10.54393/pjhs.v6i1.1972

	24	43 (32.8%)
	25	7 (5.3%)
	26	4 (3.1%)
	27	3 (2.3%)
Which Teaching Methods is liked	Lecture Based Learning	34 (26%)
	Problem Based Learning	15 (11.5%)
	Both A and B	76 (58%)
	Any other	6 (4.6%)
Which Methods Leads to Better Understanding	Lecture Based Learning	35 (26.7%)
	Problem Based Learning	25 (19.1%)
	Both A and B	66 (50.4%)
	Any Other	5 (3.8%)
The Habit of Self-Learning is Inculcated by	LBL	22 (16.8%)
	PBL	47 (35.9%)
	Both a and b	56 (42.7%)
	Any other	6 (4.6%)
Which Method Leads to Better Analytical Approach towards Problem	LBL	35 (26.7%)
	PBL	36 (27.5%)
	Both	56 (42.7%)
	Any other	4 (3.1%)
Which Method Leads to more Clarification of Concepts	LBL	31 (23.7%)
	PBL	24 (18.3%)
	Both	72 (55%)
	Any other	4 (3.1%)
Satisfied with the Availability of Resources for PBL Sessions	yes	51 (38.8%)
	no	72 (55%)
	Don't know	8 (6.1%)
Enough Syllabus is Covered by PBL Sessions	yes	47 (35.9%)
	no	65 (49.6%)
	Don't know	19 (14.5%)
Facilitators are Well Trained to Conduct PBL Sessions	yes	91 (69.5%)
	no	18 (13.7%)
	Don't know	22 (16.8%)
Satisfied with Lectures Concurrent with PBL	yes	57 (43.5%)
	no	46 (35.1%)
	Don't know	28 (21.4%)
Result of PBL Exams	Pass	100 (76.3%)
	Fail	31 (23.7%)
Result of LBL Exams	Pass	74 (56.5%)
	Fail	57 (43.5%)

72 (55%) participants were not satisfied with the availability of resources for PBL sessions. However, 65 (49.6%) of the participants reported that enough syllabus was not covered by PBL sessions. 91(69.5%) said that facilitators were well trained to conduct PBL sessions. Although, 57 (43.5%) of the participants were satisfied with lectures concurrent with PBL. While 46 (35.1%) were not satisfied with the concurrent lectures with PBL. Majority of the participants (76.3%) passed the PBL exam, however 56.5% passed the LBL exam (Figure 1).

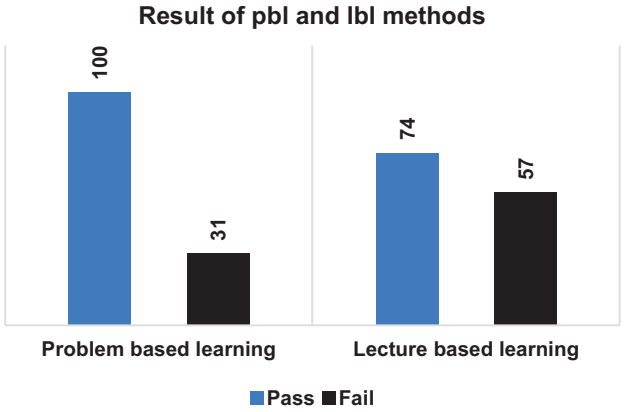

Figure 1: Result of Problem-Based Learning and Lecture-Based Learning (n=131)

The satisfaction level of the study participants was compared with the result of PBL. The study findings predicts that those who were not satisfied with the PBL method, passed the exam but none of the findings were statistically significant (p>0.05) as mentioned in Table 2.

Table 2: Comparison of Satisfaction Level of Study Population with PBL Result (N=131)

Responses of Participants Regarding PBL Method			Result of PBL Exam: Pass	Result of PBL Exam: Fail	p-Value
Satisfied with the Availability of Resources for PBL Sessions	Yes	n	35	16	0.230
		%	35.0%	51.6%	
	No	n	59	13	
		%	59.0%	41.9%	
	Don't know	n	6	2	
		%	6.0%	6.5%	
Enough Syllabus is Covered by PBL Sessions	Yes	n	36	11	0.957
		%	36.0%	35.5%	
	No	n	50	15	
		%	50.0%	48.4%	
	Don't know	n	14	5	
		%	14.0%	16.1%	
The Facilitators were Well Trained to Conduct PBL Sessions	Yes	n	69	22	0.338
		%	69.0%	71.0%	
	No	n	12	6	
		%	12.0%	19.4%	
	Don't know	n	19	3	
		%	19.0%	9.7%	
Satisfied with Lectures Concurrent with PBL	Yes	n	45	12	0.861
		%	45.0%	38.7%	
	No	n	34	12	
		%	34.0%	38.7%	
	Don't know	n	21	7	
		%	21.0%	22.6%	

The study participant's satisfaction level was compared with LBL level and satisfactory findings were observed only with the 'facilitators that they were well trained to conduct sessions' with the participants who passed the LBL exam (73%) but the findings were non-significant (p>0.05). The

DOI: https://doi.org/10.54393/pjhs.v6i1.1972

findings predict that satisfaction level has no relation with LBL exam results (Table 3).

Table 3: Comparison of Satisfaction Level of Study Population with LBL Result (N=131)

Responses of participants regarding LBL method			Result of LBL Exam		p-Value
			Pass	Fail	
Satisfied with the Availability of Resources	Yes	n	32	19	0.508
		%	43.2%	33.3%	
	No	n	38	34	
		%	51.4%	59.6%	
	Don't know	n	4	4	
		%	5.4%	7.0%	
Enough Syllabus is Covered	Yes	n	29	18	0.421
		%	39.2%	31.6%	
	No	n	33	32	
		%	44.6%	56.1%	
	Don't know	n	12	7	
		%	16.2%	12.3%	
The Facilitators were Well Trained to Conduct Sessions	Yes	n	54	37	0.497
		%	73.0%	64.9%	
	No	n	8	10	
		%	10.8%	17.5%	
	Don't know	n	12	10	
		%	16.2%	17.5%	
Satisfied with Lectures	Yes	n	36	21	0.419
		%	48.6%	36.8%	
	No	n	23	23	
		%	31.1%	40.4%	
	Don't know	n	15	13	
		%	20.3%	22.8%	

DISCUSSION

The current study explores dental students' perceptions of problem-based learning (PBL) and lecture-based learning (LBL), revealing diverse preferences. While many participants appreciated both methods, a significant portion favored LBL for its traditional approach. Nonetheless, PBL was recognized for promoting self-learning and analytical skills. Concerns about resource availability and syllabus coverage were noted, impacting PBL satisfaction. Facilitator training for PBL was generally seen as adequate, despite some dissatisfaction with concurrent lectures. Although PBL showed a higher exam pass rate compared to LBL, satisfaction levels did not correlate significantly with exam outcomes. A comprehensive review of teaching methodologies in medical and dental education globally reveals a shift towards innovative approaches aimed at enhancing learning outcomes and preparing students for clinical practice. The medical educators are facing greater challenges in order to meet the rapid development in health care needs arising globally and the relative lag in comprehensive teaching methods [14]. Prosperously, numerous researchers conducted studies on atypical pedagogies and models. These constitute methods like flipped classrooms, blended learning (combining more than single method), inquiry-based learning, problem-based learning and online learning [15,16]. Other studies found that the traditional lecture-based learning (LBL) model was used widely lags behind when it comes to problem-solving, collaborative learning and critical thinking [17, 18]. Various researchers have proposed different numbers of steps that are included in Problem-based learning (PBL). But most common of these are four steps namely: problem definition, research, implementation, reflection and evaluation [19]. Problem-Based Learning (PBL) is recognized for fostering critical thinking and self-directed learning, though comparisons with traditional lecture-based methods show varied impacts on student satisfaction and academic performance. Lecture-Based Learning (LBL) remains prevalent for its structured delivery of content, while adaptations like flipped classrooms are explored for their potential to improve engagement and retention. However, our study showed that 58% of the students were fond of both of the methodologies, while only 26% of students like lecture-based learning. These results are similar to study done by Yue et al., In their study, 46% students were fond of both methodologies, while 14% of students liked lecture-based learning [20]. While in contrast of ours, study done by Solomon Y, showed that 63.2% of students preferred lecture-based learnings while 36.6% preferred problem-based learning [21]. A meta-analysis and systematic review done by Zheng QM, et al., showed that problem-based learning was superior in clinical competence and student satisfaction compared to lecture-based learning [22]. This study showed contradictory results compared to our study. Problem-Based Learning (PBL) is increasingly recognized for its effectiveness in simulating real-world scenarios and seamlessly integrating theoretical knowledge with practical skills, making it a vital component of modern educational strategies in healthcare. This approach not only enhances critical thinking and problem-solving abilities but also fosters a deeper understanding of the material by engaging students in active learning. The varied outcomes and preferences among students for PBL and LBL highlight the need for a more personalized educational approach that caters to different learning styles and career aspirations. In the current study, a significant majority of participants (76.3%) successfully passed the PBL exam, compared to 56.5% who passed the LBL exam, indicating a clear advantage of PBL in promoting academic success. These findings are consistent with previous research by Pan et al., [14], Nakhjiri et al., [23], and O'Dea XC et al., [24] where the PBL groups demonstrated significantly higher examination scores—around 80%—compared to the

DOI: https://doi.org/10.54393/pjhs.v6i1.1972

control groups, which had an average pass rate of 39.4%. This consistent trend underscores the effectiveness of PBL in improving academic outcomes. Moreover, the successful implementation of PBL relies heavily on the quality of faculty training. Educators must be adept at designing and delivering PBL sessions, which require a different set of instructional skills compared to traditional lectures. Faculty training programs must emphasize the importance of instructional design and assessment methods that align with evolving educational paradigms in healthcare. These findings suggest that dental schools should consider integrating more PBL into their curricula to enhance student engagement and academic performance. However, the complexity of educational methodologies also indicates that a one-size-fits-all approach may not be sufficient [24]. Tailored educational strategies that incorporate both PBL and LBL, adjusted to the specific needs and learning preferences of students, could offer a more balanced and effective educational experience [25]. Future research should explore how these methodologies can be optimized and blended to better prepare dental students for the diverse challenges they will face in their professional careers. Furthermore, curriculum enhancement efforts should focus on creating a dynamic learning environment that supports the development of both theoretical knowledge and practical skills, ensuring that graduates are well-equipped to meet the demands of the ever-changing healthcare landscape. The study's limitations include a small, single-institution sample size and the use of convenience sampling, which may limit the generalizability and introduce bias. Additionally, the short duration of four months and reliance on class tests may not adequately capture long-term outcomes or fully assess the complexities of student learning, suggesting a need for more comprehensive evaluation methods.

CONCLUSIONS

The study concluded that both PBL and LBL offer valuable benefits in dental education, highlighting the importance of integrating innovative approaches with traditional teaching methods. For educators in dental schools, these findings suggest the need to balance foundational knowledge delivery with methods that enhance critical thinking and problem-solving skills. To better prepare students for the evolving demands of the healthcare system, educators should consider incorporating more PBL elements into their curriculum, ensuring that students are not only receiving information but also learning how to apply it in real-world, unpredictable situations.

Authors Contribution

Conceptualization: AK
Methodology: AK, SA
Formal analysis: AA, MOS
Writing, review and editing: AA, ZA, MOS, QI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2074

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Frequency of Erectile Dysfunction among Smokers and Non-Smoker Men Visiting Tertiary Care Hospital Nawabshah

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ARTICLE INFO

Keywords:
Erectile Dysfunction, Smoker, Non-Smokers

How to Cite:
Chandio, S. A., Bhalar, Z. A., Zardari, I. A., Ali Shar, Z., Toor, H.-U.-R., & Ghumro, A. H. (2025). Frequency of Erectile Dysfunction among Smokers and Non-Smoker Men Visiting Tertiary Care Hospital Nawabshah : Frequency of Erectile Dysfunction among Smokers and Non-Smoker Men. Pakistan Journal of Health Sciences, 6(1), 142–146. https://doi.org/10.54393/pjhs.v6i1.2074

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Received Date: 20th August, 2024
Acceptance Date: 14th January, 2025
Published Date: 31st January, 2025

ABSTRACT

Epidemiological studies have shown that cigarette smoking is the independent risk factor for erectile dysfunction (ED), with smokers 1.5–2 times more likely to develop ED than nonsmokers. Additionally, long-term research has shown that quitting smoking improves erectile function, with noticeable improvements even within 24 hours of cessation. **Objective:** To determine the frequency of erectile dysfunction among male smokers and non-smokers at PMC Hospital Nawabshah. **Methods:** This research was conducted at the Department of Urology, Peoples Medical University Hospital, Nawabshah. A formal written consent /agreement was obtained from every subject/individual who fulfilled the inclusion criteria and then decided to participate. The measure divides ED into four groups based on IIEF-5 scores: mild to moderate (12–16), mild (17–21), no ED (22–25), moderate (8–11), and severe (1–7). Data were being analyzed by computer software statistical package for social sciences version 23. Frequency and percentage were computed for variables. 85.9% are confirmed to have some degree of ED, and 14.1% are found not to have ED. **Results:** Among the smokers, 39(27%) had mild ED, but in non-smokers, 53(37%) had mild ED. Among the smokers, 50(35%) had moderate ED, and in non-smokers, 51(36%) had moderate ED. In smokers, 64(45%) had severe ED, and in non-smokers, 38(27%) had severe ED. **Conclusions:** Smoking tremendously affects the erection of patients. Whereas non-smokers had a little bit less effect on erectile function.

INTRODUCTION

The prevalence of ED is increasing, and more individuals are becoming aware that treatment options are available. ED is also thought to be a strong predictor of coronary artery disease, and a cardiovascular evaluation of a patient presenting with ED is indicated [1,2]. Aside from cardiovascular illness, there are considerable associations between Erectile dysfunction, hypertension, hypogonadism, smoking and drinking. E-cigarette usage may cause ED in men, but further research, particularly clinical trials, is needed to determine a link between e-cigarettes and ED [3]. Erectile dysfunction (ED), a health condition that greatly impairs men's quality of life around the world. Smoking is independently linked to erectile dysfunction and cardiovascular disease. This does not reduce life expectancy, but it might seriously harm one's health and standard of living [4, 5]. By 2025, there will be 200 million ED-affected males in Asia, a 130% increase from current predictions [6]. Few studies have shown to assess the frequency of ED in developing nations. Between the ages of 25 and 70, the frequency of ED in males is 19%; however, beyond the age of 50, it rises to above 25% [7]. Globally, with an estimated 322 million people expected to be affected by ED by 2025, the burden of the disease is enormous. Previous studies showed that the United States (US) and Asia have greater incidence of ED than the rest of the globe. By 2025, there will be 200 million ED-affected

DOI: https://doi.org/10.54393/pjhs.v6i1.2074

males in Asia, a 130% increase from current predictions [8]. The lack of data may also be due to the social stigma and differing cultural norms around sexual dysfunction, especially in South Asia, which discourage men from talking to their primary care doctors about it [9,10]. Remarkably, multicenter research conducted in 2003 discovered that Pakistan had the greatest frequency of ED (80.8%) among males visiting primary care clinics, comparable to Egypt (63.6%) and Nigeria (57.4%). ED is linked with many influences, including advanced age, depression, obesity, physical inactivity, and co-morbid conditions, including diabetes, cardiovascular disease, peptic ulcers, and prostate disease [11]. The frequency of ED in the general population in Pakistan is above 80%, which is rather concerning as the rate among diabetics in the US was 51.3% [12]. The population under study, terminology, and methodology affect how common ED is. Some research has been conducted to determine the occurrence and frequency of ED in healthy people, perhaps because the condition is correlated with long-lasting illnesses such as diabetes mellitus, heart disease, hypertension, and a range of neurological disorders that typically occur with age [13]. Although the etiology of smoking-related erectile dysfunction is still unclear, it may include endothelium-mediated smooth muscle relaxation impairment, similar to that of diabetes [14]. Beyond "further simple investigation upon the functional as well as chemical mechanisms which should motivate the cause, pathology, and reaction to management of the numerous methods of erectile dysfunction, the National Institutes of Health Consensus Development Panel on Impotence identified a need for future research [15]. Age and vascular variables impact the incidence of ED in Pakistan, highlighting that smoking is a significant risk factor. It also highlights a few possible influences, for example, diabetes, hypertension, and smoking, all of which tend to raise the chance of ED[16].

Thus, the current research aimed to inspect the frequency of ED at PMC Nawabshah's Department of Urology and evaluate its correlation with other parameters. The results of the research will aid medical professionals in comprehending the frequency and dynamics of erectile problems in men and also in identifying and addressing the condition's modifiable risk factors.

METHODS

Current study was conducted at the Department of Urology Peoples Medical College Hospital Nawabshah, Shaheed Benazir Abad, from July 2023 to December 2023. The design of the study was comparative cross-sectional. The non-probability convenience sampling technique was used for data collection. The sample size was calculated using the Rao soft sample size calculator using P= Prevalence 25% [2], Confidence level = 95%, Margin of Error = 5%, and Population size = 20000. The sample size was 289. The participants aged 30 years or older and willing participants were included in the study, while the participants aged above 80 years and not willing participants were excluded. The Peoples University of Medical & Health Sciences' Ethical Review Committee (ERC) gave its approval for this research to be carried out for women in Nawabshah (SBA) under letter no: ERC/2023/299. The formal approval was obtained by the Peoples Medical College Hospital Nawabshah's Medical Superintendent, who has a higher position. All participants received a pre-made questionnaire. The questionnaire was arranged according to the IIEF. The International Index of Erectile Function (IIEF) is a multidimensional self-report instrument that has been used to evaluate male sexual function. It addresses the most relevant aspects of male sexual function, such as erectile strength, orgasm, desire, satisfaction with intercourse, and overall satisfaction. This can be readily self-administered either in research or in clinical settings, and it has the requisite sensitivity and specificity needed to detect treatment-related changes in patients with ED. The IIEF classifies the severity of ED into five categories stratified by score:

1. No ED=26–30
2. Mild=22–25
3. Mild to moderate=17–21
4. Moderate=11–16
5. Severe.6–10

Data were analyzed using SPSS version 23.0. Frequency and percentage were computed for variables. The Chi-square test was applied to see the frequencies and T- the test was applied to compare the mean scores of the two groups.

RESULTS

Two groups were made. Group A were smokers and were 143, and group B were nonsmokers, and they were 142 (Table 1).

Table 1: Characteristics of Study Participants

Group	Number of Participants
Smokers	143
Non-Smokers	142

In smokers' patients aged between 30-39 years, 10 had mild ED, 7 had Moderate ED, and 8 had severe ED, respectively. Of the patients aged between 40-49 years, 15 had mild ED, 10 had Moderate ED, and 15 had severe ED, respectively. Of the patients aged between 50-59 years, 8 had mild ED, 20 had Moderate ED, and 20 had severe ED, respectively. Among patients aged between 60-69 years, 4 had mild ED, 8 had Moderate ED, and 12 had severe ED, respectively. Among patients aged between 70-80 years, 2 had mild ED, 5

DOI: https://doi.org/10.54393/pjhs.v6i1.2074

had Moderate ED, and 9 had severe ED, respectively. In non-smokers, among patients aged between 30-39 years, 12 had mild ED, 8 had Moderate ED, and 5 had severe ED, respectively. Among patients aged between 40-49 years, 18 had mild ED, 12 had Moderate ED, and 10 had severe ED, respectively. Among patients aged between 50-59 years, 10 had mild ED, 20 had Moderate ED, and 15 had severe ED, respectively. Among patients aged between 60-69 years, 7 had mild ED, 6 had Moderate ED, and 5 had severe ED, respectively. Among patients aged between 70-80 years, 6 had mild ED, 5 had Moderate ED, and 3 had severe ED, respectively. In smokers, 39(27%) had mild ED, but in non-smokers, 53(37%) had mild ED. In smokers, 50(35%) had moderate ED and in non-smokers, 51(36%) had moderate ED. In smokers, 64(45%) had severe ED, and in non-smokers, 38(27%) had severe ED (Table 2).

Table 2: Comparison of ED Severity Between Smokers and Smokers

Severity of ED	Smokers	Non-Smokers	p-Value
Mild ED	39 (27%)	53 (37%)	0.3
Moderate ED	50 (35%)	51 (36%)	
Severe ED	64 (45%)	38 (27%)	
Total	143	142	

Table no 3 shows IIEF among the smoker and non-smoker participants of the study. 55 participants had severe ED with a score range 6-10, 45 participants had moderate ED with a score range of 11-16, 25 participants had mild to moderate ED with a score range of 17-21, 10 had mild ED with a score range 22-25, and 8 participants had no ED with score range 26-30. The IIEF among the non-smoker participants of the study out of which 30 participants had severe ED with a score of range 6-10, 30 participants had moderate ED with a score range 11-16, 40 of the participants had mild to moderate ED with score range 17-21, 22 participants had mild ED with score range 22-25, and 20 participants had no ED with score range 26-30. The p-value was 0.003.

Table 3: International Index of Erectile Function (IIEF) in Smokers and Non-Smoker Participants of the Study

Score Range	Classification	No Smoker participants	No of non-smoker participants	p-Value
6-10	Severe ED	55	30	0.03
11-16	Moderate ED	45	30	
17-21	Mild to moderate ED	30	40	
22-25	Mild Ed	10	22	
26-30	No ED	8	20	

Among the smoker participants, 94.4% had ED with an 11.8 mean erectile function score, while among the non-smoker participants, 85.9% had ED with an 18.4 mean erectile function score (Table 4).

Table 4: Comparison of Smokers and Non-Smokers by Erectile Function Score

Status	ED	Mean erectile Function score
Smokers	94.4%	11.8
Non-Smokers	85.9%	18.4

DISCUSSION

In addition to the well-established harmful effects of smoking (i.e., coronary artery disease and lung cancer), the past three decades have led to a compendium of evidence being compiled into the development of a relationship between cigarette smoking and erectile dysfunction. It was observed in the current study that more smoker participants had ED than non-smokers [15]. The current study observed that smokers had more severe to moderate ED than the non-smoker participants of the study. Other studies found that erectile dysfunction should become an age-linked disorder most frequent in males with diabetes and/or cardiovascular disease. Because the physiology of erection is heavily dependent on vascular changes, many of the known cardiovascular risk factors, such as hypertension and diabetes, have been associated with the development of erectile dysfunction. It seems that comorbidities also affect the ED. In this study, it was observed that aging has a major effect on ED [16]. According to a study conducted on habitual smokers, there is important progress between nocturnal penile tumescence and rigidity within 24 hours of quitting smoking. That progress was observed even when patients received nicotine through transdermal patches, representing the influences further than nicotine plays a role in ED [17]. Cigarette smoking was the significant autonomous reason for ED in studies significant for confounding variables (e.g., age and healthy living). The findings demonstrated a dose-response effect, where in low intensities of cigarette smoking (~8.6 cigarettes/d; RR = 1.26; 95% CI, 1.10-1.44) were linked to a lower risk of ED than high intensities of current smoking (>20 cigarettes/d; risk ratio [RR] = 1.53; 95% CI, 1.31-1.80). Additionally, the meta-analysis showed that a higher risk of ED was linked to higher levels of past cigarette smoking (~23 pack-years total, <5 years since quit; RR = 1.64; 95% CI, 1.52-1.76) than lower levels (~10 pack-years total, >10 years since quit; RR = 1.17; 95% CI, 1.13-1.21). Similar findings were observed in the current study [18]. Furthermore, the severity of a patient's ED may also predict one's response to quitting. Feldman HA *et al.* observed in their study that smoker patients suffer from ED severely as compared to nonsmokers and observed that smoking has an effect on the ED of the patients. It was also observed in the current study [19]. In a subgroup analysis of other larger studies, odds ratios of patients who developed ED showed a significant difference

DOI: https://doi.org/10.54393/pjhs.v6i1.2074

when men smoked more than 10 cigarettes per day. Among smokers, a positive but non-significant trend towards increased ED occurred in relation to daily cigarette intake. Strong evidence has been found in research on erectile dysfunction with tobacco contact intensities in current smokers. Gilbert DG and Hagen RL *et al.* also observed the same [20]. Diabetes also contributes to ED through both microvascular and macrovascular damage. Studies have shown that >50% of diabetics have some degree of ED. Furthermore, men with diabetes have a threefold increase in risk for developing ED. The prevalence of the main risk factors for erectile dysfunction (smoking, alcoholism, heart illness, and diabetes) was approximately alike with sexually active and quiet groups. Which were comparable to Harte CB and Meston's study [21].

CONCLUSIONS

It is established that smoking tremendously affects the erection of patients who are smokers. Whereas non-smokers had a little bit less effect on erectile function. In smokers, age and co-morbidities also participate and enhance the ED, whereas the reverse is in the case of non-smokers.

Authors Contribution

Conceptualization: SAC
Methodology: ZAB, HURT, AHG
Formal analysis: IAZ, ZAS
Writing, review and editing: HURT

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2338

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Predictors of Antepartum Hemorrhage in Patients with Placenta Previa

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ARTICLE INFO

Keywords:
Antepartum Hemorrhage, Placenta Previa, Cesarean Sections, Advanced Maternal Age

How to Cite:
Bashir, S., Idrees, U., Chughtai, H. A., Arif, S., Khatoon, N., & Tehseen, S. (2025). Predictors Of Antepartum Hemorrhage In Patients With Placenta Previa: Antepartum Hemorrhage In Placenta Previa. Pakistan Journal of Health Sciences, 6(1), 147-151. https://doi.org/10.54393/pjhs.v6i1.2338

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Received date: 2nd November, 2024
Avveptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

Antepartum Hemorrhage (APH) is a significant complication in pregnancy that poses serious risks to both maternal and fetal health. **Objective:** To find the predictors of antepartum hemorrhage in patients with placenta previa among the local population of Pakistan. **Methods:** This cross-sectional study was conducted at PAF Hospital Mianwali from November 2023 to April 2024. A total of 208 patients were included in the analysis. Patients diagnosed with placenta previa confirmed through ultrasound examination were included in the study. **Results:** The mean age of the patients was 32.83 ± 4.56 years. Out of 208, there were 60 (28.8%) and nulliparous, 148 (71.2%) were multiparous. 85 (40.9%) had previous C-section and 30 (14.4%) were suffered from hypertension. 15 (7.2%) were diabetic and 180 (86.5%) were non-smokers. APH increased by 15% (Adjusted OR: 1.15, 95% CI: 1.05-1.26, p = 0.005). Furthermore, patients with a history of previous cesarean sections had over twice the odds of developing APH compared to those without this history (Adjusted OR: 2.12, 95% CI: 1.23-3.66, p = 0.007). **Conclusions:** This study concluded that advanced maternal age and a history of previous cesarean sections are significant predictors of antepartum hemorrhage in patients with placenta previa.

INTRODUCTION

Antepartum Hemorrhage (APH) is a major cause of maternal and fetal compromise in pregnancy whose major risks would include the following. Whereas placenta previa is a severe cause of APH that results from implantation of the placenta over or near the cervical. It goes with bleeding that can endanger the pregnancy and may potentially result in early delivery [1]. The prevalence has however been increasing mainly due to increased rates of cesarean section deliveries and advanced maternal age. Consequently, healthcare providers must be very careful and closely observe the patients with this disease [2]. The rates of occurrence of the placenta previa also vary, it is staked at 0,5-2% of all pregnancies and differences depending on geographical and demographic indicators [3]. There are four types of placenta previa, and management and prognosis vary depending on which of the four: total, partial, marginal, and low-lying placenta previa [4]. The situation in which the placenta occupies the area of the cervix is referred to as full placenta previa which poses the highest risk of bleeding and complications during labor. On the other hand, low-lying placenta previa may get better as the pregnancy progresses [5]. Frequent risk factors related to antepartum hemorrhage in placenta previa patients should be known to enhance the quality of maternal-fetal results. Some examples of risk factors include previous cesarean sections, multiparity, maternal age, and some diseases that will help in the early evaluation and treatment of such patients [6]. Meta-analyses of prior investigations have highlighted that the rate of placenta previa is higher in women who have had a previous C-

DOI: https://doi.org/10.54393/pjhs.v6i1.2338

section, possibly because of scarring of the uterine wall and hence placental attachment [7]. Furthermore, pregnant women in the advanced maternal age group are at higher risk for placenta previa and its consequential hemorrhage. Number of gestations is another important predictor that should be considered. There is increased placenta previa risk in multiparous than in nulliparous women mainly because of such changes in the structural makeup of the uterus following previous pregnancies [5]. Other factors, which include, multiple gestation and maternal medical complications like hypertension and diabetes also play a part in the development of placenta previa and consequently APH. It is of great clinical importance to identify these predictors because of the specificity of their manifestation [8]. Accurate early identification enables better assessment of the maternal condition and fetal well-being, as well as strategies regarding possible delivery. For example, women classified as high-risk deserve scheduled cesarean sections before the onset of labor, which can be useful in the prevention of severe hemorrhage and general enhancement of both maternal and neonatal health outcomes [9]. Besides clinical features, patient characteristics and the external environment, including cigarette smoking and uterine pathology, could further boost the likelihood of placenta previa and related APH [10]. Smoking is also reported to be with low birth weight preterm and even abnormal implantation of placenta during pregnancy. Any abnormality in the shape or size of the uterus whether congenital or as a result of other factors can cause developmental abnormalities in the placental locale increasing the prevalence of previa. Nonetheless, given such risk factors and predictors, more elaborate research efforts that discuss the relationships between such variables in different populations are still lacking [11-13].

The aim of this study was to find the predictors of antepartum hemorrhage in patients with placenta previa among the local population of Pakistan.

METHODS

This cross-sectional study was conducted at PAF Hospital Mianwali from November 2023 to April 2024. Approval from the hospital's ethical committee was obtained and informed consent was taken before collecting the data. Ethical approval was taken from ethical review committee Ref No. 005G Estb/EC/01/2023. A total of 208 patients were included in the analysis. Sample size was calculated using open Epi calculator. Assuming a prevalence of placenta previa, a 95% confidence interval, and a 5% margin of error, the required sample size was determined to include 208 participants, ensuring adequate power for statistical analysis. Adjustments were made for potential exclusions and dropouts. Patients diagnosed with placenta previa confirmed through ultrasound examination were included in the study. Pregnant women of all ages presented with symptoms of antepartum hemorrhage. Patients with multiple gestations, those with other complicating factors, such as placenta accreta, and who underwent elective cesarean delivery for reasons unrelated to previa were excluded. Data were collected from the patient's medical records, ensuring confidentiality and compliance with ethical guidelines. Data consists of demographic factors including; age, parity, prior pregnancies, and Socioeconomic status. Previous history of surgery, including the prior history of cesarean section; history of prior miscarriages; and history of prior placenta previa was taken. Some clinical predictors examined included a history of hypertension, diabetes, smoking status, and any observed uterine abnormalities in past pregnancies. Both maternal and neonatal details were documented concerning antepartum hemorrhage rates, number of cases requiring blood transfusions, gestational age at birth, type of delivery; vaginal or cesarean section, birth weight of the baby, and Apgar score. Data were analyzed using the software SPSS version 26.0. Descriptive statistics were calculated for all variables, including means, medians, and standard deviations for continuous variables, and frequencies and percentages for categorical variables. Univariate analysis was conducted to describe the distribution of individual variables within the study population. Continuous variables such as age, gestational age, and birth weight were summarized using means, medians, and standard deviations, while categorical variables like parity, socioeconomic status, type of delivery, and history of cesarean section were reported as frequencies and percentages.

RESULTS

Data were collected from 208 patients according to inclusion criteria of the study. The mean age of the patients was 32.83 ± 4.56 years. Out of 208, there were 60 (28.8%) and nulliparous, 148 (71.2%) were multiparous. 85 (40.9%) had previous C-section and 30 (14.4%) were suffered from hypertension. 15 (7.2%) were diabetic and 180 (86.5%) were non-smokers (Table 1).

Table 1: Demographic and Clinical Characteristics of Patients (n = 208)

Variables	Mean ± SD / Frequency (%)
Mean Age (Years)	32.83 ± 4.56
Parity	
Nulliparous	60 (28.8%)
Multiparous	148 (71.2%)
Previous Cesarean Sections	85 (40.9%)
Comorbid Conditions	
Hypertension	30 (14.4%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2338

Diabetes	15 (7.2%)
Smoking Status	
Non-Smokers	180 (86.5%)
Smokers	28 (13.5%)

120 patients with Antepartum Hemorrhage (APH), a significant proportion (50%) had a history of previous cesarean sections, compared to only 28.4% of the 88 patients without APH (p = 0.005). Although the proportions of nulliparous and multiparous women were similar between the two groups, the study did not find significant differences for other predictors, including hypertension, diabetes, and smoking, with p-values of 0.350, 0.480, and 0.450, respectively (Table 2).

Table 2: Univariate Analysis of Predictors of Antepartum Hemorrhage (n = 208)

Predictors	APH (+) Frequency (%)	APH (-) Frequency (%)	p-Value
Nulliparous	30 (25%)	30 (34.1%)	0.150
Multiparous	90 (75%)	58 (65.9%)	0.150
Previous Cesarean Sections	60 (50%)	25 (28.4%)	0.005
Hypertension	20 (16.7%)	10 (11.4%)	0.350
Diabetes	10 (8.3%)	5 (5.7%)	0.480
Smoking	18 (15%)	10 (11.4%)	0.450

In figure 1 the results of the univariate analysis conducted to identify significant predictors of antepartum hemorrhage. Predictors that were evaluated included maternal age, parity, previous cesarean section, multiple pregnancies, placental abnormalities (e.g., placenta previa, placental abruption), smoking, hypertension, and gestational diabetes. Each variable was analyzed individually to assess its association with the incidence of antepartum hemorrhage. Statistical measures, such as Odds Ratios (ORs) with corresponding 95% Confidence Intervals (CIs), were presented. Variables with statistically significant associations ($p < 0.05$) were highlighted. The graphical representation included either a forest plot or bar chart to facilitate interpretation of the results.

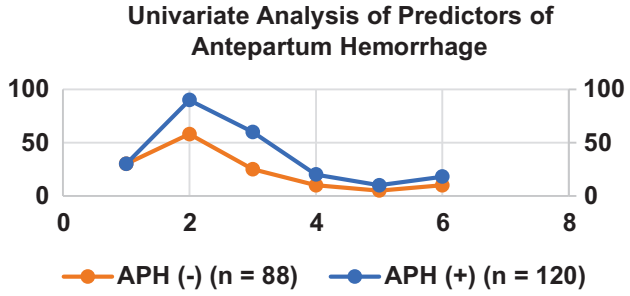

Figure 1: Univariate Analysis of Predictors of Antepartum Heomorrhage

APH increased by 15% (Adjusted OR: 1.15, 95% CI: 1.05-1.26, p = 0.005). Furthermore, patients with a history of previous cesarean sections had over twice the odds of developing APH compared to those without this history (Adjusted OR: 2.12, 95% CI: 1.23-3.66, p = 0.007). Other factors such as nulliparity, hypertension, diabetes, and smoking did not show significant associations with APH, indicating that age and prior cesarean deliveries are critical risk factors for this complication (Table 3).

Table 3: Multivariate Logistic Regression Analysis

Predictors	Adjusted OR (95% CI)	p-Value
Mean Age (Years)	1.15 (1.05-1.26)	0.005
Previous Cesarean Sections	2.12 (1.23-3.66)	0.007
Nulliparous	1.40 (0.82-2.39)	0.200
Hypertension	1.75 (0.83-3.70)	0.140
Diabetes	1.60 (0.65-3.94)	0.300
Smoking	1.25 (0.63-2.47)	0.520

This figure presented the results of the multivariate logistic regression analysis that was conducted to determine independent predictors of the outcome variable. Variables included in the model were those that had shown significance in the univariate analysis or were clinically relevant. Adjusted Odds Ratios (AORs) with corresponding 95% Confidence Intervals (CIs) were displayed to quantify the strength of association for each predictor. Variables with statistically significant associations ($p < 0.05$) were highlighted. The results were visualized using a forest plot to provide a clear comparison of the adjusted effects of each predictor (Figure 2).

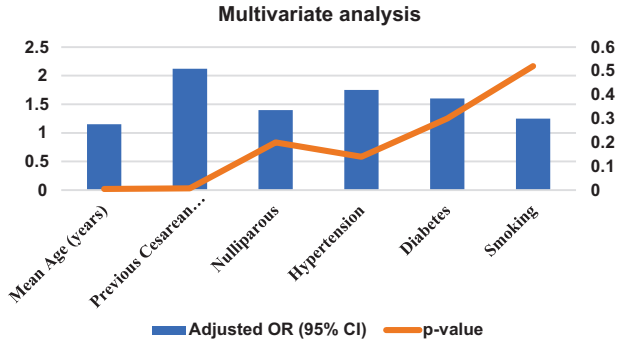

Figure 2: Multvariate Analysis of Logistic Regression Analysis

Infants in the APH group had a mean birth weight of 2,800 grams (range: 1,500-3,600), notably lower than the 3,200 grams (range: 2,500-4,000) observed in the non-APH group ($p < 0.001$). Additionally, the Apgar score at 1 minute was significantly lower in the APH group, with a median score of 7 (range: 3-9) compared to 8 (range: 6-9) in the non-APH group ($p < 0.001$). Furthermore, 33.3% of infants in the APH group were admitted to the NICU, compared to only 11.4% in the non-APH group ($p < 0.001$). The rate of preterm births was also significantly higher in the APH group, with 50% of infants born before 37 weeks gestation, compared to 22.7% in the non-APH group ($p < 0.001$) (Table 4).

DOI: https://doi.org/10.54393/pjhs.v6i1.2338

Table 4: Neonatal Outcomes Based on Antepartum Hemorrhage Status (n = 208)

Neonatal Outcomes	APH (+) Frequency (%)	APH (-) Frequency (%)	p-Value
Birth Weight (g)	2,800 (1,500-3,600)	3,200 (2,500-4,000)	<0.001
Apgar Score at 1 Minute	7 (3-9)	8 (6-9)	<0.001
NICU Admission	40 (33.3%)	10 (11.4%)	<0.001
Preterm Birth (<37 Weeks)	60 (50%)	20 (22.7%)	<0.001

In the APH group, 25% required blood transfusions, compared to only 5.7% in the non-APH group ($p < 0.001$). Additionally, a substantial majority of patients with APH (75%) underwent scheduled cesarean deliveries, while only 28.4% of those without APH had this procedure ($p < 0.001$). Conversely, vaginal delivery was much more common in the non-APH group, with 68.2% delivering vaginally compared to just 16.7% in the APH group ($p < 0.001$) (Table 5).

Table 5: Management Interventions for Antepartum Hemorrhage (n = 208)

Interventions	APH (+) Frequency (%)	APH (-) Frequency (%)	p-Value
Blood Transfusion	30 (25.0%)	5 (5.7%)	<0.001
Scheduled Cesarean Delivery	90 (75.0%)	25 (28.4%)	<0.001
Vaginal Delivery	20 (16.7%)	60 (68.2%)	<0.001
Hospital Stay > 3 Days	50 (41.7%)	10 (11.4%)	<0.001

DISCUSSION

The findings suggested that measures of gestational age and prior surgical deliveries are key contributors to APH. Also, knowledge has been gained on the effect of APH on neonatal mortality and the approaches used in the management of affected patients [14]. A variety of age-related physiological alterations may change the structure of the uterus and the mode of placental attachment, putting older women more at risk of such diseases [15]. Further, the alteration of preoperative findings toward a significantly increased risk of APH reported on patients who had a prior cesarean section was also supported by other previous studies [16]. Previous surgeries such as cesarean sections may cause scarring and changes in the endometrium, which may lead to poor placentation, causing bleeding. This underscores the need for comprehensive obstetrics history and assessment during prenatal and antenatal visits, especially for those with previous C-sections [17]. The conclusions drawn about the neonatal outcomes are indeed alarming and they establish the dangers inherent in APH. It was also established that infants born to mothers who experienced APH had low birth weights, reduced Apgar scores, and were more admitted to the NICU than the ones who did not experience APH. These outcomes can be attributed to the fact that maternal blood loss has adverse effects on placental blood flow and oxygen delivery to the fetus which in turn presents adverse effects to fetal growth and development [18]. Moreover, the APH group had more preterm births than controls, and this affirms the need for improved control of pregnancies with placenta previa complications. The disposition of antepartum hemorrhage in patients who have placenta previa continues to be one of the difficult areas of obstetrics. Consequently, this study shows that a considerable number of patients with APH needed blood transfusion and elective LSCS therefore calling for early management to prevent such complications [19, 20]. While this study provided valuable insights, it is essential to acknowledge its limitations. The retrospective design may introduce biases related to data accuracy and completeness. Additionally, the single-center nature of the study may limit the generalizability of the findings.

CONCLUSIONS

This study concluded that advanced maternal age and a history of previous cesarean sections are significant predictors of antepartum hemorrhage in patients with placenta previa. The study highlighted the critical need for careful monitoring and proactive management in at-risk populations to improve maternal and neonatal outcomes.

Authors Contribution

Conceptualization: SB, HA
Methodology: UI
Formal analysis: UI, ST
Writing, review and editing: SB, HA, SA, NK, ST

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2338

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DOI: https://doi.org/10.54393/pjhs.v6i1.2087

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Effect of Supra Choroid Triamcinolone Acetate On Intraocular Pressure

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ARTICLE INFO

Keywords:
Corticosteroids, Intraocular Pressure, Triamcinolone, Supra-Choroidal Space

How to Cite:
Bukhari, S., Haseeb, U., Ahmed, N., Ahmed, I., Ahmed, S., & Shah, S. H. (2025). Effect of Supra Choroid Triamcinolone Acetate On Intraocular Pressure: Supra Choroid Triamcinolone Acetate for Intraocular Pressure. Pakistan Journal of Health Sciences, 6(1), 152-156. https://doi.org/10.54393/pjhs.v6i1.2087

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Received Date: 15th August, 2024
Acceptance Date: 21st January, 2025
Published Date: 31st January, 2025

ABSTRACT

Intraocular pressure is a critical parameter in maintaining the physiological function of the eye. Dysregulation of Intraocular pressure can lead to ocular pathologies. **Objective:** To evaluate change in intraocular pressure after supra-choroidal triamcinolone acetonide use. **Methods:** This prospective interventional study was carried out at the vitreo-retina Department of Al Ibrahim Eye Hospital Karachi, ISRA Postgraduate Institute of Ophthalmology for six months from July to December 2023. Adult patients attending the vitreoretinal Outpatient Department with resistant macular oedema were included. Intraocular pressure readings at 1 week, 4 weeks, 8 weeks and 12 weeks were recorded and compared with baseline values by applying One-way ANOVA keeping the p-value of <0.05 as statistically significant. Data were analyzed using SPSS v 22.0. **Results:** Among all, 21 (46.67%) cases received injections to the right eye and 24 (53.33%) cases to the left eye. The mean intraocular pressure before injection was 12.07 ± 2.14 mmHg. At three months' post-injection, the mean intraocular pressure was 13.60 ± 5.2 mmHg. For the right eye; the mean pre-injection intraocular pressure was 12.38 ± 1.96 mmHg. Three months' post-injection, the mean intraocular pressure was 13.43 ± 5.59 mmHg (p<0.001). For the left eye; the mean pre-injection intraocular pressure was 11.79 ± 2.28 mmHg while three months' post-injection, the mean intraocular pressure was 13.75 mmHg ± 4.96 (p-0.06). **Conclusions:** It was concluded that supra-choroidal triamcinolone injections increase intraocular pressure but stabilized over time. These findings support earlier trials and add to the evidence of this therapy's efficacy and safety.

INTRODUCTION

The pharmacologic features of the suprachoroidal space (SCS) for ocular drug delivery, particularly triamcinolone acetonide (TA), have been the subject of several investigations [1, 2]. Compared to traditional intravitreal injection, this method yielded a much higher drug concentration in the choroid and outer retina. Injecting suprachoroidal triamcinolone acetonide (SCTA) reduces the primary side effects of steroids, which are cataracts and increased intraocular pressure (IOP) because the medication is insignificantly exposed to structures in the anterior region [2]. Supra-choroid is a unique passage in ocular treatment with steroids wherein as drug concentration decreases, it also results in decreased incidence of cataract formation and intraocular pressure elevation [3]. Triamcinolone acetonide treats thyroid eye illness, complex chalazia, iridocyclitis, scleritis, macular oedema, and allergic eye disorders. Ocular and systemic corticosteroids have been linked to high IOP, glaucoma, and cataracts [4]. Triamcinolone acetonide possesses strong anti-inflammatory and anti-edematous properties. Hence it has been commonly used in the treatment of uveitis diabetic macular edema and other inflammatory retinal disorders [5-7]. Thus, it allows a new route of drug administration owing to possible localized high-concentration drug formulations, which could be utilized with minimal systemic exposure [8, 9]. Supra-choroidal triamcinolone acetonide, although used most frequently for uveitic macular edema has demonstrated beneficial effects on IOP [10]. However, as with other corticosteroids, suprachoroidal triamcinolone can induce steroid-induced IOP elevation; therefore, its use in IOP control primarily for glaucoma is not a first-line option and should be used carefully given the high risk of increased IOP [11]. For glaucoma patients, this is very concerning because

DOI: https://doi.org/10.54393/pjhs.v6i1.2087

elevated IOP can make the condition worse [12]. A novel strategy for the treatment of DME the administration of supra-choroidal triamcinolone has just evolved. One distinct anatomical benefit of administering medication to the back of the eye through the suprachoroidal area is the reduction of risks connected with intravitreal injections.in [13]. The effectiveness of several treatment options for diabetic macular edema (DME) has been highlighted in numerous research, which has provided insight into prospective strategies to improve anatomical and functional results [13, 14]. Supra-choroidal triamcinolone users must monitor their IOP. Treating IOP elevation with topical IOP-lowering medications typically works [15]. Suprachoroidal triamcinolone acetonide may reduce IOP elevation risk compared to other corticosteroid administration techniques, but it is not used to manage IOP in glaucoma [16]. To understand its function and efficacy in this environment, careful observation and investigation are needed. The current study will assess intraocular pressure following supra-choroidal triamcinolone acetonide administration. Intraocular pressure (IOP) is a critical parameter in maintaining the physiological function of the eye. Dysregulation of IOP can lead to ocular pathologies such as glaucoma, a leading cause of irreversible blindness. Triamcinolone acetate, a corticosteroid, is widely used in ophthalmology due to its potent anti-inflammatory properties. It is commonly administered through various routes, including intravitreal injections, for conditions like diabetic macular edema, uveitis, and retinal vein occlusion. However, corticosteroids are known to elevate IOP, posing a risk for steroid-induced glaucoma. Recent advancements in drug delivery have introduced the suprachoroidal route as a minimally invasive alternative for targeted drug administration. This route enables precise delivery to the posterior segment of the eye while minimizing systemic absorption and anterior segment exposure. Despite the theoretical advantages, there is limited empirical evidence regarding the safety profile of triamcinolone acetate when administered via the suprachoroidal route, particularly its effect on IOP.

This study aims to evaluate change in intraocular pressure after supra-choroidal triamcinolone acetonide use.

METHODS

A prospective interventional study was done at the Vitreo-retina Department of Al Ibrahim Eye Hospital Karachi, ISRA Postgraduate Institute of Ophthalmology for a period of six months (IRB Approval Number ATMC/IERC/13th/01-2023)/10) from July to December 2023 using non-probability consecutive sampling. Calculation of sample size was done using Open Epi online sample size calculator keeping mean intraocular pressure at baseline 14 ± 5 mmHg, 95 % confidence interval and 80 % power [17]. Adult patients after getting informed written consent, attending the Vitreoretinal Out Patient Department (OPD) with resistant macular edema who had already undergone 3 intra-vitreal anti-Vascular endothelial growth factor(VEGF) injections one month apart but with no effect on macular edema and patients >18 years of age were included in the study. Patients having Intraocular pressure IOP of more than 20 mmHg, cataract, macular ischemia (documented on Fundus Fluorescein Angiography (FFA)), ocular hypertension and renal disease were excluded in addition to patients that lately had intra-vitreal triamcinolone or posterior sub-Tenon triamcinolone acetonide injection within 3 months were also excluded. Resistant macular edema was identified as macular edema which was not successfully responding to loading dose of any of 3 anti-VEGF injections administered at a month's time difference. No change in best corrected visual acuity with the Snellen chart and Central macular thickness measured with Optical Coherence Tomography (OCT) was regarded as no improvement. The included patients were administered suprachoroidal triamcinolone acetonide injection. Pre-injection IOP was measured using an applanation tonometer. A 1cc insulin syringe was used along with a 30 gauge (BD Insulin syringe with a BD ultrafine Needle; Becton, Dickinson and Company, New Jersey, United States). The injection used was triamcinolone acetonide (TA) 40mg/ml (Kenakort A by GlaxoSmithKline Brentford, Middlesex, TW9 9GS, United Kingdom) which was injected via the 24-gauge intravenous catheter and 1 cc needle was then removed from cannula and cut so that only 1 mm insulin needle was out from cannula edge. After taking all aseptic measures, 0.1ml triamcinolone acetonide (TA) was injected at 3.5 mm from the limbus in the infra-temporal or supra-temporal quadrant. 4 mg of 0.1ml TA was infused into the supra-choroidal area after labelling via insertion into the sclera by perpendicularly placed needle and blade facing back at a distance of 3.5 mm from the limbus. The needle was gradually detached and a cotton tip applicator was applied to ensure nominal reflux at the injection site. The surgery was followed by the instillation of moxifloxacin eye drops into the cornea. 3 months' strict follow-up was done for all the patients and follow-ups were planned at 1, 4, 8 and 12 weeks. Intraocular pressure was checked and marked at every follow-up on decided proforma. Data were analyzed using SPSS v 22.0. Discrete variables were presented as frequencies and percentages while continuous variables were presented as means and standard deviation. Intraocular pressure (IOP) readings at 1 week, 4 weeks, 8 weeks and 12 weeks were recorded and compared with baseline values by applying One-way ANOVA keeping the p-value of <0.05 statistically significant.

DOI: https://doi.org/10.54393/pjhs.v6i1.2087

RESULTS

A total of 45 injections were administered in this research. The majority 26 (57.8%) were female and 19 (42.2%) were male. The finding demonstrates the frequency distribution of injections administered between the right and left eyes among the 45 subjects, 21 (46.67 %) to the right eye and 24 (53.33 %) to the left eye (Figure 1).

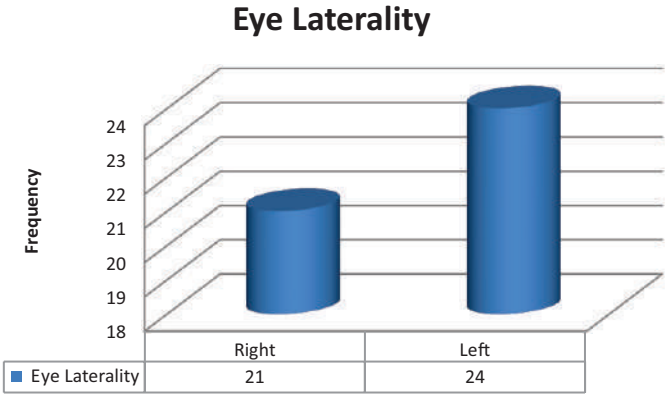

Figure 1: Frequency of Side of Eye Injected Upon (n=45)

Further finding shows intra-ocular pressure (IOP) measurement at different intervals: pre-injection, one week, one, two and at three months' post-injection. Mean IOP before injection was 12.07 ± 2.14 mmHg, ranging from 10 to 18 mmHg. One week after the injection, the mean IOP increased to 13.71 ± 3.8 mmHg and a range of 10 to 30 mmHg. At one month, the mean IOP slightly decreased to 13.22 ± 4.43 mmHg, a range of 10-36 mmHg. Two months' post-injection, the mean IOP was 13.33 ± 4.5 mmHg, range of 10-30 mmHg. Finally, at three months' post-injection, the mean IOP was 13.60 ± 5.2 mmHg and a range from 10 to 36 mmHg (Table 1).

Table 1: Mean± Standard Deviation of Intra-Ocular Pressure Before and Three Month After Injection (n=45)

Time of Checking	Intra-ocular Pressure (mmHg)		
	Mean ± SD	Minimum	Maximum
Pre-Injection	12.07 ± 2.14	10	18
One Week	13.71 ± 3.8	10	30
One Month	13.22 ± 4.43	10	36
Two Months	13.33 ± 4.5	10	30
Three Months	13.60 ± 5.2	10	36

The association between pre- and post-injection intra-ocular pressures was assessed for both the right and left eyes, (Table 2).

Table 2: Association Between Pre and Post-Injection Follow-Ups (n=45)

Laterality of Eye		n	Mean ± SD	p-value
Right	Pre-Injection	21	12.38 ± 1.96	<0.001
	One Week		14 ± 4.35	<0.001
	One Month		13.52 ± 5.72	<0.001
	Two Months		13.24 ± 4.75	<0.001
	Three Months		13.43 ± 5.59	<0.001
Left	Pre-Injection	24	11.79 ± 2.28	0.006
	One Week		13.46 ± 3.32	0.09
	One Month		12.96 ± 2.97	0.05
	Two Months		13.42 ± 4.39	0.05
	Three Months		13.75 ± 4.96	0.06

DISCUSSION

The current research investigated the effects of supra-choroidal triamcinolone injections on intraocular pressure (IOP) over three months. The main results were the post-injection changes in intraocular pressure (IOP) measured at various time points. Results showed a significant increase in IOP one week after injection, with subsequent stabilization over the next three months. Additionally, similar results were seen in other explorations as well [18-20]. The results of our study confirmed previous conclusions on corticosteroids and intraocular pressure. One week following the injection, we noted that there was a significant increase in the average IOP compared to levels before injection (mean 12.07 mmHg vs mean 13.71 mmHg), just as Yeh *et al.*, had done in one of their studies. This first increment matches with the findings of Yeh *et al.*, which implies an average increase of nearly about 3.4mm Hg at week one [21]. The possible reasons behind such an increase of IOP post-operatively could be attributed to increased resistance in the trabecular meshwork, transient inflammatory reaction post-injection leading to localized swelling, direct mechanical effect of the injection itself and insensitivity to corticosteroid activity including genetic factors. For instance, Zhang *et al.*, showed that intraocular pressure rose prominently one-month post-injection but began to decrease thereafter. Our results reflect this trend, with a mean IOP of 13.22 mm Hg at one month following injection, representing a slight decrease from its peak value at one week. This trend is consistent with those of Zhang *et al.*, work where there are more substantial decreases after higher maximums [22]. Likewise, Abdelshafy *et al.*, found that suprachoroidal triamcinolone injections caused significant IOP rise. Their findings were not far off from our own, showing an increase in average IOP after a month by as much as 3.8mmHg while our increase was around 3.15mm Hg from the baseline before injection. This consistency underscores the reproducibility of our results, supporting the notion that suprachoroidal triamcinolone injections typically cause an initial IOP rise that stabilizes subsequently [23]. Another feature in our study is the difference in IOP changes between the two eyes. The 21 cases of the right eye showed significant IOP increases at all follow-up points, with p-values consistently below 0.001. Conversely, the left eye had a major increase only pre-injection (p=0.006) while other subsequent alterations were not as significant (p-

DOI: https://doi.org/10.54393/pjhs.v6i1.2087

values ranging from 0.05 to 0.09). This indicates a probable difference in response depending on eye laterality and therefore calls for further investigations directed towards establishing the causes of such differences. Our findings have great clinical significance. It is possible to regulate the intraocular pressure (IOP) elevation that occurs after an injection since it gradually decreases over time and stays within a range that is considered to be acceptable by the majority of patients from a medical standpoint [23-25].

CONCLUSIONS

It was concluded that intraocular pressure (IOP) spiked after supra-choroidal triamcinolone injections but stabilized after a while. These results are in line with other studies and add to the growing body of information about the effectiveness and safety of this therapy method. Further research is needed to deepen our understanding and improve treatment procedures so that patients can have the best possible results.

Authors Contribution

Conceptualization: SB
Methodology: SB, IA, SHS
Formal analysis: SB
Writing review and editing: UH, NA, SA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2701

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

The Frequency of Blood Transfusion Reactions: A Retrospective Study from a Tertiary Care Hospital

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ARTICLE INFO

Keywords:

Blood Transfusion Reactions, Febrile Non-Hemolytic Transfusion Reactions, Allergic Reactions, Blood Products, Transfusion Safety

How to Cite:

Chohan, U., Najam, S., Rajput, K. K., Rajput, M. K., Waqar, S. A., & Yunus, N. (2025). The Frequency of Blood Transfusion Reactions: A Retrospective Study from a Tertiary Care Hospital: Frequency of Blood Transfusion Reactions. Pakistan Journal of Health Sciences, 6(1), 157-161. https://doi. org/10. 5439 3/pjhs .v6i1. 2701

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Received date: 27th October, 2024
Acceptance date: 18th January, 2025
Published date: 31st January, 2025

ABSTRACT

Blood Transfusion Reactions (BTRs) are complications that may occur during or after transfusion, in which allergic reactions and Febrile Non-Hemolytic Transfusion Reactions (FNHTRs) being the most common. **Objective:** To assess the frequency and types of transfusion reactions among patients at Shahida Islam Medical College Hospital and a blood transfusion service supplier. **Methods:** This study analyzed transfusion reactions reported between January, 2022, and September, 2024. A total 1936 transfused has done during this time frame. Data were collected using non-probability convenience sampling, covering patient demographics, blood products used, and Incident rate of transfusion reactions. IBM SPSS version 28.0 was utilized for statistical analysis, with categorical variables presented as frequencies and percentages. **Results:** Out of 1936 transfusions a total 12 (0.6%) reported transfusion reactions in which allergic reactions accounted for the majority (50.0%), followed by FNHTRs (33.33%) and none or very limited reactions of other reactions seen both on whole blood and PCV. The overall incidence of transfusion reactions was 0.53%. **Conclusions:** This study highlighted that allergic reactions are the most prevalent Blood Transfusion Reactions, emphasizing the need for premedication protocols for high-risk patients. Future research should focus on identifying predictive markers for allergic reactions, refining transfusion protocols.

INTRODUCTION

Adverse reactions to blood transfusions represent a significant complication in transfusion medicine. Among the various labile blood components, Platelet Concentrates (PCs) are the most frequent contributors to Hypersensitivity Transfusion Reactions (HTRs). These reactions often necessitate the cessation of PC transfusion, prolonging the transfusion process and increasing morbidity. In patients with a history of allergic transfusion reactions, premedication and heightened monitoring are often required. The French hemovigilance database, one of the largest standardized systems for tracking transfusion complications, provides critical insights into HTRs associated with labile blood products [1]. Febrile Non-Hemolytic Transfusion Reactions (FNHTRs) are among the more commonly observed complications in allogenic transfusion. These reactions are often attributed to the presence of White Blood Cells (WBCs) or leukocytes within the transfused product. During storage, these cells actively synthesize pro-inflammatory cytokines, leading to elevated cytokine levels and an

DOI: https://doi.org/10.54393/pjhs.v6i1.2701

increased risk of FNHTRs. The removal of leukocytes prior to storage, a process known as leukoreduction, significantly minimizes cytokine accumulation, thereby reducing the incidence of these febrile reactions [2]. Mild allergic transfusion reactions frequently result in the unnecessary discontinuation of transfusion, leading to wastage of blood components and repeated exposure of recipients to additional transfusion products. This repeated exposure increases the risk of alloimmunization. Recent studies have sought to identify the clinical symptoms and parameters that lead transfusionists to prematurely terminate transfusions due to mild ATRs [3]. AHTRs are characterized by a sudden onset of hypotension immediately following the initiation of transfusion, typically resolving upon cessation of the transfusion. Emerging evidence has suggested a correlation between AHTRs and preoperative administration of Angiotensin-Converting Enzyme (ACE) inhibitors. Recent case studies have documented two unrelated instances of AHTR, detailing their clinical presentation, diagnostic processes, and management strategies [4]. TRALI remains the leading cause of transfusion-related mortality in the United States, yet its characteristics in surgical populations are not well-defined. To enhance perioperative transfusion practices and mitigate TRALI risk, researchers have focused on clarifying its epidemiology, particularly in the context of interventions aimed at reducing TRALI incidence. These efforts aim to improve patient safety and refine transfusion protocols in surgical settings [5]. First identified in 1951 and 1957, Transfusion-Related Acute Lung Injury (TRALI) was formally recognized as a distinct clinical condition in 1985 following a study involving 36 patients. Earlier hypotheses in 1970 and 1971 suggested that leukoagglutinins targeting HLA and non-HLA antigens were responsible for TRALI reactions. Over the years, with advances in transfusion practices and heightened awareness, TRALI has emerged as a frequent and significant complication of blood transfusions. In recent reporting periods, it has been identified as the primary cause of transfusion-related mortality in the United States. [6]. Blood transfusion reactions can be broadly categorized into two main types that is Acute or Immediate Reactions and Delayed Reactions. Acute or Immediate Reactions occur shortly after the transfusion and include conditions such as acute hemolytic transfusion reaction, transfusion-associated sepsis, febrile non-hemolytic transfusion reaction, mild to severe allergic reactions, transfusion-associated circulatory overload, and transfusion-related acute lung injury. These reactions typically require prompt recognition and management to prevent serious complications. While Delayed Type Transfusion Reactions, develop over time following the transfusion. Examples include serological hemolytic reactions, iron overload, transfusion-associated graft-versus-host disease, and post-transfusional purpura. These delayed reactions may require long-term monitoring and specific therapeutic interventions. The most common symptoms of AHTRs include fever, chills, itching, or urticaria. These reactions typically manifest within 24 hours of transfusion and are usually self-limiting without requiring specific treatment. However, severe cases may present with symptoms such as dyspnea, hematuria, high fever, or loss of consciousness, potentially indicating a life-threatening reaction. AHTRs occur when the recipient's immune system destroys transfused red blood cells. [6]. Transfusion-Associated Sepsis (TAS) is an acute non-immune reaction caused by the transfusion of bacteria-contaminated blood products. Symptoms include a sudden rise in body temperature exceeding 2°C above baseline, rigors, and hypotension. These symptoms usually appear shortly after transfusion initiation. The risk of TAS is influenced by factors such as the type of bacterial contamination (e.g., gram-negative bacteria), patient demographics, transfused blood volume, and the storage duration of platelets [7]. FNHTRs are common complications of allogeneic red blood cell or platelet transfusions, typically occurring during or within 4–6 hours post-transfusion. These reactions, characterized by fever (>100°C), chills, and rigors, are more frequent in non-leukoreduced blood products. Patients with a history of FNHTRs are at an elevated risk of recurrence, with some cases presenting additional symptoms such as nausea, vomiting, and hypotension [8]. TRALI is characterized by sudden pulmonary insufficiency, manifesting as severe dyspnea, hypoxia, and pulmonary edema with normal cardiac function. The underlying mechanisms include leukocyte antibodies and biologically active lipids or cytokines that prime neutrophils. These processes lead to increased pulmonary microvascular permeability, causing protein-rich fluid accumulation in the lungs [9]. Mild allergic transfusion reactions, including rash, itching, and flushing, occur in 1–3% of all transfusions. Severe allergic reactions, such as anaphylactic shock, are rare but may result from IgE or anti-IgA antibodies. Less severe allergic responses may involve pre-existing antibodies to proteins or other transfused allergens [1]. Anaphylactoid reactions, while clinically similar to anaphylaxis, do not involve IgE antibodies. Instead, they arise from complement activation, bradykinin cascade, or direct activation of mast cells and basophils, leading to symptoms such as dizziness, tingling, and uneasiness. TACO results from pulmonary edema caused by circulatory overload, presenting as an underrecognized but serious complication. This condition often mimics immune-mediated pulmonary edema but arises due to fluid overload rather than immune mechanisms. These potentially life-threatening

DOI: https://doi.org/10.54393/pjhs.v6i1.2701

complications are observed in patients with sickle cell disease, presenting with hemolysis days after transfusion. Diagnosis includes monitoring acute pain episodes following transfusion [10]. Primarily seen in immunosuppressed patients, TA-GVHD manifests with fever, rash, and gastrointestinal symptoms. The condition may lead to severe outcomes like generalized erythroderma and bullae formation [11, 12].

The study aimed to evaluate the incidence rate and types of transfusion reactions associated with the administration of different blood components, including whole blood and PCV within the blood transfusion services of a tertiary care hospital.

METHODS

The study population consisted of patients with the symptoms of transfusion reactions. This was a retrospective observational study conducted at Shahida Islam Medical College Hospital; a tertiary care hospital in Lodhran and Hamdard Blood Bank and Transfusion center; a blood transfusion center providing blood bank related services. Data collection was based on the number of transfusion reactions reported in last 2 years and 9 months (15th January 2022 to 11th September 2024) which was total 1936 transfusion done in the both settings. Convenient sample techniques were used after establishing and using digital and latest equipment's in Blood banking. In this study only the incident rate of transfusion reactions was checked from the different type blood components like Whole blood and PCV. The data were collected by the transfusion service provider like Patient transfusion date, type of blood component transfused and patient history. The diagnosis and all reactions were assessed clinically through the experienced haematologist through proper guidelines like donor blood group and Rh factor, re-cross match, Gram stain, Complete blood count, culture sensitivity and specificity and urine analysis, all these parameters are not including in the study. Data on incident were focused on rate of transfusion reaction and which component of blood being transfused. Total 12 blood transfusion reactions out of 1936 that occurred during 15th January 2022 to 11th September 2024. A non-probability convenience sampling technique was used to select samples after approval of Institutional Review Board. (Letter No# SIMC/ET.C/0009/24). This data was analysed to identify different type of blood transfusions reactions and their incident rate. Categorical variables were summarized as frequencies in the form of percentages. Mean and Standard Deviation (SD) were calculated for continuous variables. Statistical analysis was performed using SPSS version 28.0, and significance was also assessed at a 5% level.

RESULTS

Total 12 (0.6%) reactions from all transfusions (1936) were reported in the particular chosen time. Among these, Allergic reactions were 06 (50%), showing the highest frequency. FNHTR were 4 (33.33%), and Anaphylactoid reactions were 2 (16.67%) (Table 1).

Table 1: Frequency of Blood Transfusion Reactions

Reactions	Frequency (%)
Allergic Reaction	6 (50%)
FNHTR	4 (33.33%)
Anaphylactoid reactions	2 (16.67%)
TA-GVHD	0 %
TRALI	0 %
Total	12 (100%)

This figure 1 illustrated the distribution of various types of blood transfusion reactions (BTRs) reported among 1936 transfusions conducted between January 15, 2022, and September 11, 2024. The majority of the reactions were allergic reactions, accounting for 50% of the reported cases, followed by Febrile Non-Hemolytic Transfusion Reactions (FNHTRs) at 33.33%. A minimal number of cases involved other types of reactions, observed in both whole blood and Packed Cell Volume (PCV) transfusions. The figure highlights the overall incidence rate of BTRs at 0.53%, underscoring the predominance of allergic reactions as the primary complication.

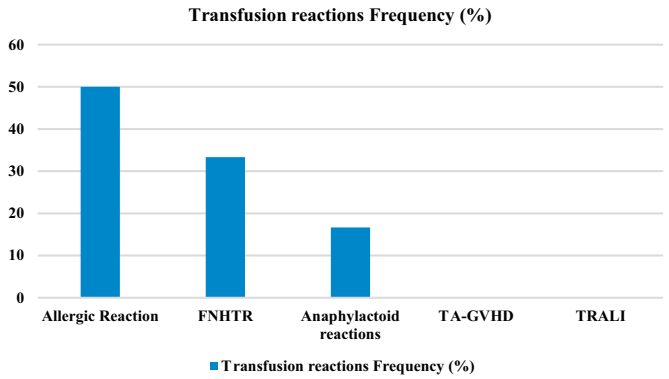

Figure 1: Frequency of Blood Transfusion Reactions

Out of the total 12 transfusion reactions, 8 were associated with whole blood products, of which 5 (62.5%) were allergic reactions, 2 (25%) were Febrile Non-Hemolytic Transfusion Reactions (FNHTRs), and 1 (12.5%) was an anaphylactoid reaction (Table 2).

Table 2: Frequency of Blood Transfusion Reactions due to Whole Blood

Reactions	Frequency (%)
Allergic Reaction	5 (62.5%)
FNHTR	2 (25.0%)
Anaphylactoid reactions	1 (12.5%)
TA-GVHD	0 %

DOI: https://doi.org/10.54393/pjhs.v6i1.2701

TRALI	0 %
Total	8 (100%)

The remaining 4 transfusion reactions were associated with packed cell products, including 1 (25%) allergic reaction, 2 (50%) Febrile Non-Hemolytic Transfusion Reactions (FNHTRs), and 1 (25%) anaphylactoid reaction (Table 3).

Table 3: Frequency of Blood Transfusion Reactions due to Pack Cells

Reactions	Frequency (%)
Allergic Reaction	1 (25.0%)
FNHTR	2 (50.0%)
Anaphylactoid reactions	1 (25.0%)
TA-GVHD	0 %
TRALI	0%
Total	4 (100%)

DISCUSSION

Blood transfusion is a common and generally safe procedure in which blood or blood components are administered intravenously to replace lost blood or address conditions that impair the body's ability to produce blood. Each year, approximately 5 million Americans undergo blood transfusions. While most transfusions proceed smoothly, mild complications may occur, and serious reactions, though rare, can develop. Blood transfusions are essential for replacing blood lost during surgeries, treating injuries, and addressing conditions like anemia and blood disorders that affect blood production [14]. In this study, the overall incidence of transfusion reactions was 0.53%, comparable to hemovigilance reports from countries such as India and China. A study in India reported a 0.27% incidence, while another healthcare center in India found a rate of 0.2 [15, 16]. Similarly, a meta-analysis from China identified a rate of 0.4%, but the incidence was markedly higher in Ghana [17]. The variance in rates reflects differences in healthcare systems, blood product screening protocols, and transfusion practices. This study identified 12 acute transfusion reactions, with allergic reactions being the most frequent, accounting for 6 cases (50%). Febrile non-hemolytic transfusion reactions (FNHTR) were the second most common, reported in 4 cases (33.33%), followed by transfusion-associated circulatory overload (Anaphylactoid Reactions) in 2 cases (16.67%). Allergic Reactions (50%): These were the most prevalent, typically presenting as mild allergic responses, such as itching or hives, but they did not escalate to anaphylaxis. FNHTR (33.33%): These reactions, characterized by fever and chills, occurred frequently in recipients of whole blood and packed cell transfusions. Anaphylactoid Reactions (16.67%): Though the risk of Anaphylactoid Reactions is usually higher with whole blood due to the larger volume, it also appeared with packed cells, likely due to multiple units being transfused. Possibly this was due to multiple blood units being transfused to the patient. These findings aligned with previous studies highlighting the predominance of allergic reactions and FNHTR. The reported incidence of allergic reactions in this study (50%) mirrors trends observed in other hemovigilance reports [18, 19]. Whole blood transfusions were more likely to cause reactions than packed red cells, likely due to the higher volume and complexity of the product. Additionally, cases of Anaphylactoid Reactions with packed cells though less common can occur due to cumulative volume overload from multiple transfusions. This underscores the importance of careful monitoring and transfusion protocols to prevent circulatory overload. While Transfusion-Associated Graft-Versus-Host Disease (TA-GVHD) and Transfusion-Related Acute Lung Injury (TRALI) have been reported in other studies, no such cases were observed in the dataset. A UK hemovigilance report documented 13 cases of TA-GVHD between 1996 and 2005, highlighting the need for continued vigilance [20].

CONCLUSIONS

This study highlights the incidence and distribution of transfusion reactions in patients receiving whole blood and packed red cell transfusions. Allergic reactions were the most frequently observed, accounting for 50% of all reported reactions, followed by FNHTR (33.33%), Anaphylactoid Reactions (16.67%), and no cases report for TA-GVHD and TRALI (0%). Whole blood transfusion was more frequently associated with allergic reactions, while FNHTR and Anaphylactoid Reactions cases were reported with both whole blood and packed cell transfusions, suggesting that even smaller volumes may carry risks when multiple units are transfused.

Authors Contribution

Conceptualization: UC
Methodology: SN
Formal analysis: MKR
Writing, review and editing: UC, KKR, SAW, NY

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2701

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DOI: https://doi.org/10.54393/pjhs.v6i1.2286

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Relationship of Hypoalbuminemia in Colistin-Induced Acute Kidney Injury (AKI) among Adult Intensive Care Patients

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ARTICLE INFO

Keywords:
Acute Kidney Injury, Colistin Therapy, Intensive Care Unit, Hypoalbuminemia

How to Cite:
Memon, S. U., Samad, S., Misbah, N., Muzaffar, S., Ishaque, S., & Kamran, S. (2025). Relationship of Hypoalbuminemia in Colistin-Induced Acute Kidney Injury (AKI) among Adult Intensive Care Patients: Hypoalbuminemia in Colistin-Induced Acute Kidney Injury. Pakistan Journal of Health Sciences, 6(1), 162-167. https://doi.org/10.54393/pjhs.v6i1.2286

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Received date: 5th October, 2024
Acceptance date: 18th January, 2025
Published date: 31st January, 2025

ABSTRACT

Acute kidney injury incidence ranges from 30-60% among critically ill patients and stands as the primary death cause within this population. A serious concern is a global rise in major drug-resistant-gram-negative organisms among hospital-acquired infections. **Objectives:** To determine the incidence of colistin-induced acute kidney injury in intensive care patients receiving colistin therapy and to investigate its relationship with albumin levels. **Methods:** It was a follow-up prospective cohort study executed at Shaheed Mohtarma Benazir Bhutto Institute of Trauma Pakistan in an adult intensive care unit over 6 months. The study end-point was an injury in intensive care injury at the end of colistin therapy. A total of 250 patients were studied. **Results:** The median age of patients was 40 (IQR=22-48) years with an age range of 18-70 years. The majority of patients were male (75.2%). Median colistin dosage was 4 (IQR=3.5-4.5) MIU. In univariate analysis, the risk of developing injury in intensive care was significantly increased with increased age, use of nephrotoxic drugs, and increasing colistin dosage whereas injury in intensive care risk was decreased with increasing albumin levels. In a multivariable model, only colistin dosage was found to be significantly associated with increasing injury in intensive care risk with increasing colistin dosage. **Conclusions:** It was concluded that the present study analyzed a higher burden of acute kidney injury incidence following colistin therapy. Albumin levels were not found to be linked to acute kidney injury incidence in the multivariable model. Acute kidney injury incidence was significantly related to increasing colistin dosage.

INTRODUCTION

Acute kidney injury (AKI) is a frequent issue in patients with deteriorating health, leading to higher morbidity and mortality rates. It also results in longer hospital stays and increased healthcare expenses [1]. In critically ill patients, AKI occurs in about 30% to 60% of cases, making it a major cause of death in this group. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define AKI as a rapid loss of kidney function, indicated by a rise in serum creatinine (SCr) of 0.3 mg/dL or more within 48 hours, or an increase to at least 1.5 times the baseline level within the past seven days [2]. The worldwide increase in antibiotic resistance presents a significant public health issue [3]. A significant concern in healthcare is the rising prevalence of multidrug resistance and the proliferation of extensively drug-resistant Gram-negative bacteria, particularly in hospital-acquired infections [4]. Colistin, a polymyxin-class antibiotic originally developed in the late 1940s and approved by the Food and Drug Administration (FDA) in 1962, has demonstrated in vitro efficacy against the majority of aerobic Gram-negative bacilli. Colistin efficacy has also been demonstrated against a broad spectrum of Gram-negative pathogens including extensively diverse and multiple-drug organisms [7, 8]. Though initially it was effective its utilization was not encouraged owing to the high risk of AKI. Subsequently, colistin was revived into medical practice in the early 2000s as a fundamental rescue therapy for countering the harmful impacts of these infections [8, 9]. In multiple studies, colistin-induced AKI

DOI: https://doi.org/10.54393/pjhs.v6i1.2286

ranges from 20% to 76% [10, 11]. In these studies, the nephrotoxicity rate was varying with different dosing regimens. Numerous determinants were reported to contribute to colistin-induced AKI such as diabetes, CKD, anemia and exposure to events which are harmful to the kidney (trauma, sepsis, use of nephrotoxic agents in critical illness) [11, 12]. Colistin-induced AKI is generally reversible and rarely results in lasting kidney damage. It is crucial to balance the potential for nephrotoxicity with the risks associated with not adequately treating a severe infection [13]. Hypoalbuminemia, commonly characterized by albumin levels below 3.5–4.0 g/dL or ≤ 3.5 mmol/L, is a notable risk factor for higher rates of morbidity and mortality. Moreover, it has been linked to an increased likelihood of developing AKI [14]. Further in the literature of the study enrolled participants in both intensive care unit (ICU) and surgical patients demonstrated that hypoalbuminemia could serve as a useful indicator to predict death in AKI patients [15-17]. However, despite these findings, the overall effect of hypoalbuminemia remains questionable due to conflicting outcomes from various studies, partly owing to diverse heterogeneity and the occurrence of different types of infection [5, 8]. Data on the prevalence of colistin-associated AKI in our local context is limited.

This study aims to assess the incidence of colistin-induced AKI among intensive care unit (ICU) patients and investigate the relationship between serum albumin levels and the development of AKI in ICU patients receiving colistin therapy.

METHODS

This prospective cohort (follow-up) study was conducted in the adult intensive care unit at the "Shaheed Mohtarma Benazir Bhutto Institute of Trauma, Pakistan", from August 2023 to December 2023. The study commenced following the approval of "Ethics Review Committee (ERC-000113/SMBBIT)". After obtaining dual linguistic consent, all patients aged 18 years who were admitted to the ICU and receiving intravenous colistin therapy for 72 hours as part of their infection treatment were included in the study. Patients with AKI injury before receiving colistin therapy, requiring renal replacement therapy before colistin initiation and those patients receiving only inhaled colistin were excluded. An informed consent was taken. WHO sample size calculator was used for a Sample size of 229 patients, estimated by taking 68.8% AKI injury among patients on colistin therapy [14] at a 95% confidence interval and 6% margin of error. Patients were enlisted into the study using non-probability consecutive sampling. In this study, the duration of colistin therapy was set at either 7 or 14 days. This study used KDIGO guidelines [2], while the primary outcomes of the study were the incidence of AKI at 48 hours and after colistin therapy (Table 1).

Table 1: KDIGO Guidelines

Stages	Serum Creatinine
Stage 1	1.5 to 1.9 Baseline OR ≥0.3 mg/dL (≥26.5 µmol/L)
Stage 2	2.0 to 2.9 Times Baseline
Stage 3	3.0 Times Baseline OR Increase in Serum Creatinine to ≥4.0 mg/dL (≥353.6 µmol/L) OR Initiation of Renal Replacement Therapy, OR inpatient <18 Years, Decrease in eGFR to <35mL/min/1.73m2

The statistical analysis was performed using SPSS version 26. Categorical data were shown as counts and percentages, whereas continuous data, due to their non-normal distribution, were displayed as medians with "interquartile ranges (IQR)". The "Shapiro-Wilk test" evaluated the normality of numerical data. "Pearson's Chi-square" or "Fisher's exact test" for categorical variables, and the "Mann-Whitney U" test for continuous data, were employed to compare patients with and without AKI. The independent sample t-test was used for inferential analysis of continuous data. A "Kaplan-Meier survival curve" assessed the likelihood of AKI recovery after therapy. A "Cox proportional hazards regression model" was used to obtain "hazard ratios (HRs)" with 95% confidence intervals. Variables with significant unadjusted hazard ratios were included in the model to compute adjusted hazard ratios. Statistical significance was set at a two-sided p-value of 0.05.

RESULTS

A total of 250 patients were studied. On Shapiro-Wilk the normality of the residual was >0.05. The median age of patients was 40 (IQR=22-48) years with an age range of 18-70 years. The majority of patients were male 200 (80%). More than three-fourths of patients were receiving concomitant antibiotics 195 (78%). Of 195 (78%) patients who were receiving concomitant antibiotics, 93 (47.7%) were on vancomycin and 72 (37%) were on meropenem. Around a quarter of them were administered with nephrotoxic drugs 204 (81.6%). Median colistin dosage was 4 (IQR=3.5-4.5) MIU (Table 2).

Table 2: Comorbidities and Diagnosis of the Patients Presented at ICU

Variables	Frequency (%)
Gender	
Male	200 (80%)
Female	50 (20%)
Hypertension	
Present	175 (70%)
Absent	75 (30%)
Diabetes	
Present	150 (60%)
Absent	100 (40%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2286

Heart Disease	
Present	137 (55%)
Absent	112 (45%)
Chronic Kidney Disease	
Present	50 (20%)
Absent	200 (80%)
Respiratory Tract Infection	
Present	100 (40%)
Absent	150 (60%)
Infection in Blood	
Present	125 (50%)
Absent	125 (50%)
Infection in Urine	
Present	75 (30%)
Absent	17.5 (70%)
Infection in Sputum	
Present	25 (10%)
Absent	225 (90%)
Infection in CNS	
Present	12.5 (5%)
Absent	237.5 (95%)
Hypoalbuminemia	
Present	175 (70%)
Absent	75 (30%)
Concomitant Antibiotics	
Patients Receiving Concomitant Antibiotics	195 (78%)
Receiving Vancomycin	93 (47.7% of 78%)
Receiving Meropenem	72 (37% of 78%)
Patients Administered Nephrotoxic Drugs	204 (81.6%)
Median Colistin Dosage	4 MIU (IQR: 3.5-4.5)

The incidence rate of AKI at the end of therapy was 5.1 per 100 patients. The survival probability from AKI at the end of therapy was 2.1%. Median survival days were 14 days (95% CI: 13.3-14.7). The Kaplan-Meier survival analysis demonstrates a progressive decline in cumulative survival throughout the study, with significant drops indicating clustered event occurrences and censored data points reflecting incomplete follow-up for certain subjects. The survival analysis on the 5th, 10th, 15th and 20th days were 0.85, 0.75, 0.55, and 0.35 respectively where the curve has a visible decrease indicating more events occurring (Figure 1).

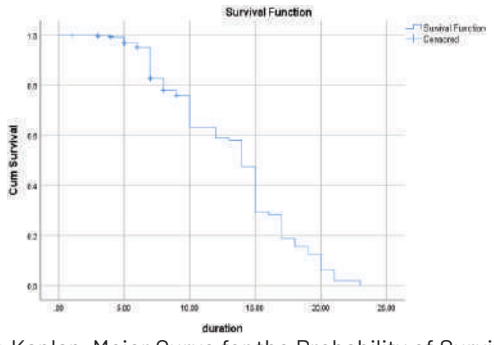

Figure 1: Kaplan-Meier Curve for the Probability of Survival from AKI During Colistin Therapy During the Study Period

At baseline and 48 hours, the median serum creatinine level was 0.5 (IQR=0.2-0.6) and 0.5 (IQR=0.5-0.3-0.9) and at the end of therapy it was 0.6 (IQR=0.3-1.4). At 48 hours, AKI was developed in 32% of patients whereas at the end of therapy, AKI incidence was seen in 42.8% which is the highest among all the stages of AKI. The serum levels at baseline and after colistin therapy and AKI incidence are displayed (Table 3).

Table 3: Serum Creatinine and AKI Incidence Following Colistin Therapy

Variables	Frequency (%)
Serum Creatinine at Baseline	0.5 (IQR=0.2-0.6)
Serum Creatinine at 48 Hours	0.5 (IQR=0.5-0.3-0.9)
Serum Creatinine at End of Therapy	0.6 (IQR=0.3-1.4)
AKI Incidence at 48 Hours	80 (32%)
AKI Staging at 48 Hours	
Stage 1	28 (35%)
Stage 2	23 (28.8%)
Stage 3	29 (36.3%)
AKI Incidence at End of Therapy	107 (42.8%)
AKI Staging at the End of Therapy	
Stage 1	37 (34.6%)
Stage 2	20 (18.7%)
Stage 3	50 (46.7%)

Patients developing AKI at the end of therapy were elderly ($p<0.001$). All co-existing diseases were significantly higher among patients developing AKI. The use of nephrotoxic drugs was significantly higher among AKI patients ($p<0.001$). Albumin levels were significantly lower in patients having AKI than those who did not have AKI at the end of therapy ($p<0.001$) (Table 4).

Table 4: Comparison of Patient's Characteristics with AKI (with and without) at the End of Colistin Therapy

Variables	Groups	AKI at the End of Therapy		p-Value
		Yes n (%)	No n (%)	
Age (in years)	-	Mean 58 (Range: 50-63)	Mean 35 (Range: 22-25)	*<0.001
Gender	Male	78 (41.5%)	110 (58.5%)	0.466
	Female	29 (46.8%)	33 (53.2%)	
Comorbid	Hypertension	36 (80%)	9 (20%)	*<0.001
	Diabetes	36 (75%)	12 (25%)	*<0.001
	CKD	12 (75%)	4 (25%)	*0.007
	Heart Diseases	16 (66.7%)	8 (33.3%)	*0.013
Concomitant Use of Antibiotics	Yes	83 (42.6%)	112 (57.4%)	0.887
	No	24 (43.6%)	31 (56.4%)	
Nephrotoxic Drugs	Yes	44 (95.7%)	2 (4.3%)	*<0.001
	No	66 (36.5%)	115 (63.5%)	
Site of Infection	Blood	83 (50.3%)	82 (49.7%)	*0.001
	Urine	14 (40%)	21 (60%)	0.718
	Sputum	9 (42.9%)	12 (57.1%)	0.996
	CNS	7 (50%)	7 (50%)	0.575

DOI: https://doi.org/10.54393/pjhs.v6i1.2286

	Respiratory tract	63 (43.2%)	83 (56.8%)	0.894
Albumin Level (Mean ± SD)		Mean 1.7 (Range: 1.3-2.3)	Mean 3.6 (Range: 3.4-4.0)	*<0.001

AKI: Acute kidney injury, CKD: Chronic kidney disease, CNS: Central nervous system, **=0.05, aIndependent Sample t-test applied, bChi Square test applied

In univariate analysis, the risk of developing AKI was significantly increasing with increased age, use of nephrotoxic drugs, and increasing colistin dosage whereas AKI risk was decreasing with increasing albumin levels. In a multivariable model, only colistin dosage was found to be significantly associated with increasing AKI risk with increasing colistin dosage (Table 5).

Table 5: Patients' Characteristics with AKI at the End of Colistin Therapy in Univariate and Multivariable Regression

Variables	HR (95% CI)	p-Value	A HR (95% CI)	p-Value
Age	1.04 (1.02-1.05)	0.176	1.01 (0.98-1.02)	0.693
Gender, Male	1.16 (0.75-1.80)	0.485	1.10 (0.90-1.35)	0.560
Hypertension	0.94 (0.63-1.40)	0.748	0.97 (0.70-1.20)	0.720
Diabetes	1.30 (0.86-1.96)	0.209	1.15 (0.85-1.45)	0.450
CKD	0.98 (0.53-1.78)	0.943	0.99 (0.65-1.52)	0.930
Heart Diseases	1.41 (0.82-2.41)	0.210	1.20 (0.95-1.60)	0.250
Concomitant Antibiotics Use	1.20 (0.76-1.89)	0.432	1.05 (0.80-1.40)	0.650
Nephrotoxic Drugs	1.48 (1-2.19)	*0.050	1.28 (0.85-1.93)	0.228
Colistin Dosage	1.08 (1.03-1.15)	*0.006	1.06 (1.01-1.14)	*0.049
Albumin	0.72 (0.53-0.98)	*0.038	0.82 (0.58-1.14)	0.232

CI: Confidence Interval at 95%, HR: Hazard ratio, *=0.05

DISCUSSION

This study of 250 patients (75.2% male, median age 40) found high exposure to nephrotoxic drugs and antibiotics, with a median colistin dose of 4 MIU. The AKI incidence rate was 5.1 per 100 patient days, and survival at therapy's end was only 2.1%, with a median survival of 14 days. Kaplan-Meier analysis showed a steady decline in survival over the treatment period, underscoring significant risks associated with colistin use. At the 48-hour mark, 32% of patients had developed AKI, which increased to 42.8% by the end of therapy, marking the highest incidence among AKI stages. Elderly patients and those with pre-existing conditions were more likely to develop AKI (p<0.001), and AKI was significantly associated with the use of nephrotoxic drugs. Lower albumin levels were noted in patients with AKI (p<0.001). Univariate analysis indicated that AKI risk increased with age, nephrotoxic drug use, and higher colistin doses, while higher albumin levels were protective. Multivariable analysis confirmed that increased colistin dosage was the only significant independent risk factor for AKI. Our study identified a rise in AKI after colistin therapy. The incidence was 11.1% at 48 hours and 25% by treatment completion, mirroring the findings of a retrospective study conducted by Deniz (12% at 48 hours, 29% by day 7) [18]. However, discrepancies exist with prior literature reporting a wider range of AKI risk (44.3%-76.1%) [19-21]. These variations likely stem from differing AKI criteria, therapy duration, infection severity, underlying conditions, and concomitant nephrotoxic medications. We observed a high prevalence of AKI stages following colistin use. At 48 hours, 35.0%, 28.8%, and 36.3% of patients had Stage I, II, and III AKI, respectively. Notably, Stage III AKI prevalence rose to 46.7% by treatment conclusion, accompanied by a decrease in Stages I (34.6%) and II (18.7%). These findings align with previous research demonstrating a link between colistin and AKI development [19]. Similar studies support this, with Alotaibi et al., reporting a distribution of AKI stages at treatment completion as 24.5% Stage I, 37.32% Stage II, and 14.5% Stage III [20]. Likewise, Moghnieh et al., documented an incidence of AKI at Stages I, II, and III of 21.2%, 28.8%, and 50.0%, respectively [21]. Univariate analysis revealed a significant correlation between increasing age and AKI occurrence, but not on multivariable analysis. This discrepancy might be due to our limited sample size. Nevertheless, our findings are consistent with prior research highlighting increasing age as a key factor in colistin-induced AKI [18, 20]. Hypoalbuminemia, frequently observed in critically ill patients, serves as an indicator of malnutrition and inflammation and is also predictive of AKI and mortality [22]. In our study, univariate analysis showed a significant association between higher albumin levels and a reduced risk of AKI, aligning with previous research that identifies hypoalbuminemia as a risk factor for colistin-induced AKI [14-15]. However, Alotaibi et al., reported no such association [20]. The link between hypoalbuminemia and colistin-induced AKI is likely multifaceted, with albumin's various physiological functions playing a significant role [14]. Shah et al., in their retrospective study, reported Kaplan-Meier survival analysis as significantly lower survival for patients with AKI-related kidney failure compared to other etiologies (log-rank test, p<0.001). Sensitivity analysis, excluding AKI patients who started dialysis with arteriovenous access and non-AKI patients who recovered renal function, yielded hazard ratios consistent with the primary model, with a marginal attenuation of roughly 10% [23]. In a study conducted by Nagata et al., Kaplan-Meier survival analysis revealed that transient AKI, persistent AKI, and AKD were all significantly linked to an increased incidence of events characterized by a reduction in estimated glomerular filtration rate (ReGFR<0.7) compared to individuals without AKI, especially within the first year. Among these groups, the rates of adverse outcomes were substantially higher in those with persistent AKI and AKD than in those with transient AKI [24]. The findings of this study carry

DOI: https://doi.org/10.54393/pjhs.v6i1.2286

important implications for clinical practice and patient management. The high incidence of AKI, particularly among elderly patients and those exposed to nephrotoxic drugs, emphasizes the need for vigilant monitoring of renal function during colistin treatment. The frequent use of concomitant antibiotics, such as vancomycin and meropenem, points to the importance of optimizing antibiotic regimens to minimize cumulative nephrotoxic effects. Additionally, the significant relationship between higher colistin dosages and increased AKI risk suggests that dose adjustments may be necessary to achieve a balance between efficacy and safety. Identifying high-risk patients, such as those with comorbidities or lower albumin levels, could inform more personalized treatment strategies to mitigate AKI risk. Overall, these results provide valuable insights for guiding future research aimed at developing safer treatment protocols and protective measures for patients undergoing colistin therapy.

CONCLUSIONS

It was concluded that this analysis identified a higher incidence of AKI following colistin therapy. However, albumin levels did not show a significant association with AKI risk in the multivariable model. Conversely, a significant correlation was observed between increasing colistin dosage and AKI incidence.

Authors Contribution

Conceptualization: SUM
Methodology: SUM, SS, NM, SK
Formal analysis: SM, SK
Writing review and editing: SI

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2467

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Effectiveness of Cognitive Behavioral Techniques for Diabetes Distress in Patients Presenting With Diabetes Related Distress at a Tertiary Care Hospital

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ARTICLE INFO

Keywords:
Cognitive Behavioral Techniques, Diabetes-Related Distress, Quasi-Experimental Study

How to Cite:
Mahmood, S., Fatima, I., Khan, S. A., Ahmed, M., Zubair, F., Arshad, F., & Tahir, M. (2025). Effectiveness of Cognitive Behavioral Techniques for Diabetes Distress in Patients Presenting With Diabetes Related Distress at a Tertiary Care Hospital: Cognitive Behavioral Techniques for Diabetes . Pakistan Journal of Health Sciences, 6(1), 168-173. https://doi.org/10.54393/pjhs.v6i1.2467

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Received date: 24th October, 2024
Acceptance date: 19th January, 2025
Published date: 31st January, 2025

ABSTRACT

Diabetes-related distress is a common psychological issue among diabetic patients, often affecting their ability to manage the condition effectively. **Objective:** To determine the effectiveness of cognitive behavioral techniques for diabetes distress in patients presenting with diabetes related distress at a tertiary care hospital. **Methods:** This study was conducted in the General Medicine Department at Nishtar Medical University and Hospital, Multan, a tertiary care hospital, over a period of 12 months. It was a Quasi Experimental Study. Sample size was 64 patients with diabetes related distress, (32 in each group) calculated by using sample size formula for comparing two proportions. Sampling technique was non probability consecutive sampling. **Results:** The mean age of patients experiencing diabetes-related distress was 51.45 ± 8.34 years, with an age range of 37 to 65 years. Among the 64 participants, only 20 (31.3%) had controlled diabetes, while 41 (64.1%) had uncontrolled diabetes. Efficacy was observed in 23 (35.9%) of the study cases. Specifically, 17 (53.1%) participants in group an exhibited efficacy, compared to 6 (18.8%) in group B (P=0.004). **Conclusions:** The findings of the study supported cognitive behavioral techniques for the management of diabetes related distress as these techniques were found effective and reliable in the management of diabetes related distress. Effectiveness of therapy was significantly higher among experimental group as compared with control group.

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by the body's impaired capacity to utilize and absorb glucose, leading to abnormal blood sugar levels. Diabetes mellitus comprises a group of disorders marked by elevated blood sugar levels (hyperglycemia) caused by insulin resistance, insufficient insulin production, or excessive glucagon release [1, 2]. Globally, diabetes is the seventh leading cause of mortality, affecting approximately 422 million people worldwide, as reported by the World Health Organization (WHO) in 2020. Projections indicate that this number will increase by 25% over the next decade, reaching 454 million, and by 51% over the next 25 years, reaching 548 million and the number will increase by 51% (700 million) in 2045 [3, 4]. In 2015, diabetes mellitus contributed to over 1.5 million deaths worldwide. Diabetes mellitus, reported to be one of most prevalent metabolic disorders, has been the sixth leading cause of mortality globally while most burden of the diabetes is harbored in developing countries which show poor compliance with management and treatment that leads to the progression of long-term complications in these patients. Hence, these patients from low and middle income countries are at higher risk of future adverse events and exert more pressure on healthcare systems of their respective

DOI: https://doi.org/10.54393/pjhs.v6i1.2467

countries [5]. Type 1 Diabetes (T1D) is an autoimmune disease that results in the destruction of pancreatic beta cells, which are responsible for producing insulin. In contrast, Type 2 Diabetes (T2D), the more common form, is marked by a gradual decline in blood sugar regulation due to a combination of insulin resistance and reduced beta cell function in the pancreas. Leading a sedentary lifestyle and engaging in inadequate physical activity substantially elevates the risk of developing type 2 diabetes. The World Health Organization highlights that regular exercise enhances insulin sensitivity, helping to lower the risk of diabetes [6]. Prediabetes is diagnosed based on specific blood test results. A diagnosis is typically made when Fasting Plasma Glucose (FPG) levels fall between 100-125 mg/dL. Additionally, results from a 2-hour oral glucose tolerance test ranging from 140-199 mg/dL or hemoglobin A1c (HbA1c) levels between 5.7% and 6.4% can also indicate prediabetes [7]. The growing prevalence of diabetes is primarily attributed to aging populations. However, improvements in medical care leading to lower mortality rates among individuals with diabetes, along with rising diabetes incidence in certain countries due to an increase in risk factors particularly obesity are also significant contributors to the higher prevalence [8]. Individuals may experience discouragement from struggling to maintain stable blood sugar levels, leading to a sense of failure or frustration. This emotional strain can result in avoiding essential diabetes care tasks, such as skipping glucose checks or insulin doses. Over time, the constant pressure of managing the condition can lead to emotional exhaustion and burnout [7, 8]. Symptoms of diabetic distress include feeling overwhelmed by the ongoing demands of managing diabetes, along with persistent worry about the condition's impact on daily life and long-term health [8]. Diabetes can impair the blood vessels that provide blood to the retina, leading to a condition called retinopathy. Elevated blood glucose levels can damage these smaller blood vessels, resulting in vision loss and, in severe cases, blindness [9]. High blood glucose levels can damage kidney blood vessels, reducing their ability to filter waste from the bloodstream. This leads to waste buildup in the body, causing fatigue, weakness, and swelling in the legs and ankles [10]. Almost 90 % of the diabetic patients have type 2 diabetes mellitus and its treatment demands a comprehensive, multidisciplinary and complicated strategies. These treatment strategies include; strict diet control, proper medication, adequate physical activity, regular blood glucose monitoring and treatment awareness [11]. Management of diabetes is associated with extra economic burden on suffering families so it leads to the anxiety, helplessness and depression so T2DM management entails to the emotional health of diabetic patients. An Insulin Adherence Protocol is a systematic plan designed to help individuals with diabetes consistently follow their insulin therapy. These protocols are essential for effective diabetes management and reducing the risk of complications [9, 10]. Living with diabetes has significant impact on the patients and when it involves self-care management practices, these sufferers may be stressed out, disturbed or depressed.

Diabetes treatment primarily involves lifestyle counseling and education on diet, exercise, and weight management, alongside pharmacological therapy to regulate blood glucose levels and address or prevent related complications [11, 12].

METHODS

This Quasi Experimental Study was carried out in the General Medicine Department at Nishtar Medical University and Hospital, Multan, over a period of twelve months, following the approval of the research synopsis. The study included 64 patients experiencing diabetes-related distress, divided equally into two groups of 32 participants each. The sample size was calculated using specific parameters: P1 = 51%, P2 = 18% [13]. A non-probability consecutive sampling technique was used to sequentially include eligible participants.

$$n = \frac{\left\{ z_{1-\alpha}\sqrt{2\bar{P}(1-\bar{P})} + z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{(P_1-P_2)^2}$$

On February 27, 2021, a meeting of the Institutional Ethical Review Board (IERB) was held, chaired by the patron of the IERB Committee at Nishtar Medical University, Multan. Following the meeting, the Institutional Ethical Review Board issued an approval letter with the reference number 4411/NMU and H on March 11, 2021. The inclusion criteria for the study require participants to be between 32 and 70 years of age and of either gender. Eligible patients should be experiencing diabetes-related distress as defined by the operational criteria. The exclusion criteria rule out patients with a known history of coronary artery disease, stroke, Chronic Renal Failure (CRF), or Chronic Liver Disease (CLD). Additionally, individuals with a previous history of psychological disorders, hypothyroidism confirmed through medical records, or a prior diagnosis of brain tumors supported by medical history are not eligible. Pregnant women and patients who do not provide consent to participate are also excluded from the study. A customized proforma was designed to collect data for this study. Following a rigorous pilot study, the questionnaire's reliability was established, yielding a Cronbach's alpha coefficient of 0.78 (78%). A total of 64 eligible diabetes patients were conveniently selected from the Outpatient Department (OPD) of Nishtar Hospital, Multan. The study received the required approval from the Institutional

DOI: https://doi.org/10.54393/pjhs.v6i1.2467

Ethical Committee. Prior to participation, informed consent was obtained from each patient, ensuring they understood the study's objectives, were assured of confidentiality, and were notified that participation posed no risks. These patients was randomly assigned two groups using lottery method i.e. group A (undergoing cognitive therapy) and group B (does not undergo cognitive therapy) patients was followed fortnightly for eight weeks to observe the outcome of therapy and all the information was noted on the proforma specifically designed for the study along with other data such as age, gender, residential status, control of diabetes, obesity, family history, hypertension and monthly family income will also be recorded on proforma by the researcher. Data analysis was performed using SPSS version 23.0, which calculated the mean and standard deviation for variables including age, BMI, and duration of diabetes. Frequencies and percentages were computed for categorical variables, including the outcomes of cognitive therapy, age groups, diabetes management, gender, residential status, history of hypertension, and family history of diabetes. Therapy outcomes were evaluated using the chi-square test, with statistical significance set at $p < 0.05$. Effect modifiers, including age, gender, hypertension, diabetes control, family history of diabetes, residential status, and obesity, were adjusted for through stratification. A post-stratification chi-square test was conducted to assess their impact on the outcomes, with a p-value of 0.05 or less considered statistically significant. Diabetes Distress Score more than 80/102 on DDS – 17 scale (is a 17-item self-report tool used to measure the emotional and psychological distress related to managing diabetes. It evaluates aspects like emotional, regimen, physician, and interpersonal distress) was deemed as positive which is attached as Annexure. The World Health Organization (WHO) defines obesity as "an abnormal or excessive accumulation of fat that poses a health risk" [14]. It is typically assessed using the Body Mass Index (BMI), which is calculated by dividing weight in kilograms by height in meters squared (kg/m^2). The WHO categorizes BMI as follows: Normal weight: BMI 18.5–24.9, Overweight: BMI 25–29.9, and Obesity: BMI ≥ 30.

RESULTS

The study enrolled 64 patients with diabetes-related distress, comprising 28 males (43.8%) and 36 females (56.2%). Mean age of these patients with diabetes related distress was 51.45 ± 8.34 years (range; 37-65 years). The mean age of male and female patients with diabetes-related distress was comparable, with males averaging 51.86 ± 7.58 years and females averaging 51.14 ± 8.98 years (p = 0.735). Additionally, 35 (54.7%) of these patients were over the age of 50Among the 64 participants, 29 (45.3%) resided in rural areas, while 35 (54.7%) lived in urban areas. A significant proportion of participants 40 (62.5%) had a poor socioeconomic status, compared to 24 (37.5%) who belonged to middle-class families. Family History of Diabetes was present in 25 (39.1 %). The average Body Mass Index (BMI) of the participants in this study were 26.23 ± 2.53 kg/m^2, with obesity observed in 13 (20.3%) of the patients experiencing diabetes-related distress.

Table 1: Demographic Distribution

Trait	Categories	Frequency (%)
Gender	Male	28 (43.8%)
	Female	36 (56.2%)
Age Groups	≤ 50 Years	29 (45.3%)
	≥ 50 Years	35 (54.7%)
Socioeconomic Status	Poor	40 (62.5%)
	Middle Income	24 (37.5%)
Family History	Yes	25 (39.1%)
	No	39 (60.9%)
Residential Status	Rural	29 (45.3%)
	Urban	35 (54.7%)
Obesity	Yes	13 (20.3%)
	No	51 (79.7%)

Table 2 highlighted the role of cognitive behavioral therapy in reducing diabetes related distress as compared with control group i.e. P=0.004 which is statistically significant

Table 2: Distribution of Efficacy among Study Cases with Diabetes Related Distress in both Groups (n = 64)

Groups Efficacy	Group A Frequency (%)	Group B Frequency (%)
Yes	17 (53.1%)	06 (18.8%)
No	15 (46.9%)	26 (81.2%)
p-Value	0.004	

The efficacy of the study was analyzed and stratified based on various factors, including gender, age, residential status, socioeconomic status, family history of diabetes, presence of hypertension, obesity, and control of diabetes. This table summarizes the relationship between efficacy (Yes/No) and various factors in the study, along with their p-values. Efficacy results showed no statistically significant difference between male and female participants ($p = 0.793$), or between age groups of ≤50 and ≥50 years ($p = 0.201$). Similarly, socioeconomic status showed no significant impact, with no differences between poor and middle-income groups ($p = 0.282$). Residential status revealed a borderline difference in efficacy between rural and urban residents ($p = 0.073$). Additionally, neither obesity ($p = 0.755$) nor family history ($p = 0.993$) had a significant influence on efficacy (Table 3).

DOI: https://doi.org/10.54393/pjhs.v6i1.2467

Table 3: Stratification of Efficacy among Study Cases with Diabetes Related Distress (n=64)

Variables	Categories	Efficacy		p-Value
		Yes	No	
Gender	Male (n=28)	11	17	0.793*
	Female (n=36)	12	24	
Age	≤50 Years (n=29)	13	16	0.201*
	≥50 Years (n=35)	10	25	
Socioeconomic status	Poor (n=40)	12	28	0.282*
	Middle Income (n=24)	11	13	
Residential Status	Rural (n=29)	14	15	0.073*
	Urban (n=35)	9	26	
Obesity	Yes (n=13)	4	9	0.755*
	No (n=51)	19	32	
Family History	Yes (n=25)	09	16	0.993*
	No (n=39)	14	25	

*Statistically Insignificant

DISCUSSION

Cognitive-Behavioral Therapy (CBT) is a widely used approach in addressing diabetes-related distress. CBT is a type of psychotherapy which is focused on identifying and changes in negative thoughts patterns and behaviors that may contribute to psychological distress. A total of 64 patients experiencing diabetes-related distress met the study's inclusion criteria, comprising 28 males (43.8%) and 36 females (56.2%). Fayed A *et al.*, from Saudi Arabia has reported 65 % female gender preponderance in diabetes related distress, which aligns with these findings [15]. Wardian J *et al.*, from the United States also found a 56% predominance of diabetes-related distress in females, consistent with these results [16]. Grulovic N *et al.*, from France reported a 52% predominance of males, which is somewhat higher than the proportions observed in this study [17]. Chew BH *et al.*, from Malaysia also identified a higher prevalence of females among patients with diabetes-related distress, aligning with these findings [18]. Nguyen *et al.*, from Vietnam reported that 52.7% of patients experiencing diabetes-related distress were female, which is comparable to these findings [19]. In contrast to these findings, Kamrul-Hasan *et al.*, from Bangladesh observed a predominantly male population, accounting for 54.8% [20]. The study's participants had a mean age of 51.45 years (SD = 8.34), spanning a range of 37 to 65 years. The mean age for male patients was 51.86 ± 7.58 years, and for female patients, it was 51.14 ± 8.98 years, with no statistically significant difference (p = 0.735). Additionally, 35 (54.7%) of these patients were over the age of 50 [15]. Wardian J *et al.*, from United States of America has also reported 55.2 ± 8.82 years mean age among patients with diabetes related distress, similar to these results [16]. Grulovic N *et al.*, from France reported a mean age of 48.11 ± 15.53 years in patients with diabetes-related distress, which aligns with these findings [17]. These findings are consistent with those of Chew BH *et al.*, from Malaysia, who reported a mean age of 56.9 years in patients experiencing diabetes-related distress [18]. Nguyen VB *et al.*, from Vietnam reported a mean age of 53.8 ± 11.9 years in patients with diabetes-related distress, which aligns with these results [19]. Kamrul-Hasan AB *et al.*, from Bangladesh reported 50.36 ± 12.7 years mean age in diabetes related distress, similar to the study results [20]. This study comprised 64 participants, of whom 29 (45.3%) were rural residents and 35 (54.7%) were urban residents. Poor socioeconomic status was noted in 40 (62.5%) while 24 (37.5%) had middle class family background. Fayed A *et al.*, from Saudi Arabia has reported findings that are consistent to the results of this study [15]. Nguyen VB *et al.*, from Vietnam has also reported 85.7 % patients with diabetes related distress from urban localities, similar to this results [19]. Kamrul-Hasan AB *et al.*, from Bangladesh reported 55.9 % patients with diabetes related distress were from urban areas, similar to this study results [20]. Chew BH *et al.*, from Malaysia has also reported a high prevalence of hypertension (80%) in patients with diabetes related distress, which is consistent with these findings [18]. Nguyen VB *et al.*, from Vietnam has also reported 28.6 % hypertension among patients with diabetes related distress, similar to this results [19]. Kamrul-Hasan AB *et al.*, from Bangladesh reported a similar finding, with a 66.8% prevalence of positive family history of diabetes among individuals experiencing diabetes-related distress, comparable to the study's results [20]. This study revealed a mean Body Mass Index (BMI) of 26.23 ± 2.53 kg/m^2 among participants, with 13 (20.3%) cases categorized as obese. Wardian J *et al.*, from United States of America has reported 30.32 ± 6.40 kg/m^2 mean body mass index in patients with diabetes related distress, indicating higher BMI levels in American population as compared with the local population [16]. Nguyen VB *et al.*, from Vietnam has reported 67 % overweight or obese patients with diabetes related distress, quite higher from these results [19]. Kamrul-Hasan AB *et al.*, from Bangladesh reported 23.9 ± 3.7 kg/m^2 mean body mass index in diabetes related distress consistent with the results of this study [20]. Out of the 64 study participants, only 20 (31.3%) patients had their diabetes under control, whereas 41 (64.1%) had uncontrolled diabetes. Fayed A *et al.*, from Saudi Arabia has reported 19 % controlled diabetes in diabetes related distress, in line with these study findings [15]. Nguyen VB *et al.*, from Vietnam has also reported 47.3 % patients with diabetes related distress had their HbA1c higher than 7 %, comparable to the results of this study [19]. Kamrul-Hasan AB *et al.*, from Bangladesh reported 25.7 % controlled blood glucose levels in diabetes related distress, as observed in these study results [20]. Efficacy was observed in 23

DOI: https://doi.org/10.54393/pjhs.v6i1.2467

(35.9%) of these study cases. In group A, efficacy was observed in 17(53.1%) participants, compared to 6(18.8%) in group B (P=0.004). Newby J *et al.*, also reported remission of depression in 51 % with these therapies compared with 18 % in control groups, similar to these findings [21].

CONCLUSIONS

The findings of these study endorse the application of cognitive behavioral methods in managing diabetes-related distress, as these techniques were found to be both effective and reliable. Effectiveness of therapy was significantly higher among experimental group as compared with control group. Clinicians treating such patients with diabetes related distress can effectively employ cognitive behavioral techniques for its effective management and to achieve desired clinical outcomes. The current study has some limitations. First, patients were taken only from outpatient departments. Secondly, limited generalizability of the results due to small sample size and study access within single institute.

Authors Contribution

Conceptualization: SM
Methodology: MA
Formal analysis: IF, MA
Writing, review and editing: IF, SAK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2694

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Mortality Associated with Tuberculosis Meningitis in HIV Infected Patients and Non-HIV Infected Patients

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ARTICLE INFO

Keywords:
Tuberculosis Meningitis, Human Immunodeficiency Virus, Mortality, Infarction

How to Cite:
Haji, S., Afzal, M., Akram, W., Ahmed, A., Memon, B., & Kumari, M. (2025). Mortality Associated with Tuberculosis Meningitis in HIV Infected Patients and Non-HIV Infected Patients: Tuberculosis Meningitis in Infected and Non-HIV Infected Patients. Pakistan Journal of Health Sciences, 6(1), 174-178. https://doi.org/10.54393/pjhs.v6i1.2694

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Received date: 4th December, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

Human Immunodeficiency Virus (HIV) infection significantly worsens Tuberculosis meningitis (TBM) outcomes, leading higher mortality rate in HIV-positive patients compared to HIV-negative individuals. **Objectives:** To find out the frequency of HIV Infected Patients with TBM and their outcome as mortality and to compare their mortality of TBM without HIV infection. **Methods:** This cross-sectional-observational study was conducted at Jinnah Postgraduate Medical Center Karachi, from September 2020 to October 2024. All patients diagnosed with TBM on clinical findings and Cerebrospinal Fluid analysis as TBM were admitted an HIV test was carried out and a CD4 cell count was done in HIV-positive patients. Treatment with Anti-Tuberculosis Therapy and Antiretroviral Therapy was done, the outcome as mortality was recorded up to 1 year and results were analyzed by SPSS version 26.0. **Results:** A total of 260 patients were enrolled who presented with TBM. The mean age was 39 ± 12.7 years. 20/260 (7.69%) were HIV positive and 240/260 (92.3%) were HIV negative TBM patients. 130/240 (54.16%) were male and 110/240 (45.93%) were female in HIV-negative and HIV-positive TBM 12/20 (60%) were male and 8/20 (40%) patients were female. The average age in HIV-positive patients was 32.5 ± 5.5 and 38.5 ± 6 in HIV-negative patients. 13/20 (65%) HIV-positive patients expired and 55/240 (22.9%) of HIV-negative patients expired. **Conclusions:** It was concluded that HIV Infected patients in our setup were increasing and had a high mortality rate as compared to HIV-negative patients of TBM and TBM patients presented in stage 3 had high mortality in both HIV-positive and HIV-negative patients.

INTRODUCTION

Tuberculous meningitis (TBM) is a fatal disease that causes significant disability and high mortality rates, particularly in patients presenting in Stage 3, where complications such as hyponatremia and hydrocephalus are common causes of death [1]. According to Luo *et al.*, TBM is classified into three stages based on clinical presentation. Stage 1 includes alert patients with symptoms such as vomiting but no focal neurological deficits and a Glasgow Coma Scale (GCS) score of 15/15. Stage 2 involves patients with a GCS score of 11–14 and focal neurological deficits, while Stage 3 includes unconscious patients or those with a GCS score of ≤10 [2]. The typical distribution of TBM presentation is 30% in Stage 1, 60% in Stage 2, and 10% in Stage 3 [3]. Mortality in TBM is particularly high in Stage 3 patients. In addition, TBM with HIV co-infection presents unique challenges, including differences in clinical presentation, treatment responses, and outcomes. The mean age of HIV-positive TBM patients has been reported as 36.7 years, compared to 23.35 years for HIV-negative TBM patients. Furthermore, 90% of HIV-infected TBM patients present in Stage 2, compared to 72.5% of non-HIV-infected TBM patients [4]. Globally, TBM prevalence in India accounts for 26% of cases

DOI: https://doi.org/10.54393/pjhs.v6i1.2694

among HIV-negative patients and 34% among HIV-positive patients [4]. HIV-infected TB patients are five times more likely to develop central nervous system (CNS) involvement like seizures and epilepsy, often leading to severe morbidity or death if untreated [5, 6]. To reduce mortality, the National AIDS Control Organization and WHO recommend initiating antiretroviral therapy (ART) in HIV-positive patients regardless of CD4 count [7]. However, multi-drug resistant TBM increases mortality risk, though initiating ART two months after TBM treatment reduces the likelihood of drug-related adverse effects, such as rash, headache, hepatitis, and nephritis [8]. Common findings in TBM include cerebrospinal fluid (CSF) abnormalities such as low glucose, high protein, and increased lymphocytes. Imaging studies, such as CT or MRI scans, often reveal hydrocephalus or tuberculosis in HIV-positive TBM patients. The rationale for this study stems from the observed high mortality in TBM patients, which is further compounded by HIV co-infection. While HIV prevalence is generally perceived to be high in Pakistan [9], its association with a significant number of TBM patients is becoming increasingly evident. This highlights an information gap regarding the frequency and outcomes of HIV co-infection in TBM within the local context.

This study aimed to address this gap by determining the exact prevalence of HIV among TBM patients, calculating mortality rates for both HIV-infected and non-HIV-infected TBM patients, and comparing these outcomes. By filling this knowledge gap, the findings will provide valuable insights to clinicians and the medical community about the impact of HIV co-infection on TBM outcomes along with that it will help educate healthcare professionals on the importance of early referral and timely initiation of ART and anti-tuberculosis therapy (ATT) to prevent mortality.

METHODS

This cross-sectional study was conducted in the Neurology Ward at Jinnah Postgraduate Medical Center (JPMC), Karachi from 1st September 2020 to 1st October 2024 after obtaining permission from the ethical committee JPMC vide letter No.F.2-80/2020-GENL/213/JMPC. All patients aged 18 years and older, with confirmed TBM through GeneXpert, CSF analysis, or imaging studies indicating meningeal enhancement, hydrocephalus, or tuberculosis, were included via non-probability consecutive sampling method. Patients with co-existing neurological conditions unrelated to TBM individuals who had received partial or incomplete treatment for TBM before admission, and cases with concurrent infections or illnesses (e.g., bacterial meningitis or viral encephalitis) were excluded from the study. Informed written consent was taken from each participant for inclusion in the research process. Patients classified as Stage 1 TBM presented with symptoms such as fever, headache, vomiting, and neck rigidity and were subsequently admitted. Those categorized as Stage 2 TBM exhibited altered sensorium accompanied by focal neurological deficits. Meanwhile, patients presenting in an unconscious state were identified as Stage 3 TBM. Consent was taken for lumber puncture and CSF was sent for analysis as part of standard management protocol. High protein, low glucose and increased lymphocyte count were noted to diagnose TBM. GeneXpert analysis of cerebrospinal fluid (CSF) was conducted, and CSF cultures were performed. Serum HIV serology was assessed for all patients, alongside a complete blood count, serum glucose, creatinine, urea, and liver function tests (LFTs). A CT scan of the brain (without contrast) was conducted to identify tuberculosis and hydrocephalus for confirmation of tuberculous meningitis (TBM). Additionally, brain MRI was utilized to assess meningeal enhancement indicative of TBM. Patients were treated with anti-tuberculosis therapy (ATT), consisting of rifampicin, isoniazid (INH), ethambutol, and pyrazinamide for an initial two months, followed by rifampicin and INH for the subsequent ten months. Outcomes were documented in terms of survival or mortality over one year. Cases of TBM with concurrent HIV infection were recorded, and antiretroviral therapy (ART) was initiated. Patients were classified into TBM stages 1, 2, and 3 based on their clinical presentation, and mortality outcomes were analyzed separately for each stage. A sample size of 260 achieves a statistical power of 99.476% to detect a difference (P1–P0P_1-P_0) of -0.1100 using a two-sided exact test with a significance level (α\alpha) of 0.050. These calculations are based on the assumption that the population proportion under the null hypothesis (P0P_0) is 0.264 [10]. The results were analyzed using SPSS version 26.0. Mortality rates were calculated for HIV-infected TBM patients at each stage of the disease and separately for non-HIV-infected TBM patients. The p-values were calculated using the Chi-square test to ensure statistical validity.

RESULTS

A total of 260 patients with TBM were included in the study. The average age was 38.5 ± 6.7 years in HIV-negative patients and 32.5 ± 5. years 5 in HIV-positive patients. Among the total, 240 out of 260 (92.30%) were HIV-negative, while 20 out of 260 (7.69%) were HIV-positive. In the HIV-negative group, 130 out of 240 (54.16%) were male, and 110 out of 240 (45.83%) were female (Figure 1).

DOI: https://doi.org/10.54393/pjhs.v6i1.2694

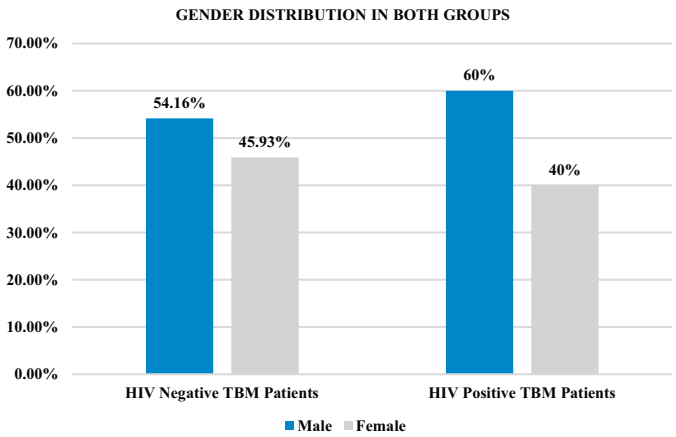

Figure 1 : Distribution of Gender According to HIV Status of TBM Patients

Mortality among tuberculosis meningitis (TBM) patients showed significant variation across stages and HIV status. In Stage 1(n=145, 55.8%), HIV-positive patients had a higher mortality rate (20%) compared to HIV-negative patients (3.57%), with a significant difference (p=0.012). In Stage 2 (N=59, 22.7%), mortality was 50% in HIV-positive patients versus 18.18% in HIV-negative patients (p=0.020). Stage 3 (N=56, 21.5%) recorded the highest mortality rates, with HIV-positive patients at 90.9% and HIV-negative patients at 88.88% (p=0.024). Overall, HIV-positive patients had significantly higher mortality (65%) compared to HIV-negative patients (22.9%), with an overall p=0.031. These findings underscore the increased risk of mortality in HIV-positive TBM patients, particularly in advanced stages. (Table 1).

Table 1: Mortality Among TBM Patients by Staging and HIV Status

TBM Stage	HIV-Positive Patients	HIV-Negative Patients	p-value
Stage 1 n=145 (55.8%)	1/5 (20%)	5/140 (3.57%)	0.012
Stage 2 n=59 (22.7%)	2/4 (50%)	10/55 (18.18%)	0.020
Stage 3 n=56 (21.5%)	10/11 (90.9%)	40/45 (88.88%)	0.024
Total	13/20 (65%)	55/240 (22.9%)	0.031

DISCUSSION

Tuberculosis meningitis (TBM) is a lethal disease resulting in death and disability. TBM with HIV-positive patients is increasing. Mortality in HIV-negative patients was 40% and in HIV-positive patients of TBM had a mortality of 70% [11]. In this study mortality in HIV-positive patients was 65% and HIV negative patients was 22.91%. A study conducted in South Africa showed 15-90% of patients had TBM with HIV positive and had more than twice the mortality than HIV-negative TBM patients [12]. So significant high mortality was found in HIV-positive TBM patients. The same findings were presented in this study. The mean age was 36.75 years in HIV-positive TBM patients and 29.35 in HIV-negative patients. Most patients presented in stage 2 and stage 3. Mortality was 87.5% in HIV-positive patients and 25% in HIV-negative patients in a study concluded in Mumbai, India [13]. In this study age was 38 ±5 years in negative HIV TBM patients and 32±5 years in HIV positive patients. In this study 7.69%were HIV positive patients of TBM. The most common symptom is altered sensorium so they are diagnosed usually in stage 2 and stage 3. Stage 2 and stage 3 had high mortality as compared to stage 1 so mortality must be decreased if TBM is diagnosed in stage 1. The involvement of HIV-positive patients by TBM is 15-21 times more than HIV HIV-negative patients globally [14]. and 37.7 million people are HIV-positive [15]. so TBM in these patients causes high mortality. ART can lead to severe immune syndrome so should start after 2 months of treatment [16]. ART can be reduced but still high mortality in HIV positive patients even after ART treatment. The same result was found in this study. TBM in HIV-positive patients had very low sodium which causes death [17]. In this study, hyponatremia was positive in all patients of TBM who expired. So preventing HIV infection can prevent TBM and reduce mortality. So in Pakistan HIV HIV-positive patients can be reduced by public awareness programs because TBM is 21 times more in HIV-positive patients. Patients of TBM with HIV-positive infection in a study in Europe revealed high mortality and ART-receiving patients also had high mortality [18]. HIV-infected TBM patients had high morbidity as well. 50-70% of patients developed disability and prognosis related to the stage of TBM and patients of GCS less than 10 had high mortality. Increased resistance to drugs also is a risk factor for complications in patients infected with TB. Then HIV infection can activate the silent TBM so HIV infection is a predisposing factor for the activation of TBM [19]. In stage I, TBM brain damage is less as compared to the other two stages. There is no infarction of the brain in stage I so if the diagnosis is made earlier then it could lead to the prevention of morbidity and mortality in patients. In stage II morbidity like cranial nerve palsy is less common so early diagnosis would be essential to prevent further complications of TBM leading to death of the patient. So health education of patients for the prevention of HIV spread and TB spread is important to prevent mortality. Early diagnosis of TBM in stage 1 is important to prevent morbidity and mortality. CSF analysis, GeneXpert and some modern tests like Fuji film can detect TBM in 80% of patients [20]. Prevention of HIV infection is mandatory. Some patients of TBM may have lost to follow-up and their outcome was not recorded so they can slightly affect the result. The sample size of HIV-infected Patients was low and further study was needed to exactly know the mortality in HIV-infected patients. Moreover, the non-probability consecutive sampling may introduce selection bias and a single-center study limits the generalizability of the findings to the broader population.

DOI: https://doi.org/10.54393/pjhs.v6i1.2694

CONCLUSIONS

It was concluded that HIV-infected patients in our setup experience higher mortality rates compared to HIV-negative TBM patients. Furthermore, TBM patients presenting in Stage 3 have a significantly higher mortality rate in both HIV-positive and HIV-negative groups, indicating that TBM is indeed linked to higher mortality among HIV-infected patients.

Authors Contribution

Conceptualization: SH
Methodology: SH, MA, WA, AA, MK
Formal analysis: BM
Writing review and editing: MA, WA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2636

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Association of Physical Activity With Perceived Stress and Well-Being in the Third Trimester of Pregnancy

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ARTICLE INFO

Keywords:
Physical Activity, Perceived Stress, Prenatal Care, Third Trimester of Pregnancy

How to Cite:
Ahmed, W., Akhter, P., Soomro, F., Channar, H. B., Ahmed, W., Raza, S., & Qudoos, A. (2025). Association of Physical Activity With Perceived Stress and Well-Being in the Third Trimester of Pregnancy: Physical Activity in the Third Trimester of Pregnancy . Pakistan Journal of Health Sciences, 6(1), 179-184. https://doi.org/10.54393/pjhs.v6i1.2636

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Received date: 5th December, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

Physical inactivity is considered a worldwide pandemic that leads to numerous health problems. The World Health Organization advises pregnant women to participate in at least 150 minutes of moderate exercise each week to enhance health outcomes. As in the last trimester of pregnancy, considerable physical, hormonal, and psychological changes at this stage need further exploration. **Objectives:** To determine the association between physical activity, perceived stress, and well-being in the third trimester of pregnancy. **Methods:** A cross-sectional study of 245 third-trimester pregnant mothers was conducted at a local healthcare center using non-probability purposive sampling from June 2024 to November 2024. The Pregnancy Physical Activity Questionnaire (PPAQ) was used to quantify physical activity, stress levels were measured with the Perceived Stress Scale-04 (PSS-04), and well-being was assessed using the WHO-5 Well-Being Index. Spearman correlation analysis and descriptive statistics were used to investigate the connections among stress, physical activity, and well-being. **Results:** Increased physical activity is associated with decreased levels of stress, based on the data, It demonstrated a strong inverse relationship between physical activity and perceived stress (ρ=-0.342, $p<0.01$). Additionally, there was a positive correlation between well-being and physical exercise (ρ=0.232, $p<0.01$). **Conclusions:** It was concluded that physical activity decreased stress and improved well-being in the third trimester of pregnant women. This implies that medical professionals should recommend physical activities in prenatal care, especially in various cultural needs programs. More research is needed with larger, diverse groups.

INTRODUCTION

Physical inactivity has become a global public health issue, with over 80% of adolescents and 31% of adults not reaching the World Health Organization's (WHO) recommended levels of physical activity. Recently, physical inactivity has been recognized as the fourth leading contributor to premature deaths worldwide, escalating to pandemic proportions [1, 2]. This widespread inactivity has been linked to several chronic health problems, such as obesity, diabetes, and cardiovascular diseases, as well as a rise in psychological disorders, such as depression, anxiety, and stress [3]. One effective way to prevent these chronic diseases is by increasing physical activity. Encouraging active lifestyles addresses the root causes of many emerging chronic conditions. This strategy supports "more active people for a healthier world" as outlined in the WHO's Global Action Plan on Physical Activity (2018–2030) [4]. In recent times, most developed nations have changed their policies toward maternal care and the prevention of ailments rather than treatment. In this regard, the approach is to catch the illness before it develops; likewise, in pregnancy, everything is related to the mom and the kid. Furthermore, early development of health behaviour will help reduce a specific chronic disease [7]. Pregnancy, especially during the third trimester, is a transformative period marked by significant physical, emotional, psychological, and hormonal changes as the body prepares

DOI: https://doi.org/10.54393/pjhs.v6i1.2636

for childbirth. Hormonal fluctuations during this stage can affect mood, energy levels, and overall well-being. These changes, coupled with physical discomfort and concerns about childbirth, can lead to heightened stress and anxiety. These factors highlight the importance of understanding and addressing the unique needs of pregnant women during this critical phase [6]. Mental well-being during pregnancy is important because high levels of stress are known to affect not just the mother but also her unborn child. Pregnancy stress affects not only the emotional and physical health of the pregnant mother but also the growth and development of the unborn baby, contributing to low birth weight, preterm delivery, and developmental delays. It is, therefore, very important to ensure that mental health is considered during pregnancy for the well-being of both mother and child [7, 8]. Studies suggest that regular physical activity can play a significant role in preventing prenatal depression by improving mood and alleviating stress [9]. To improve health outcomes, the WHO advises pregnant mothers to engage in at least 150 minutes of moderate exercise each week [10]. However, approximately one in five pregnant women continue to experience suicidal thoughts, primarily due to untreated or severe depression, underscoring the need for effective interventions to address mental health challenges during pregnancy [11]. While global research supports the benefits of physical activity in stimulating the release of mood-enhancing hormones like serotonin [12], studies focusing on its impact during the third trimester when hormonal changes are most pronounced are limited, particularly in Pakistan. This gap in research highlights the importance of investigating the relationship of physical activity with perceived stress, also well-being during this critical period in Pakistan's unique cultural context. This research aims to create a healthier population by promoting increased physical activity, ultimately reducing the global burden of chronic diseases. Public health initiatives that encourage regular exercise strive to lower the rates of conditions like diabetes, heart disease, and obesity, thereby improving overall quality of life and reducing healthcare costs worldwide [13]. These efforts also support achieving Sustainable Development Goal 3 (SDG 3), which aims to promote well-being and healthy lives [14]. The findings from this study aim to provide valuable insights for healthcare organizations and policymakers in Pakistan, enabling them to develop strategies that integrate physical activity promotion into prenatal care programs. This research contributes to global efforts to address health disparities, improve maternal health outcomes, and foster healthier, more active populations, ultimately supporting sustainable development and a better quality of life. Physical inactivity is a global issue linked to poor health outcomes [15]. The WHO recommends 150 minutes of moderate exercise weekly [10], but cultural norms in Pakistan often discourage activity during pregnancy [16]. Addressing this gap can improve health outcomes and align with global health goals like SDG 3.

This study aims to assess physical activity levels during the third trimester of pregnancy and investigate their relationship with perceived stress and well-being.

METHODS

An analytical cross-sectional study was conducted at the Gynecology and Obstetrics Outpatient Department (OPD) of Liaquat University Hospital, Hyderabad, to explore the association of physical activity with stress and well-being in the third trimester of pregnancy. The study was conducted over six months, from June 2024 to November 2024, after obtaining approval from the Ethical Review Committee (ERC) of Liaquat University of Medical and Health Sciences(LUMHS)(Approval number: LUMHS/REC/-303). A sample size of 245 was calculated using OpenEpi (prevalence: 17.6%, confidence level: 95%, margin of error: 5%), with an additional 10% included to account for non-responses or dropouts. Pregnant women in their third trimester were selected using non-probability purposive sampling. Participants included women aged 18–35 years attending the Gynecology OPD who provided informed consent and were free from severe medical or obstetric complications affecting physical activity, stress, or well-being. Women were excluded if they did not consent, were advised against physical activity for medical reasons, had physical disabilities, or were on psychological medications. Data were collected using structured questionnaires, which were freely available, validated, and reliable. Minor modifications were made to adapt to the local context, and experts reviewed the validation of these modifications. The demographic details section collected participant information, including age, residence, education, and other pertinent variables. The Pregnancy Physical Activity Questionnaire (PPAQ) assessed daily physical activity, with higher scores indicating greater activity levels. This tool has shown strong reliability, with a Cronbach's alpha greater than 0.7. The Perceived Stress Scale (PSS-04) evaluated stress levels using four items rated on a 0–4 Likert scale, where higher scores correspond to increased stress. This scale also shows good reliability (Cronbach's alpha >0.7). The WHO-5 Well-Being Index also measured overall well-being through five items rated on a 0–5 scale, with higher scores reflecting better well-being. This index has a high reliability level, with a Cronbach's alpha of more than 0.8. To analyze the data, SPSS version 22.0 was used. Descriptive statistics, such as percentages and frequencies, were computed for categorical variables. Correlation analysis between physical activity, stress, and

DOI: https://doi.org/10.54393/pjhs.v6i1.2636

well-being was conducted using the Pearson correlation test, with confidence intervals added for comprehensive reporting. At a 95% confidence level, a p-value of less than 0.05 was deemed statistically significant. Ethical considerations included obtaining written informed consent, ensuring participant confidentiality, and adhering to ERC guidelines.

RESULTS

A total of 245 women in their third trimester participated in the study. The sample's demographic characteristics offer a meaningful context for understanding the study findings. The average age of the participants was 25.05 ± 4.60 years, with an age range extending from 18 to 35 years. Most of the participants were between the ages of 18 and 30 years, which is reflective of the typical reproductive age range in this population. This data suggests that most participants were Urdu-speaking (76.3%), followed by Sindhi (20.0%) and others (3.7%). Additionally, 48.2% of participants had education above the secondary level, while 29.4% had no formal education. These demographics may have influenced the findings, which are interrelated with physical activity, well-being, and stress during pregnancy (Table 1).

Table 1: Sociodemographic Characteristics of Participants

Variable	Categories	Frequency (%)
Age group (Years)	18-25	146 (59.6)
	26-30	78 (31.8)
	31-35	21 (8.6)
Ethnicity	Urdu	187 (76.3)
	Sindhi	49 (20.0)
	Other (Saraiki, Punjabi)	9 (3.7)
Education Level	None	72 (29.4)
	Primary	55 (22.4)
	Secondary and Above	118 (48.2)

The analysis of physical activity levels among participants revealed that most engaged in light physical activity, contributing 69% (9,767 METs), followed by moderate activity at 20% (2,806 METs). Sedentary behaviour accounted for 11% (1,564 METs), with no participants reporting vigorous physical activity. These findings underscore a preference for low-intensity activities during pregnancy, highlighting the need for interventions to encourage moderate-intensity activities for better maternal health outcomes (Figure 1).

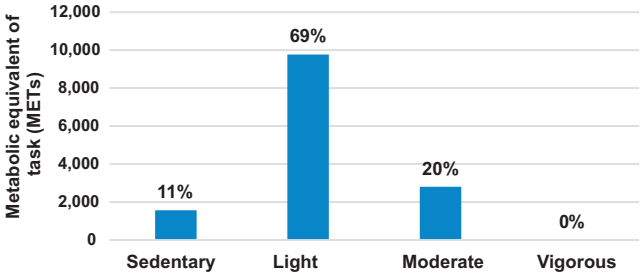

Figure 1: Cumulative Physical Activity Distribution Across Participants

Stress levels were assessed among participants, revealing that 63.7% experienced normal stress levels, while 36.3% exhibited elevated stress levels. This finding emphasizes the need for targeted interventions to alleviate stress, especially during the third trimester when pregnancy's physical and emotional demands peak (Figure 2).

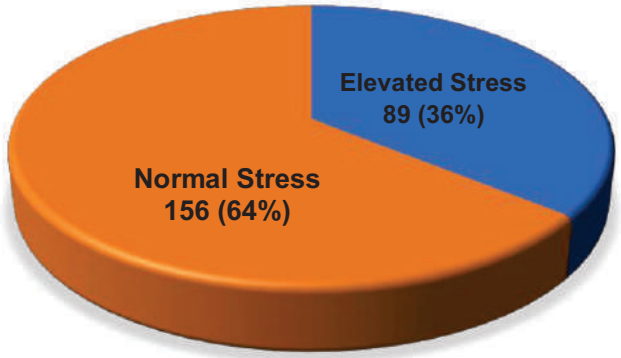

Figure 2: Distribution of Stress Levels Among Participants

Mental well-being analysis indicated that 21.2% of pregnant women experienced depression, 31.8% reported poor well-being, and 46.9% had better well-being. These results underscore the mental health challenges prevalent during pregnancy, particularly in the third trimester, highlighting the need for focused interventions (Figure 3).

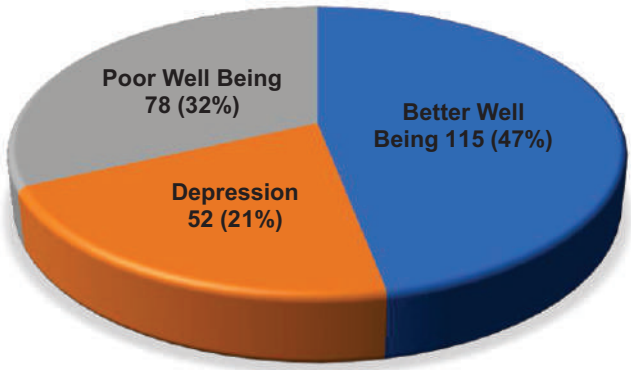

Figure 3: Distribution of mental well-being Levels Among Participants

Spearman's correlation analysis revealed a negative and moderate relation between perceived stress with physical activity engagement ($r=-0.342$, $p<0.01$), which means high physical activity levels are associated with lower perceived stress (Table 2).

DOI: https://doi.org/10.54393/pjhs.v6i1.2636

Table 2: Spearman's Correlation Analysis Between Physical Activity and Perceived Stress

Variable	Physical Activity	Perceived Stress
Physical Activity	1.000	-0.342 (p<0.01)
Perceived Stress	-0.342 (p<0.01)	1.000

Similarly, a weak but significant positive correlation was found between physical activity and well-being (r=0.232, p<0.01). This indicates that increased physical activity is mildly associated with improved well-being (Table 3).

Table 3: Spearman's Correlation Analysis Between Physical Activity and Well-Being

Variable	Physical Activity	Well-Being
Physical Activity	1.000	0.232 (p<0.01)
Well-Being	0.232 (p<0.01)	1.000

DISCUSSION

The sample's demographic characteristics offer a meaningful context for understanding the study findings. The average age of the mothers was 25.05 ± 4.60 years, with the age range extending from 18 to 35 years as shown in Table 1. reflecting the typical reproductive age range. Younger participants, generally more active than older women, may have influenced physical activity and psychological health findings. The relatively young age of the participants is important to note as it may influence both physical activity and psychological health, given that younger women generally engage in more physical activity than older women [17]. This demographic information helps contextualize the physical activity behaviours observed in the study. In this study, the majority of physical activity was light, accounting for 69% of the total activity. Moderate physical activity constituted 20%, while sedentary activity made up 11%. Notably, no participants reported engaging in vigorous physical activity. This distribution aligns with previous research, which shows that Pregnant women mostly engaged in light to moderate-intensity physical activities [18]. This study found no evidence of vigorous physical activity during the third trimester. Similarly, a North Carolina study on pregnant women reported that vigorous activity was uncommon during pregnancy [19]. Results showed that 63.7% of participants had normal stress, while 36.3% experienced elevated levels. Elevated stress during pregnancy is linked to risks like preterm births and low birth weights. Elements like hormonal changes, social support, and discomfort can increase stress, consistent with findings from previous studies [20]. Well-being was measured using the WHO-5 index. A score above 50 indicated better well-being, 50 or below indicated poor well-being, and below 28 signified depression. The total score, scaled to 100, was calculated by multiplying the raw score by 4, as defined in previous studies [21]. 21.2% of pregnant women experienced depression, while 31.8% reported poor well-being, indicating common mental health challenges during the third trimester. However, 46.9% maintained better well-being, highlighting resilience in many mothers. These findings align with WHO reports that nearly 1 in 5 women, or 20%, face mental health issues during pregnancy or postpartum, including suicidal thoughts or self-harm. Neglecting maternal mental health can negatively impact both the mother's and the infant's development [22]. The results underline the connection between perceived stress and physical activity, indicating that some lower stress levels while pregnant may be a result of increased physical activity. The Spearman correlation analysis supports this observation, showing a moderate negative relationship between perceived stress and physical activity (r=-0.342, p<0.01), showing that being more active is linked to lower levels of perceived stress, these results align with existing evidence emphasizing the stress-reducing benefits of physical activity, Being more active is known to stimulate the release of endorphins, which can improve mood and reduce stress hormones like cortisol [23]. Additionally, The Spearman correlation analysis reveals a significant positive relationship between physical activity and well-being (r=0.232, p<0.01. Although the correlation is weak, this could be because well-being is influenced by other factors such as social support, personal circumstances, and access to healthcare [24]. Despite the modest strength of the correlation, the results suggest that physical activity can play a role in enhancing well-being. These findings are consistent with research showing that physical activity helps reduce stress and contributes to better overall well-being. Encouraging pregnant women to engage in regular physical activity, even at light or moderate levels, can promote mental and physical health during pregnancy [25, 26]. The study emphasizes the importance of promoting safe, moderate physical activity during pregnancy to reduce stress and improve well-being. Culturally sensitive programs, community involvement, and stress-reduction strategies like counselling and mindfulness should be integrated into prenatal care. Enhanced mental health services and family support are also essential. Further research is needed to explore how ethnicity influences physical activity, stress, depression, and well-being during pregnancy.

CONCLUSIONS

It was concluded that a significant positive correlation was found between physical activity and well-being, and a significant negative correlation was found between physical activity and perceived stress, suggesting that increased activity is slightly associated with better well-being and reduced stress. It was also found that most mothers were performing light and fewer mothers were

DOI: https://doi.org/10.54393/pjhs.v6i1.2636

performing moderate physical activity, which the World Health Organization recommends. These findings emphasize the importance of promoting physical activity during pregnancy for improved mental health and overall well-being.

Authors Contribution

Conceptualization: WA[1]
Methodology: WA[1], PA, AQ
Formal analysis: WA[1], PA, FS, HBC, WA[2], SR, AQ
Writing review and editing: WA[1], PA, FS, HBC, WA[2], SR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2610

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Plastic Surgery Awareness and Perceptions among Healthcare Professionals: A Single Centre Study at Liaquat University Hospital

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ARTICLE INFO

Keywords:
Awareness, Perception, Plastic Surgery, Healthcare Professionals

How to Cite:
Sanober, A., Siddiqui, A. S., Sheikh, S., Irshad, S., Sangrasi, H., & Qureshi, P. N. A. A. (2025). Plastic Surgery Awareness and Perceptions among Healthcare Professionals: A Single Centre Study at Liaquat University Hospital: Plastic Surgery Awareness and Perceptions among Healthcare Professionals. Pakistan Journal of Health Sciences, 6(1), 185-190. https://doi.org/10.54393/pjhs.v6i1.2610

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Received date: 29th November, 2024
Acceptance date: 22nd January, 2025
Published date: 31st January, 2025

ABSTRACT

Plastic surgery encompasses both reconstructive and aesthetic procedures, addressing functional and cosmetic needs. Misconceptions about its scope are common, even among healthcare professionals, underscoring the need to evaluate their awareness and perceptions. **Objectives:** To assess the level of awareness and perceptions of plastic surgery as a speciality among healthcare professionals at Liaquat University Hospital, Hyderabad and Jamshoro. **Methods:** A cross-sectional questionnaire-based study was carried out at Liaquat University Hospital, Hyderabad, and Jamshoro. Participants included 108 house officers and postgraduate residents working in nonsurgical specialities. The study excluded doctors from other specialities related to surgery and dermatology due to overlaps in the scope of practice with plastic surgery. **Results:** A majority of participants (79.6%) recognized that cosmetic surgery was a component of plastic surgery, while 12% considered them to be the same, and 3.7% disagreed. In terms of the origin of the term "plastic surgery," 82.4% of participants did not know the reason behind the term. Regarding the aesthetic procedures, participants reported rhinoplasty as done by plastic surgeons (61.1%), with 37% favouring ENT surgeons. Non-surgical procedures such as Botox were mostly attributed to dermatologists (51.9%), with 40.7% selecting plastic surgeons. **Conclusions:** It was concluded that the study revealed significant gaps in both awareness and perceptions regarding plastic surgery among healthcare professionals. There was a noticeable misunderstanding regarding the appropriate speciality for aesthetic procedures, such as liposuction and breast reduction, where other surgeons were preferred over plastic surgeons, indicating a need for improved education and awareness in the medical community.

INTRODUCTION

Plastic surgery, which includes both cosmetic and reconstructive procedures, is a multifaceted surgical speciality encompassing diverse subspecialties such as microvascular surgery, hand surgery, and cranio-maxillofacial surgery. Despite its growing demand globally, Pakistan faces a significant shortage of adequately trained plastic surgeons [1]. Similar to other countries, this disparity arises from the limited number of residency training slots available relative to the rapid expansion of the field. Globally, this trend is expected to persist unless training programs are expanded [2, 3]. Globally, plastic surgery is often misconceived as purely aesthetic due to media representations that prioritize cosmetic enhancements over reconstructive procedures. This misrepresentation has led to a limited understanding of the specialty's broader scope, which includes life-saving interventions such as burn treatment, trauma repair, and congenital anomaly corrections. In Pakistan, these global misconceptions are further shaped by cultural and societal factors [4]. A conservative outlook, insufficient media representation, and limited public awareness often portray plastic surgery as a luxury rather than a necessity. These

DOI: https://doi.org/10.54393/pjhs.v6i1.2610

perceptions can lead to stigma, underutilization of services, and challenges within the medical community, such as inappropriate referrals or neglect of reconstructive possibilities [4]. In Pakistan, medical education typically spans five years of undergraduate training followed by a house job, after which specialization is pursued through a fellowship or board certification in plastic surgery, requiring an additional five years. The exposure to plastic surgery during undergraduate medical training is limited, often restricted to select procedures, such as burn management or wound care. Research highlights that increasing early exposure to plastic surgery can significantly influence students' interest and understanding of the speciality [5]. However, similar to other nations, studies on this topic in Pakistan are often region-specific and fail to provide a national perspective [6]. Cultural and societal factors also contribute to misconceptions about plastic surgery in Pakistan. A conservative societal outlook, combined with insufficient media representation and limited public awareness, often portrays plastic surgery as purely cosmetic. These misperceptions extend into the medical community, leading to challenges such as erroneous referrals and underutilization of reconstructive procedures. Addressing these challenges is crucial to reducing stigma, enhancing awareness, and promoting interest in this competitive field [7, 8]. Identifying misconceptions early can enable curriculum reforms, improve interdisciplinary collaboration, and contribute to addressing the growing shortage of plastic surgeons in Pakistan.

This study aims to evaluate these perceptions and awareness of healthcare providers regarding plastic surgery as a speciality among healthcare professionals at Liaquat University Hospital, Hyderabad and Jamshoro.

METHODS

A cross-sectional study was carried out at Liaquat University Hospital, Hyderabad, and Jamshoro. The duration of the study was from Nov 2021 to April 2022. A structured questionnaire was developed and administered to a sample of 108 participants, which included 108 house officers and postgraduate residents working in nonsurgical specialities. The study excluded doctors from general surgery, surgical super-specialities, orthopedics, Ear, Nose, Throat (ENT), ophthalmology, and dermatology due to overlaps in the scope of practice with plastic surgery. Only individuals holding an MBBS or higher qualification were included in the study. The study population size was determined to be 1,050 (600 house officers and 450 postgraduate residents), working in a study setting. All participants were selected using a non-probability consecutive sampling technique, ensuring that all eligible individuals meeting the inclusion criteria were included consecutively to reduce selection bias. The sample size was calculated using the Rao Soft Calculator [9], with a margin of error of 7.5%, a confidence level of 90%, and a response distribution of 50%. The final calculated sample size was 108 participants. The study was approved by the Ethical Review Committee of Liaquat University of Medical and Health Sciences, Jamshoro vide letter No. LUMHS/REC/-166. Informed written consent was obtained from every participant before being included in the study. The questionnaire comprised two sections, each designed with multiple-choice options to ensure structured responses. The Perceptions section (3 questions) explored general beliefs about plastic surgery, including its distinction from cosmetic surgery, the origin of its name, and its perceived exclusivity to wealthy individuals. The Awareness and Knowledge Gaps section (5 questions) assessed understanding of surgical outcomes, potential risks, and the appropriate specialists for conditions such as hypospadias, cleft lip/palate, and burns. The second section presented a series of clinical scenarios involving trauma, pathological conditions, reconstructive procedures, and cosmetic surgeries. The questionnaire was validated by 4 independent subject matter experts to face content validity before administration, aligning with standard research practices. Participants were asked to identify the speciality they believed to be most appropriate for managing each scenario. Options included various surgical specialities such as ENT surgery, ophthalmic surgery, neurosurgery, orthopedic surgery, pediatric surgery, urology, oral and maxillofacial surgery, dermatology, and plastic surgery. The exclusion criteria ensured a focused evaluation of nonsurgical specialities, minimizing bias from related fields. SPSS version 25.0 was used to analyze the data. The qualitative data were presented as frequency and percentages. The chi-square test was used to find the association between perception and awareness concerning gender and age group. p-value<0.05 was considered statistically significant.

RESULTS

The mean age of participants was 28.6 ± 7.21 years. Most participants were aged between 26–30 years (48, 44.4%), followed by 21–25 years (31, 28.7%), 31–35 years (21, 19.4%), and >35 years (8, 7.4%). Regarding gender distribution, 60 participants (55.6%) were male, and 48 (44.4%) were female. Participants were drawn from various nonsurgical specialities, with the highest representation from internal medicine (30, 27.8%), followed by pediatrics (25, 23.1%), psychiatry (20, 18.5%), cardiology (18, 16.7%), and radiology (15, 13.9%)(Table 1).

DOI: https://doi.org/10.54393/pjhs.v6i1.2610

Table 1: Association of Maternal Hemoglobin Levels with Maternal Outcomes

Variables	Frequency (%)
Mean Age	28.6 ± 7.21 Years
Age Groups	
21–25 Years	31 (28.7%)
26–30 Years	48 (44.4%)
31–35 Years	21 (19.4%)
>35 Years	8 (7.4%)
Gender	
Male	60 (55.6%)
Female	48 (44.4%)
Specialties	
Internal Medicine	30 (27.8%)
Pediatrics	25 (23.1%)
Psychiatry	20 (18.5%)
Radiology	15 (13.9%)
Cardiology	18 (16.7%)

The perception of plastic surgery among healthcare professionals varies in terms of its differentiation from cosmetic surgery. A majority of participants (79.6%) recognized that cosmetic surgery is a part of plastic surgery, while 12% considered them to be the same, and 3.7% disagreed. In terms of the origin of the term "plastic surgery," 82.4% of participants did not know the reason behind the term, with only 5.6% associating it with the use of plastic materials in surgery. A significant portion (37%) viewed plastic surgery as expensive and for the rich, while 54.6% disagreed, and 8.3% were uncertain (Table 2).

Table 2: Perceptions Regarding About Plastic Surgery

Questions	Responses	Frequency (%)
Do you believe that plastic surgery? And cosmetic surgery are the same fields?	Yes	13 (12%)
	No	4 (3.7%)
	Cosmetic Surgery is a Part of Plastic Surgery	86 (79.6%)
	I Do Not Know	5 (4.6%)
What is the reason behind the Name of "plastic" surgery?	Because It Involves the Use of Plastic	6 (5.6%)
	After Surgery, The Face Looks Like Plastic	5 (4.6%)
	Don't Know	89 (82.4%)
	Other Reason	8 (7.4%)
Is plastic surgery expensive and only meant for rich people?	Yes	40 (37%)
	No	59 (54.6%)
	Not Sure	9 (8.3%)

Regarding awareness of the outcomes of plastic surgery, 74.1% of participants believed that plastic surgery did not leave scars on the face, while only 18.5% acknowledged the presence of scars. Concerning the risk of plastic and cosmetic surgeries, 87% believed the risk was similar to other surgical procedures, whereas only 7.4% thought they were very risky. In terms of appropriate specialities for various conditions, there was clear recognition of the plastic surgeon's role in treating burns (86.1%) and cleft lip/palate (54.6%). However, for hypospadias, opinions were more divided, with 38% considering pediatric surgeons as the most suitable, and plastic surgeons and urologists both received 25.9% of the responses (Table 3).

Table 3: Awareness and Knowledge Gaps in Plastic Surgery

Awareness Areas	Responses	Frequency (%)
Do you think plastic surgery leaves scar marks on the face?	Yes, There Are Scars	20 (18.5%)
	No, There Are No Scars	80 (74.1%)
	Don't Know	8 (7.4%)
Risk in plastic/ cosmetic surgeries?	High Risk	8 (7.4%)
	Similar Risk As of Other Surgeries	94 (87%)
	No Risk	5 (4.6%)
	Don't Know	1 (0.9%)
Appropriate Specialty for Hypospadias	Plastic Surgeon	28 (25.9%)
	Pediatric Surgeon	41 (38%)
	Urologist	28 (25.9%)
Appropriate Specialty for Cleft Lip/Palate	Plastic Surgeon	59 (54.6%)
	Other	49 (45.4%)
Appropriate Specialty for Burns	Plastic Surgeon	93 (86.1%)
	Other	15 (13.9%)

Regarding the aesthetic procedures, responses indicated some misunderstandings regarding the most appropriate specialities. For liposuction, 52.8% of participants preferred general surgeons over plastic surgeons (47.2%). This disparity was even more significant for breast reduction/augmentation, where 78.7% of participants favoured general surgeons over plastic surgeons (21.3%). Rhinoplasty showed a more favourable view of plastic surgeons (61.1%), with 37% favouring ENT surgeons. For hair transplantation, 61.1% opted for plastic surgeons, while 37% selected dermatologists. Non-surgical procedures such as Botox were mostly attributed to dermatologists (51.9%), with 40.7% selecting plastic surgeons (Table 4).

Table 4: Aesthetic Procedures and Misunderstanding of Plastic Surgery Scope

Questions	Preferred Specialty	Frequency (%)
Liposuction	Plastic Surgeon	51 (47.2%)
	General Surgeon	57 (52.8%)
Breast Reduction/Augmentation	Plastic Surgeon	23 (21.3%)
	Breast Surgeon	85 (78.7%)
Rhinoplasty	Plastic Surgeon	66 (61.1%)
	ENT Surgeon	40 (37.0%)
Hair Transplantation	Plastic Surgeon	66 (61.1%)
	Dermatologist	40 (37.0%)
	General Surgeon	2 (1.9%)
Botox (Non-Surgical)	Dermatologist	56 (51.9%)
	Plastic Surgeon	44 (40.7%)
	Dental Surgeon	8 (7.4%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2610

Male and female participants had comparable misconceptions, with most agreeing that cosmetic surgery is part of plastic surgery (p=0.65) and a majority unaware of the reason behind the term "plastic" (p=0.81). Perceptions about plastic surgery being expensive and exclusive to the wealthy were similar across genders (p=0.98). While females leaned slightly more toward general surgeons for liposuction and breast reduction preferences, these differences were not statistically significant (p=0.19 and p=0.21, respectively) (Table 5).

Table 5: Gender Vs. Perceptions and Aesthetic Procedures Preferences

Questions / Procedure	Male (n=60)	Female (n=48)	p-Value
Do You Believe Plastic and Cosmetic Surgery Are the Same?			
Yes	8 (13.3%)	5 (10.4%)	0.65
No	2 (3.3%)	2 (4.2%)	
Part of Plastic Surgery	46 (76.7%)	40 (83.3%)	
Don't Know	4 (6.7%)	1 (2.1%)	
Plastic Surgery Is Called "Plastic" Because?			
Involves Plastic	4 (6.7%)	2 (4.2%)	0.81
Looks Plastic	3 (5.0%)	2 (4.2%)	
Don't Know	48 (80.0%)	41 (85.4%)	
Other	5 (8.3%)	3 (6.2%)	
Is Plastic Surgery Expensive and Meant for the Rich?			
Yes	22 (36.7%)	18 (37.5%)	0.98
No	33 (55.0%)	26 (54.2%)	
Not Sure	5 (8.3%)	4 (8.3%)	
Liposuction Specialty Preference			
Plastic Surgeon	32 (53.3%)	19 (39.6%)	0.19
General Surgeon	28 (46.7%)	29 (60.4%)	
Breast Reduction/Augmentation Preference			
Plastic Surgeon	10 (16.7%)	13 (27.1%)	0.21
Breast Surgeon	50 (83.3%)	35 (72.9%)	

Younger (≤30 years) and older (>30 years) participants had similar views, with most identifying cosmetic surgery as part of plastic surgery (p=0.79) and expressing a limited understanding of why it is called "plastic" (p=0.83). Both age groups showed comparable perceptions about cost exclusivity (p=0.71). While younger participants slightly favoured plastic surgeons for liposuction and breast reduction, the differences were not significant (p=0.78 and p=0.17) (Table 6).

Table 6: Age Groups Vs. Perceptions and Aesthetic Procedures Preferences

Questions / Procedure	≤30 Years (n=79)	>30 Years (n=29)	p-Value
Do You Believe Plastic and Cosmetic Surgery Are the Same?			
Yes	9 (11.4%)	4 (13.8%)	0.79
No	3 (3.8%)	1 (3.4%)	
Part of Plastic Surgery	63 (79.7%)	23 (79.3%)	
Don't Know	4 (5.1%)	1 (3.4%)	
Why Is Plastic Surgery Called "Plastic"?			
Involves Plastic	4 (5.1%)	2 (6.9%)	0.83
Looks Plastic	4 (5.1%)	1 (3.4%)	
Don't Know	63 (79.7%)	26 (89.7%)	
Other	8 (10.1%)	0 (0%)	
Is Plastic Surgery Expensive and Only for the Rich?			
Yes	28 (35.4%)	12 (41.4%)	0.71
No	43 (54.4%)	16 (55.2%)	
Not Sure	8 (10.1%)	1 (3.4%)	
Liposuction Specialty Preference			
Plastic Surgeon	38 (48.1%)	13 (44.8%)	0.78
General Surgeon	41 (51.9%)	16 (55.2%)	
Breast Reduction/Augmentation Preference			
Plastic Surgeon	14 (17.7%)	9 (31.0%)	0.17
Breast Surgeon	65 (82.3%)	20 (69.0%)	

DISCUSSION

This study highlighted the significant knowledge gaps and misconceptions about plastic surgery among young healthcare professionals at Liaquat University Hospital, Hyderabad, and Jamshoro. While 79.6% correctly identified cosmetic surgery as a subset of plastic surgery, 12% conflated the two entirely, and 4.6% were uncertain. This finding aligns with previous studies indicating that healthcare professionals often lack clarity regarding the distinction between reconstructive and aesthetic procedures in plastic surgery. A study by Perrault *et al.*, found that even medical professionals frequently associated plastic surgery primarily with aesthetic enhancements rather than its reconstructive aspects, which encompass burn treatment, trauma management, and congenital anomaly corrections [10]. Interestingly, 82.4% of participants were unaware of the origin of the term "plastic surgery," with only 5.6% erroneously attributing it to the use of plastic materials in surgery. This reflects a common public and professional misconception that the term "plastic" relates to synthetic materials rather than its etymological origin from the Greek word plastikos, meaning "to mold" [11]. A similar observation was made in a study by Gili *et al.*, where a majority of participants lacked basic knowledge about the nomenclature of the field [12]. These misconceptions could lead to misdiagnoses and underutilization of plastic surgery services, negatively impacting patient outcomes. Over time, they may hinder the growth of plastic surgery as a speciality in Pakistan by limiting interest and training opportunities. Financial barriers and perceptions regarding the affordability of plastic surgery were another focus area. While 37% viewed plastic surgery as expensive and primarily for affluent individuals, 54.6% disagreed. Many professionals perceived plastic surgery as expensive and primarily accessible to wealthy individuals, which limits its perceived

DOI: https://doi.org/10.54393/pjhs.v6i1.2610

relevance in public healthcare settings. This disparity may reflect differences in exposure to public versus private healthcare systems [13]. Public hospitals often offer subsidized reconstructive surgeries, contrasting with the high costs associated with cosmetic procedures in private settings. Studies in similar settings, such as the work by Hery *et al.*, have shown that perceptions of cost frequently deter patients from seeking even medically necessary reconstructive procedures [14]. The awareness of plastic surgeons' roles in specific medical conditions also revealed inconsistencies. While a majority correctly identified burns (86.1%) and cleft lip/palate (54.6%) as domains of plastic surgery, only 25.9% associated hypospadias correction with this speciality. Pediatric surgeons were favoured for this condition (38%). The limited knowledge about plastic surgeons' roles in reconstructive procedures is possibly due to insufficient exposure during medical training. This misperception is supported by findings from Petmeza *et al.*, which reported confusion about the scope of plastic surgery among medical professionals, particularly regarding pediatric conditions [15]. The study also assessed knowledge about risks and outcomes. A majority of healthcare professionals (87%) believed the risks of plastic and cosmetic surgery were similar to those of other surgical procedures, indicating a sound understanding of surgical risks, similar to the findings of the study done in the UK among undergraduate medical students [16]. However, the finding that 74.1% believed plastic surgery does not leave scars suggests an overly optimistic view of surgical outcomes, potentially influenced by media portrayals. Media portrayal often exaggerates aesthetic outcomes and focuses on cosmetic procedures, shaping unrealistic expectations and skewed perceptions of the full scope of plastic surgery. A systematic review by Shauly *et al.*, emphasized the role of media in shaping unrealistic expectations among both healthcare providers and the public [17]. Misunderstandings regarding the management of aesthetic procedures were pronounced. For liposuction and breast augmentation, general surgeons were favoured over plastic surgeons by 52.8% and 78.7% of participants, respectively. This contrasts with findings from studies in high-income countries, where plastic surgeons are predominantly recognized as specialists for these procedures [18]. Healthcare professionals often conflated cosmetic surgery with plastic surgery and incorrectly attributed procedures like liposuction and breast reduction to general surgeons instead of plastic surgeons. [19]. On the other hand, the study revealed stronger recognition of plastic surgeons' expertise in rhinoplasty (61.1%) and hair transplantation (61.1%), similar to findings by Alosfoor *et al.*, in a comparable resource-limited setting [20]. The variability in participants' responses regarding aesthetic procedures may stem from limited exposure to plastic surgery and the dominance of general surgery in doctor's perceptions. The cultural stigma around aesthetic procedures and gaps in medical education contribute significantly to misconceptions about the roles and expertise of plastic surgeons. Cultural taboos, media portrayals, and a lack of formal education on the broader scope of plastic surgery likely contribute to these misconceptions. The use of convenience sampling in our study and single-centred study limits the generalizability of findings. Moreover. Future research could employ random sampling and include multiple hospitals across regions to improve representativeness and reduce bias.

CONCLUSIONS

It was concluded that the study identified key knowledge gaps among healthcare professionals regarding plastic surgery. A significant portion (82.4%) of participants lacked understanding of the term "plastic surgery," and misconceptions about its scope and procedures were prevalent. For instance, general surgeons were incorrectly preferred over plastic surgeons for aesthetic procedures like liposuction and breast reduction. Additionally, while the majority did not view plastic surgery as excessively risky, misunderstandings about its cost and perceived exclusivity persisted. Integrating educational modules into training programs for healthcare professionals from non-surgical specialities can help correct misconceptions and foster a more informed understanding of the speciality.

Authors Contribution

Conceptualization: AS
Methodology: AS, ASS, SS, SI, PNAAQ
Formal analysis: ASS, SS, HS
Writing review and editing: PNAAQ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.1936

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Enhancing Neonatal Sucking Reflex: A Study on the Efficacy of Magnesium Sulphate in Severe Birth Asphyxia

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ARTICLE INFO

Keywords:
Birth Asphyxia, Neonatal Sucking Reflex, Magnesium Sulphate, Sucking Reflex

How to Cite:
Akram, M., Malik, A. R., Ahmad, M., & Arshad, R. T. (2025). Enhancing Neonatal Sucking Reflex: A Study on the Efficacy of Magnesium Sulphate in Severe Birth Asphyxia: Neonatal Sucking Reflex: Magnesium Sulphate in Severe Birth Asphyxia. Pakistan Journal of Health Sciences, 6(1), 191-196. https://doi.org/10.54393/pjhs.v6i1.1936

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Received date: 5th July, 2024
Acceptance date: 17th January, 2025
Published date: 31st January, 2025

ABSTRACT

One of the main causes of prenatal deaths and a known factor in neuromotor disabilities is perinatal asphyxia. **Objectives:** To compare the efficacy of magnesium sulphate on the appearance of a good sucking reflex in cases of birth asphyxia with controls (without magnesium sulphate). **Methods:** This randomized controlled trial was conducted at the Department of Neonatology, The Children's Hospital and the Institute of Child Health, Multan, from January 2024 to June 2024. A total of 80 full-term newborns of both genders with severe birth asphyxia admitted within six hours of life were randomly assigned to either the study group or the control group. The study group received 3 doses of magnesium sulphate 24 hours apart by intravenous infusion at 250 mg/kg/dose, and the control group did not receive this treatment. Supportive care was given to both study groups. Both groups were examined for sucking reflexes. **Results:** 46 (57.5%) were male, while 43 (53.8%) had a body weight of ≥2.5 kg. The mean age at the time of presentation was 3.2 ± 1.5 hours. Overall efficacy was observed in 48 (60.0%) babies. The distribution of efficacy in terms of the appearance of a good sucking reflex was significantly better in the magnesium sulphate group versus the control group (75.0% vs 45.0%, p=0.0062). **Conclusions:** It was concluded that magnesium sulfate was found to significantly improve the appearance of a good sucking reflex among newborns with severe birth asphyxia, highlighting its potential as a neuroprotective intervention in neonatal care.

INTRODUCTION

Perinatal asphyxia is a leading cause of prenatal deaths and a significant contributor to neuromotor disabilities. Research in neurobiology has elucidated mechanisms underlying neuronal death following hypoxic-ischemic insult, highlighting the brain as the organ most vulnerable to hypoxia. Asphyxia fatalities are often characterized by respiratory arrest accompanied by bradycardia and asystole, due to the failure of the brainstem's respiratory centers caused by hypoxia [1, 2]. These adverse outcomes underscore the critical need for effective interventions in managing birth asphyxia. Among the mechanisms mediating hypoxic-ischemic neuronal death, glutamate plays a central role [3]. Glutamate-induced neuronal death occurs through two primary pathways: instantaneous cell death due to glutamate receptor activation and delayed cell death, which unfolds over hours and is predominantly mediated by the activation of N-Methyl-D-aspartate (NMDA) receptors [4-7]. Magnesium (Mg), a natural NMDA receptor antagonist, has been shown to block the NMDA ion channel at rest by occupying a binding site within the channel [8]. Hypoxia-ischemia, however, disrupts this voltage-dependent blockade by causing axonal depolarization. Increasing extracellular magnesium concentrations has been suggested as a means to restore this blockade and protect neurons. Experimental evidence from animal models has demonstrated that systemic magnesium treatment can reduce neuronal damage following simulated hypoxic-ischemic insults [9, 10]. Despite promising preclinical findings, evidence regarding the clinical use of magnesium sulfate for treating birth

DOI: https://doi.org/10.54393/pjhs.v6i1.1936

asphyxia remains inconsistent. Prior studies have been limited by methodological variability and small sample sizes, which have hindered conclusive outcomes [11]. Neurological assessment of newborns with birth asphyxia often includes the elicitation of a good sucking reflex. In a study by Kumar P *et al.*, neonates treated with magnesium sulfate demonstrated better outcomes, with 71.4% capable of oral feeding compared to 33.3% in the control group [12]. In South Punjab, Pakistan, where poverty and limited healthcare resources prevail, birth asphyxia represents a significant challenge. At Children's Hospital Multan, a tertiary care teaching hospital, approximately 30.6% of neonatal admissions are due to birth asphyxia [13]. This high burden underscores the urgent need for locally relevant evidence to guide clinical management.

This study aims to investigate the effectiveness of magnesium sulfate in managing severe birth asphyxia. We hypothesize that neonates treated with magnesium sulfate will demonstrate improved neurological outcomes, as assessed by the elicitation of a good sucking reflex, compared to untreated neonates. The findings from this study aim to provide a local reference for managing birth asphyxia, potentially improving outcomes in this underserved population.

METHODS

This randomized control trial was conducted at the Neonatology Unit, Department of Neonatology, "The Children's Hospital and the Institute of Child Health, Multan", Pakistan, from January 2024 to June 2024. The Institutional Ethical Committee obtained the study's approval before its commencement (letter number: 2354). RCT no (NCT06468475). A sample size of 80 (40 in each group) was calculated considering the percentage of neonates capable of having feed by mouth in the magnesium sulfate-treated group (P1) as 71.4% and the percentage of neonates capable of having feed by mouth in the control group (P2) as 33.3% [12]. The confidence interval was kept at 95% and the power of the study at 90%. Sample selection was made using a simple random sampling technique. The inclusion criteria were full-term babies (≥37 weeks of gestation) of both genders with severe birth asphyxia, admitted within six hours of life. The exclusion criteria were babies who were premature or had congenital malformations. The babies born to mothers receiving general anesthesia or whose mothers received magnesium sulfate, pethidine, and other drugs (likely to depress the baby) were also excluded. Severe birth asphyxia was described as a 1-minute Apgar score between 0 and 3 (as per the medical record) [14]. Informed and written consents were obtained from the parents or caregivers after describing the study objectives, safety, and data secrecy to them. Once the patients were enrolled, necessary demographics were recorded, and then the babies were randomly assigned to the study group (n=40) and control group (n=40). Randomization was performed using the lottery method, where sealed opaque envelopes containing group assignments were shuffled and picked by an independent staff member not involved in the study. This ensured allocation concealment and minimized selection bias. The study group received 3 doses of magnesium sulphate 24 hours apart by intravenous infusion at 250 mg/kg/dose (0.5 mL/kg/dose of injection magnesium sulphate 50% w/v diluted in 5 mL/kg of 5% glucose) over half an hour by an infusion pump, and the control group did not receive this treatment. Both groups received supportive care as per standard practice for birth asphyxia. Both groups were examined daily in the morning for sucking reflexes. The sucking reflex is an involuntary sucking movement of the lips of a newborn elicited by touching the lips or skin near the mouth. After washing hands, the infant was placed in the supine position, the index finger (pad towards the palate) was placed in the infant's mouth, and the power of sucking movements was judged after 5 seconds. If the sucking reflex appeared, it was said to be effective. This was noted after 72 hours of treatment in both study groups. All the data were analyzed by "IBM SPSS Statistics" version 26.0. The mean and standard deviation were shown for quantitative variables whereas frequency and percentage were calculated for categorical data. Comparison of Outcomes variables like the appearance of good sucking reflex and mortality were compared by applying a chi-square test between both study groups. For all inferential statistics, $p<0.05$ was considered significant.

RESULTS

Out of a total of 80 babies, 46 (57.5%) were male. The mean body weight was noted to be 2.5 ± 0.5 kg, while 43 (53.8%) babies had a body weight ≥2.5 kg. The distribution of age at the time of presentation showed that 9 (11.3%) babies were presented within 2 hours following birth, 23 (28.8%) between 2 and <4 hours and the remaining 48 (60.0%) were presented between 4 and 6 hours following birth. The mean age at the time of presentation was 3.2 ± 1.5 hours. Overall, mean gestational age was 37.8±1.0 weeks, whereas gestational age was between 37 and 39 weeks in 65 (81.2%) cases. Comparisons of baseline characteristics among newborns of both study groups are shown in Table 1.

DOI: https://doi.org/10.54393/pjhs.v6i1.1936

Table 1: Frequency Distribution of Study Characteristics in Both Groups(n=80)

Characteristics		Total	Groups		p-Value
			Magnesium Sulphate (n=40)	Control (n=40)	
Age Groups (Hours)	<2	9 (11.2%)	6 (15.0%)	3 (7.5%)	0.338
	2 to <4	23 (28.8%)	9 (22.5%)	14 (35.0%)	
	4-6	48 (60.0%)	25 (62.5%)	23 (57.5%)	
Gestational Age Groups (Weeks)	37-39	65 (81.3%)	30 (75.0%)	35 (87.5%)	0.152
	>39	15 (18.7%)	10 (25.0%)	5 (12.5%)	
Gender	Male	46 (57.5%)	24 (60.0%)	22 (55.0%)	0.651
	Female	34 (42.5%)	16 (40.0%)	18 (45.0%)	
Body Weight (Kgs)	<2.5	37 (46.2%)	16 (40.0%)	21 (52.5%)	0.262
	≥2.5	43 (53.8%)	24 (60.0%)	19 (47.5%)	

Efficacy in terms of the appearance of a good sucking reflex was observed in 48 (60.0%) babies. Mortality was reported in 9 (11.3%) cases during the study period. No treatment-related complications or side-effects were observed in both study groups. Distribution of efficacy in terms of the appearance of a good sucking reflex in both study groups revealed that the appearance of a good sucking reflex was significantly better in magnesium sulphate group versus control group (75.0% vs 45.0%, p=0.0062), as shown in table 2.

Table 2: Distribution of Appearance of Good Sucking Reflex after 72 Hours in Both Groups(n=80)

Appearance of Good Sucking Reflex	Groups		p-Value
	Magnesium Sulphate (n=40)	Control (n=40)	
Yes	30 (75.0%)	18 (45.0%)	0.0062
No	10 (25.0%)	22 (55.0%)	

Stratification of study variables concerning the appearance of good sucking reflex showed that there existed no significant differences concerning age groups (p=0.422), gestational age (p=0.559), and gender (p=0.518). Birth weight ≥2.5 kg was significantly associated with the appearance of good sucking reflex (p=0.001), and the details are shown in table 3.

Table 3: Association of Appearance of Good Sucking Reflex with Characteristics of Neonates(n=80)

Characteristics		Appearance of Good Sucking Reflex		p-Value
		Yes (n=48)	No (n=32)	
Age Groups (Hours)	<2	6 (12.5%)	3 (9.4%)	0.422
	2 to <4	16 (33.3%)	7 (21.9%)	
	4-6	26 (54.2%)	22 (68.8%)	
Gestational Age Groups (Weeks)	37-39	40 (83.3%)	25 (83.3%)	0.559
	>39	8 (16.7%)	7 (16.7%0	
Gender	Male	29 (61.4%)	17 (60.4%)	0.518
	Female	19 (39.6%)	15 (39.6%)	
Body Weight (Kgs)	<2.5	15 (31.2%)	22 (68.8%)	0.001
	≥2.5	33 (68.8%)	10 (31.2%)	

No statistically significant differences were noted between both study groups concerning mortality (p=0.2885), and the details are shown in table 4.

Table 4: Distribution of Mortality in Both Groups(n=80)

Mortality	Groups		p-Value
	Magnesium Sulphate (n=40)	Control (n=40)	
Yes	3 (7.5%)	6 (15.0%)	0.2885
No	37 (92.5%)	34 (85.0%)	

There was no significant association of mortality with age groups (p=0.084), gestational age (p=0.234), and gender (p=0.191). Low birth weight (<2.5 kg) was associated with significantly higher mortality rates (77.8% vs. 42.3%, p=0.044), and the details are shown in table 5.

Table 5: Association of Mortality with Characteristics of Neonates(n=80)

Characteristics		Mortality		p-Value
		Yes (n=9)	No (n=71)	
Age Groups (Hours)	<2	3 (33.3%)	6 (8.4%)	0.084
	2 to <4	2 (22.2%)	21 (29.6%)	
	4-6	4 (44.4%)	44 (62.0%)	
Gestational Age Groups (Weeks)	37-39	6 (66.7%)	59 (83.1%)	0.234
	>39	3 (33.3%)	12 (16.9%)	
Gender	Male	7 (77.8%)	39 (54.9%)	0.191
	Female	2 (22.2%)	32 (45.1%)	
Body Weight (Kgs)	<2.5	7 (77.8%)	30 (42.3%)	0.044
	≥2.5	2 (22.2%)	41 (57.7%)	

DISCUSSION

Hypoxemia (lack of oxygen) and hypercapnia arise from impaired blood-gas exchange, which causes asphyxia (accumulation of carbon dioxide). Hypoxia and ischemia, when present together, cause the body to experience a cascade of metabolic changes that culminate in the loss of neuronal cells and brain injury [14]. The fundamental factor causing neonatal asphyxia is a blockage in placental blood flow, which causes brain cell ischemia and anoxia and sets off anaerobic conditions. As a result, Adenosine triphosphate (ATP) stores are heavily used, and lactic acid builds up [15]. In the present study, 57.5% of babies were male. Our findings are consistent with Mamo *et al.*, examining neonates with birth asphyxia, where they noted 61.7% of cases to be male [16]. Bhat *et al.*, noted 52.5% of babies with perinatal asphyxia to be male [17]. Mamo *et al.*, also revealed that birth weight was normal in 77.2% of cases of birth asphyxia [16]. It was found that 53.8% of babies had a birth weight of ≥2.5 kg. In this study, the distribution of efficacy in terms of the appearance of a good sucking reflex was noted to be statistically significantly better among babies who were given magnesium sulphate versus controls (75.0% vs 45.0%, p=0.0062). A local study done by Sajid *et al.*, from Faisalabad showed that neonatal reflexes among patients with severe birth asphyxia were improved in 75.8% of subjects using IV magnesium sulphate in comparison to

DOI: https://doi.org/10.54393/pjhs.v6i1.1936

45.4% in the control group (p=0.01). Oral feeding was found to be statistically significantly better with magnesium sulphate for 75.7% of babies in comparison to 39.4% (p=0.002) [18]. Normal computed tomography (CT) brain was seen in 84.9% of subjects in the magnesium sulphate group in comparison to 51.5% in the control group (p=0.003) [18]. Siddiqui *et al.*, showed that magnesium sulphate was better in exhibiting the appearance of a sucking reflex and minimizing the time taken to seizure cessation among babies born with birth asphyxia [19]. Nanda and colleagues documented that neonates who were administered magnesium sulphate were able to initiate feeds significantly quicker than controls (32 hours vs. 63 hours, p<0.001) [20]. Previously, a multi-center, randomized controlled experiment was carried out by Ichiba *et al.* Additionally, they noticed that newborns with severe birth hypoxia responded better to postnatal magnesium sulphate infusion therapy (250 mg/kg/day for 3 days) [21]. As per cranial CT, electroencephalogram (EEG), and the initiation of oral feeds by day 14, it was projected that the magnesium group had significant outcomes more frequently than the control group [21, 22]. Current study shows that magnesium sulphate treatment improved the appearance of a good sucking reflex among newborns with severe birth asphyxia. Due to the potential for subsequent neuronal damage to extend up to 72 hours, we administered magnesium sulphate in three doses (each 250 mg/kg) at 24-hour intervals [23]. Magnesium sulphate infusion was discovered by Bhat *et al.*, to be neuroprotective in their study, as evidenced by the fact that there were fewer newborns with neurologic irregularities and more babies taking oral feedings at the time of discharge in the therapy group [17]. An overall mortality rate of 11.3% was noted in present study, while there was no statistically significant difference between groups (p=0.2885). Bhat *et al.*, noted an overall mortality rate of 10% among term neonates with severe perinatal asphyxia [17]. Some researchers have found higher mortality rates among neonates treated for hypoxic-ischemic encephalopathy [24]. Sreenivasa et al., found a mortality rate of 14% among neonates with birth asphyxia who were managed with magnesium sulphate [25]. Magnesium sulfate offers several broader implications beyond improving the sucking reflex in neonates. Its neuroprotective properties, primarily through NMDA receptor blockade, may reduce excitotoxicity and neuronal injury, potentially lowering the risk of long-term complications like cerebral palsy and cognitive delays [26]. It also exhibits anticonvulsant and anti-inflammatory effects, which could prevent seizures and mitigate inflammatory cascades associated with hypoxic-ischemic injury [27]. By stabilizing cerebral perfusion and enhancing neural functions, magnesium sulfate may improve feeding readiness and overall growth trajectories. Its integration as an adjunct therapy alongside approaches like therapeutic hypothermia could create a multimodal strategy for managing severe birth asphyxia, reducing long-term disabilities and improving quality of life [28].

CONCLUSIONS

It was concluded that magnesium sulfate was found to significantly improve the appearance of a good sucking reflex among newborns with severe birth asphyxia, highlighting its potential as a neuroprotective intervention in neonatal care. This finding suggests that magnesium sulfate could play a vital role in enhancing early feeding readiness and neurological recovery, potentially reducing the risk of long-term developmental impairments. Incorporating magnesium sulfate into the management protocol for severe birth asphyxia, especially in resource-limited settings, may improve short-term outcomes and contribute to better long-term neurodevelopmental health in affected neonates. Further large-scale metacentric trials with larger sample sizes are required to validate the findings of this study.

Authors Contribution

Conceptualization: MA[1]
Methodology: MA[1], ARM, MA[2], RTA
Formal analysis: MA[1]
Writing review and editing: MA[1]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2653

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Frequency and Pattern of Retinopathy in Newly Diagnosed Type 2 Diabetic Patients

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ARTICLE INFO

Keywords:
Diabetic Retinopathy, Creatinine, Cholesterol, Hemoglobin

How to Cite:
Mehmood, F., Mazhar, S. A., Farooq, N., & Afzal, M. A. (2025). Frequency and Pattern of Retinopathy in Newly Diagnosed Type 2 Diabetic Patients: Retinopathy in Type 2 Diabetic Patients . Pakistan Journal of Health Sciences,6(1), 197-202. https://doi.org/10.54393/pjhs.v6i1.2653

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Received date: 3rd December, 2024
Acceptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

Diabetic Retinopathy (DR) is among the leading causes of blindness in adults, particularly in individuals with type 2 Diabetes Mellitus (T2DM). Diabetic Retinopathy (DR) is one of the commonest reasons for blindness in the adult population especially in the type 2 Diabetes Mellitus (T2DM) population. It is important to detect and manage these diseases early to prevent vision loss. **Objective:** To evaluate the prevalence and pattern and the associated risk factors of Diabetic Retinopathy (DR) in newly diagnosed T2DM. **Methods:** The study design was descriptive cross-sectional which was conducted at Arif Memorial Teaching Hospital/Rashid Latif Medical College, Lahore. The study enrolled 300 participants (age≥35 years) with newly diagnosed T2DM. After a general and systemic examination, data were collected, including laboratory data with blood glucose, HbA1c, serum cholesterol, and serum creatinine. Retinopathy grading was performed by fundoscopic examination into background, pre-proliferative and proliferative grades. The statistical analysis was performed in SPSS version 23.0. **Results:** In newly diagnosed T2DM, the overall prevalence of DR was 22% (66/300). Among cases of DR, 78% were NPDR, and 22% were PDR. Most of the NPDR was moderate (43%), mild (35%) and severe (22%). DR risk factors were HbA1c > 8% (OR: 3.5, $p < 0.001$) and hypertension (65% DR, $p < 0.05$). DR was not significantly correlated with BMI and other biochemical markers including serum creatinine. **Conclusions:** The prevalence of diabetic retinopathy was notably high among newly diagnosed T2DM patients, with HbA1c levels and hypertension identified as significant risk factors.

INTRODUCTION

Diabetic Retinopathy (DR) is one of the first diseases associated with diabetes, being one of its most serious complications and also ranking as the leading cause of preventable blindness worldwide. It is common in patients that have type 2 diabetes mellitus (T2DM) which is characterized by insulin resistance and relative insulin deficiency [1]. Diabetic retinopathy is becoming a progressively more prevalent health problem as the number of type 2 diabetic patients worldwide increases. It usually develops quietly without initial signs, so it is important every person goes for an eye examination frequently for early identification and management. The major stages of diabetic retinopathy include non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR), which is the more advanced stage of DR associated with the highest risk of vision loss [2, 3]. DR is highly prevalent in type 2 diabetes and about a third of patients with type 2 diabetes will develop diagnosis of retinopathy during their lifetime, according to some studies. A multitude of factors, including diabetes duration, poor glycemic control, hypertension, and abnormalities in lipid levels, increases the risk of DR [4]. Signs of retinopathy are detectable even in newly diagnosed diabetes patients, which indicates the importance of uncontrolled blood glucose for the development of the condition. So, early screening is important to stop the development of DR and the risk of vision loss [5, 6]. Chronic hyperglycemia (elevated levels of

DOI: https://doi.org/10.54393/pjhs.v6i1.2653

glucose in the blood) is pathogenesis of diabetic retinopathy because it can result in vascular damage in the retina [7]. The injury leads to endothelial dysfunction, heightened vascular permeability, and microaneurysm formation. NPDR begins with microaneurysms, retinal hemorrhages and exudates [8]. With worsening disease, pre-proliferative changes including venous beading and cotton wool spots. PDR occurs when DR progresses to its most advanced stage, which is readily identified by the presence of new and fragile blood vessels that will cause vitreous hemorrhage, retinal detachment and blindness without treatment [9, 10]. Since many cases of diabetic retinopathy are asymptomatic in early stages, regular eye examinations are crucial, particularly for individuals newly diagnosed with type 2 diabetes. Identification in the early stages of the disease greatly minimizes the risk of significant vision loss, as maximum benefit from intervention such as laser therapy or anti-VEGF injection or vitrectomy is obtained when the disease is first diagnosed. Hence the frequency and pattern of diabetic retinopathy in first diagnosed patients need to appreciate so that early and proper management can be done [11]. The early identification of diabetic retinopathy (DR) in newly diagnosed T2DM patients is crucial, as DR may be asymptomatic in the initial stages but can progress rapidly if left undetected. Screening at the time of diagnosis provides a critical opportunity to identify patients who already have signs of DR, emphasizing the need for early intervention. This study focuses on newly diagnosed patients to underline the importance of routine DR screening at the time of diabetes diagnosis, which is often overlooked in clinical practice.

To evaluate the prevalence and pattern and the associated risk factors of diabetic retinopathy (DR) in newly diagnosed T2DM.

METHODS

This descriptive, cross-sectional investigation was conducted at Arif Memorial Teaching Hospital/Rashid Latif Medical College, Lahore from November 2023 to April 2024. The formula used for calculating sample size is: n= Z2·p·(1–p)/ E2. The required sample size was approximately 300 participants to estimate the prevalence of diabetic retinopathy in newly diagnosed type 2 diabetic patients, with a z=95% confidence level, P=0.15% and a E=5% margin of error [12]. The total number of participants was who had newly acquired a diagnosis of type 2 diabetes within the past month and attended diabetic clinics at these esteemed facilities were recruited for participation in the investigation. The investigation recruited patients ranging in age from 30 to 70 years who had not previously received a diagnosis of type 2 diabetes or treatment via prescription medication. Exclusion criteria encompassed individuals with prior identification of type 2 diabetes, type 1 diabetes, hypertension, preexisting retinal conditions including vasculitis and vascular occlusion, as well as sickle-cell retinopathy. Formal ethical approval for the probe was secured, and informed consent to take part was obtained from all participants. Structured forms were applied to collect data. The general and systemic examinations included weight, body mass index (BMI), blood pressure, and a monofilament assessment for neuropathy. Laboratory investigations included fasting and postprandial blood (samples were collected from vein using a sterile syringe), HbA1c, urine protein, serum cholesterol and serum creatinine. Diabetic retinopathy was categorized as follows: Mild Non-Proliferative Diabetic Retinopathy (NPDR) by the presence of microaneurysms. Moderate and severe NPDR included intraretinal hemorrhages, venous beading, and microvascular abnormalities based on the ETDRS criteria. Proliferative Diabetic Retinopathy (PDR) was identified by the presence of neovascularization or vitreous hemorrhage. Fasting and postprandial blood glucose were measured using the enzymatic glucose oxidase method. HbA1c was analyzed via High-Performance Liquid Chromatography (HPLC). Urine protein was assessed using the dipstick method, while serum cholesterol and creatinine were measured through enzymatic colorimetric assays and the Jaffe reaction, respectively. Referrals to an ophthalmologist for examination of visual acuity and slit-lamp examination were also provided to participants. Retinopathy type (background, pre-proliferative, and proliferative) was based on fundoscopic findings. Statistical analysis was carried out using SPSS version 23.0. Student ś t-test was used for continuous variables like age, HbA1c, cholesterol level etc., and chi-square test was applied for categorical data like presence of retinopathy. This study design is good for investigating the association between diabetic retinopathy and newly diagnosed diabetes, as well as searching for associated factors including glycemic control, hypertension, and BMI. Informed consent was obtained from all participants, and approval from the Institutional Review Board (IRB) was secured for the study. This study was approved by institutional review board IRB00010673 Rashid Latif Medical College, Lahore.

RESULTS

The study analyzed n=300 newly diagnosed Type 2 diabetes through the age group of 30-70 years (mean: 52 ± 8.2 years) were included in the study, majority being men of 55 %. Mean HbA1c was 9.4 ± 1.2%, indicating poor glycemic control, and fast plasma glucose was 190 ± 25 mg/dl on average. Although blood pressure levels were borderline

DOI: https://doi.org/10.54393/pjhs.v6i1.2653

hypertensive (systolic: 138 ± 15 mmHg, diastolic: 85 ± 10 mmHg), and serum cholesterol (210 ± 30 mg/dl) was elevated indicating dyslipidemia. Renal function was preserved, with serum creatinine levels within normal limits (0.9 ± 0.2 mg/dl). This underlines the importance of early treatment of glycemia, cardiovascular and lipid parameters to avert sequelae see table 1.

Table 1: Demographics and Clinical Characteristics

Variables	Value (Mean ± SD)
Age Range (Years)	30-70
Mean Age (Years)	52 ± 8.2
Gender Distribution Frequency (%)	
Males	165 (55%)
Females	135 (45%)
HbA1c	9.4 ± 1.2
Blood Pressure (mmHg) (Mean ± SD)	
Systolic	138 ± 15
Diastolic	85 ± 10
Fasting Plasma Glucose (mg/dL)	190 ± 25
Serum Creatinine (mg/dL)	0.9 ± 0.2
Serum Cholesterol (mg/dL)	210 ± 30

The overall prevalence of DR was 22% (66/300) in the study among 300 newly diagnosed Type 2 diabetic patients. Out of all cases of DR, 78% (51/66) of the cases were NPDR and 22% (15/66) were PDR. They are highlights of the fact that NPDR is the most prevalent changes of DR in newly diagnosed diabetic patients, but a considerable number present with the more advanced form of DR-PDR, which indicates the screening and management should be started much before and before the gross manifestation of disease (Table 2).

Table 2: Frequency and Types of Diabetic Retinopathy included Diabetic retinopathy (DR), Non-proliferative DR and proliferative DR

Total Cases	Types of Diabetic Retinopathy		
	Prevalence of DR Frequency (%)	NPDR (Non-Proliferative Diabetic Retinopathy) Frequency (%)	PDR (Proliferative Diabetic Retinopathy) Frequency (%)
300	66 (22%)	51 (78%)	15 (22%)

A comparison of DR vs No DR cases helped to identify a number of highly significant risk factors. The DR group also showed significantly higher HbA1c levels (10.2 ± 1.1% vs 8.9 ± 1.2%, $p < 0.001$), which is expected due to the close relation of poor glycemic control and development of DR. In addition, blood pressure readings also differed significantly, with DR patients having higher systolic (142 ± 10 mmHg vs 134 ± 12 mmHg, $p < 0.05$) and diastolic blood pressure (88 ± 8 mmHg vs 83 ± 9 mmHg, $p < 0.05$) reflecting the potential role of hypertension in DR risk. Hyperglycemia proved to be significantly associated with diabetic retinopathy, as fasting plasma glucose levels were clearly higher among those with DR compared to the control group. Specifically, readings reached 200 ± 20 mg/dl for DR patients versus 185 ± 15 mg/dl for others, firmly establishing a link between raised blood sugar and retinopathy. Cholesterol issues may also bear responsibility for increasing the likelihood of DR, since levels of this lipid measured 225 ± 25 mg/dl among those affected as opposed to 205 ± 20 mg/dl in individuals without the eye complication. Nonetheless, variations in BMI and kidney function as gauged by serum creatinine did not reliably differentiate the two clusters herein. This suggests that factors like weight and renal health may exert limited sway over whether retinopathy surfaces amongst a given set of people with diabetes see table 3.

Table 3: Comparison of Risk Factors Between DR and No DR Cases

Risk Factor	DR Cases (n=66) (Mean ± SD)	DR Cases (n=66) (Mean ± SD)	p-value
HBA1C (%)	10.2 ± 1.1	8.9 ± 1.2	< 0.001 (Significant)
BMI (Kg/m^2)	31.2 ± 3.5	30.5 ± 3.0	> 0.05 (Not Significant)
Systolic BP (mmHg)	142 ± 10	134 ± 12	< 0.05 (Significant)
Diastolic BP (mmHg)	88 ± 8	83 ± 9	< 0.05 (Significant)
Fasting Plasma Glucose (mg/dL)	200 ± 20	185 ± 15	< 0.001 (Significant)
Serum Creatinine (mg/dL)	1.0 ± 0.3	0.9 ± 0.2	> 0.05 (Not Significant)
Serum Cholesterol (mg/dL)	225 ± 25	205 ± 20	< 0.05 (Significant)

Regarding Diabetic Retinopathy (DR) pattern among the study subjects, we found that the most DR was NPDR which constituted 78% of all DR cases. Among patients with NPDR, severity distribution indicated that moderate NPDR was the most prevalent, accounting for 43% of patients. Mild NPDR followed that, with 35% of cases, whereas severe NPDR was the simplest in only 22% of patients. The majority of patients with DR have NPDR but, in fact, the moderate NPDR form has dominated over the mild and severe forms [15]. The order with the majority of them classified as very mild NPDR showed the importance of screening and regulating NPDR early on so it does not reach worse stages (like proliferative diabetic retinopathy PDR). Statistical analysis The statistical analysis was performed with descriptive statistics that gave the frequency and percentage of each NPDR severity level (Table 4).

Table 4: Diabetic Retinopathy Pattern included moderate NPDR, Mild NPDR, severe NPDR

Types of Diabetic Retinopathy	
Severity of NPDR	**Frequency (%)**
Mild NPDR	35%
Moderate NPDR	43%
Severe NPDR	22%

DOI: https://doi.org/10.54393/pjhs.v6i1.2653

DISCUSSION

Diabetic Retinopathy (DR) continues to be a common and important complication of diabetes but has not been systematically evaluated in DMT2 [13]. Understanding the early stages of DR, the frequency, pattern, and risk factors of DR are critical, and the findings of this study will help in planning interventions to prevent vision impairment. The following section describes the findings in detail and compares them with the existing literature for a larger frame of reference regarding clinical implications [14, 15]. Overall, the prevalence of diabetic retinopathy (DR) was 22% in a newly diagnosed cohort of Type 2 diabetic patients in this study. This finding is similar to other studies on prevalence of DR on newly diagnosed diabetic patients, which reported varying rates of DR with a general range of 20–30%. The previous study showed DR prevalence to be 22.4% amongst patients diagnosed with Type 2 diabetes [16]. Nonetheless, DR prevalence can be significantly dissimilar in another population depending on genetic factors, socioeconomic status, and the presence of other chronic diseases for example hypertension and dyslipidemia. This cohort had a relatively high DR prevalence emphasizing how important regular retinal screening is for newly diagnosed diabetics to help detect DR at an early-stage and hopefully prevent future irreversible vision loss [17, 18]. It also assessed types of DR pattern including distribution NPDR and PDR. The results showed 78% of DR was NPDR, of which mild NPDR (35%) and moderate NPDR (43%) was the most common, while 22% of patients had severe NPDR. In DR cases, 22% had proliferative DR (PDR) [19]. It fitted with what is often seen in the literature: Proliferative Diabetic Retinopathy (PDR) is seen less often early on in diabetes than Non-Proliferative Diabetic Retinopathy (NPDR). For example, DRS and ETDRS studies demonstrate that most people with DR are diagnosed with NPDR, and only a limited number of these persons proceed to PDR, which correlates with a greater chance of serious vision loss [20]. In accordance with previous studies like in Beijing Eye Study, moderate NPDR was also the predominant form of DR among newly diagnosed diabetic patients in this study. Notably, 22% of patients in the current study had severe NPDR, which is worrisome, because severe NPDR can rapidly progress to PDR, especially in the absence of early treatment. This emphasizes the essential need for early diagnosis and proper responsive treatment to reduce subsequent advancement to PDR and consequences such as diabetic macular edema (DME). This study was agreed with the previous study [21, 22]. The present study explored the various risk factors that are associated with developing DR in newly diagnosed Type 2 diabetic patients using a retrospective, cross-sectional study clinic population. Examples are uncontrolled diabetes (HbA1c > 8%), hypertension, increased serum cholesterol, and so forth. Glycemic Control (HbA1c). The DR group had a HbA1c that was markedly higher (10.2 ± 1.1%) than in the No DR group (8.9 ± 1.2%). This finding is also consistent with previous studies that have reported to close associations between glycemic control and DR 17-21, and have shown that improved glycemic control significantly reduces the risk of DR progression in patients with type 1 diabetes in the DCCT (Diabetes Control and Complications Trial) and in patients with type 2 diabetes in the UKPDS (United Kingdom Prospective Diabetes Study). In fact, the results of the current study highlight the importance of keeping HbA1c below 7% to prevent DR [23]. The study found that a whopping 65% of those with DR had hypertension, nearly 20% higher than the group without retinopathy who registered at 45% with high blood pressure. This research reinforces existing evidence that hypertension notably drives the development and progression of DR. Two seminal studies, ETDRS and UKPDS, similarly emphasized that keeping vascular stress low via blood pressure control is key to stunting the deterioration of retinal health. This study aligned with the previous study when uncontrolled, hypertension exacerbates damage by ratcheting up strain on the delicate vasculature of the retina, leading to worsening of both non-proliferative and proliferative stages [24]. Elevated cholesterol levels and impaired endothelial function likely contributed to the worse microvascular changes seen in those patients with diabetic retinopathy. Serum cholesterol was markedly higher at an average of 225 compared to 205 milligrams per deciliter for those without the condition. This finding aligns with the well-known ARIC study that identified dyslipidemia as an independent risk factor for both developing and worsening diabetic eye disease. While body mass index and kidney function as assessed by serum creatinine did not notably differ, other research has connected obesity defined as a BMI over 30kg to increased risk of retinopathy. Some projects have also linked deteriorating renal health, especially at advanced stages, to a heightened chance of retinal complications, though no significant link was observed in this group. Adiposity may weakly impact the eyes, but the association here was tenuous [25]. Moreover, the pattern observed in this cohort, with a sizable portion already presenting with moderate no proliferative diabetic retinopathy, implies that timely intervention can prevent worsening to more severe stages like proliferative diabetic retinopathy. The findings bolster recommendations from the United Kingdom Perspective Diabetes Study and Diabetes Control and Complications trial stressing rigorous glycemic control as a pivotal step in stalling or delaying the onset and development of diabetic retinopathy.

DOI: https://doi.org/10.54393/pjhs.v6i1.2653

CONCLUSIONS

These findings emphasized the need for early detection and management of glycemic control and hypertension in T2DM patients to prevent DR progression.

Authors Contribution

Conceptualization: FM
Methodology: SAM
Formal analysis: MF
Writing, review and editing: MAA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2411

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Impact of Team-Based Learning on Medical Students Academic Performance

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ARTICLE INFO

Keywords:
Team-Based Learning, Small Group Discussion, Satisfaction Level, Academic Performance

How to Cite:
Abdullah, Z., Khan, M., Asfandyar, A., Aman, K., Asim, B., & Haris, S. (2025). Impact of Team-Based Learning on Medical Students Academic Performance: Team-Based Learning on Academic Performance of Medical Students . Pakistan Journal of Health Sciences, 6(1).203 -208. https://doi.org/10.54393/pjhs.v6i1.2411

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Received date: 12th November, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

The effectiveness of different educational strategies in medical education is still essential to students' academic performance and satisfaction. **Objectives:** To determine the effect of Team-Based Learning versus Small Group Discussion (SGD) on academic outcomes for students in a medical curriculum. **Methods:** The study design was a quasi-experimental non-equivalent control group design involving 100 medical students divided into two groups of 50 for Team-Based Learning and 50 for Small Group Discussion. Data collection comprised pre-test and post-test scores, changes in scores, and levels of satisfaction measured using structured surveys. Statistically, independent t-tests were used to compare academic performance and satisfaction between the two groups. **Results:** The Team-Based Learning group had significantly higher post-test scores, 76.42 ± 9.14 as compared to the Small Group Discussion group, 68.00 ± 9.45. The difference in change scores was significant: 16.56 ± 7.50 for Team-Based Learning versus 9.24 ± 6.50 for Small Group Discussion, $p<0.0001$. Satisfaction levels were also higher in the Team-Based Learning group at 4.14 ± 0.88 than in the Small Group Discussion group at 2.94 ± 0.79, with a statistically significant difference $p<0.0001$. **Conclusions:** It was concluded that Team-Based Learning versus Small Group Discussion generated significant differences in the academic performance and satisfaction levels of medical students. Team-Based Learning appears to be a more effective teaching-learning strategy compared to Small Group Discussion in enhancing engagement and better learning outcomes in medical education.

INTRODUCTION

In the rapidly changing field of medical education, the demand for innovative teaching methods has increased significantly [1]. Traditional educational approaches usually fail to create the student engagement needed to maximize learning outcomes [2]. Studies show that healthcare education needs teaching approaches which build students' ability to think critically through group activities and interactive learning that supports essential clinical capabilities [3]. Academic success depends on these core competencies which also serve as essential preparation for students to navigate the diverse multidisciplinary healthcare domain. Team-based learning combines educational periods into one active unit that increases student collaboration and boosts educational accountability [4]. A study reported that by using Team-Based Learning (TBL) students' progress through higher cognitive levels by working together to solve problems [5]. Through this approach, students transform into active problem-solving since TBL maintains essential skills defined by 'The Accreditation Council for Graduate Medical Education (ACGME)' focusing on physician practice that demands teamwork and communication abilities [6]. TBL

DOI: https://doi.org/10.54393/pjhs.v6i1.2411

standardization creates equivalent educational results among various student cohorts. Various academic research has documented the successful ways TBL helps students develop meaningful learning experiences. Multiple research studies have proven that TBL creates better learning effectiveness and increased content satisfaction across different educational settings [7-9]. Additionally, TBL helps students retain information longer and understand deeper concepts through classmate participation [10]. Through a detailed evaluation, researchers found that TBL generates increased student engagement since the framework encourages active learning and student-driven examinations [11]. TBL stands out as a crucial method in medical education because its benefits support interactive learning of complex clinical concepts. The educational strategy of small group Discussion (SGD) persists as one of the most commonly implemented methods in medical courses. The impact of SGD on student learning depends on how effectively students work together and the operating standards achieved by their facilitator [12]. This study indicates that while the SGD lead to learning improvements in most cases it doesn't deliver complete outcomes because of its unstructured nature as compared to TBL frameworks [13]. Given the limitations of SGD, alternative approaches that combine structure with interactive learning, such as TBL, need to be explored to optimize academic outcomes.

This study aims to examine how TBL influences medical student achievement levels as well as educational satisfaction against the traditional SGD curriculum. Contrasting the academic effects of TBL-based and SGD-based medical education required extensive qualitative and statistical research. The research findings offer significant benefits to policymakers and educators who are working to advance medical education quality standards. Resolving healthcare challenges with evidence-based TBL teaching methods helps researchers create skilled and adaptable healthcare practitioners of the future.

METHODS

This study design was a non-equivalent control group with randomisation, a type of quasi-experimental conducted at Rawal Institute of Medical Sciences, to investigate the impact of TBL on the academic performance of medical students compared to SGD, from January 2018- January 2019, involving 100 medical students and was conducted following ethical principles outlined in the Declaration of Helsinki. The written informed consent was obtained from all participants before their inclusion in the study. All Participants were informed about the study objectives, procedures, potential risks, and benefits. Each participant received clear assurances about their choice to stay in the study being voluntary with complete freedom to withdraw at any time. All participants received guaranteed confidentiality protection with anonymous research data during the complete study period. A stratified random sampling technique was used for the experiment design which separated participants between the TBL and SGD groups. To minimise biases, stratification was performed based on basic demographic variables: gender, age, and academic background. Students received their group assignment through a random number generator which distributed them between two different groups in each academic division. During assignment, the technique used random selection in combination with stratification to achieve equitable respondent profiles across groups lowering the potential impact of confounding variables on the study. The inclusion and exclusion criteria were all students taking MBBS pre-clinical classes at Rawal Institute of Medical Sciences in (2018-2019) qualified to enrol in the study. The study analyzed participants who gave their informed consent and attended at least 80% of the TBL or SGD intervention sessions. Exclusion criteria helped preserve the study's result integrity. Students who had participated in TBL before in other classes were excluded from the research to minimize potential biases in results. A comprehensive and reliable dataset was established following the exclusion of participants who did not complete the pre-test, post-test assessments or satisfaction survey. The required sample size emerged from G*Power software computations that considered a 0.05 significance level with an 80% statistical power and a 0.8 effect size (Cohen's d). Test result evaluations performed on the same cohort served to calculate variance for objective consistency. Research data were collected from 100 medical students who were studying MBBS preclinical throughout the study duration. The detailed teaching guidelines that tutors used to deliver teaching methods reliably. During TBL sessions, tutors established a structured framework consisting of three phases preparation, individual testing then group collaboration followed by immediate responses. The facilitators of SGD sessions utilized standard scripts to maintain consistent discussion topics while controlling their facilitation methods and session lengths. Before conducting sessions facilitators received periodic training programs to become proficient with the standardized protocol and reduce variation in session delivery methods. The study team conducted periodic assessments of session documentation to confirm instructional consistency and received feedback from independent observers. These assessments verified that the instructional approaches were delivered as planned thereby reducing any bias that might result from variations in delivery style or method.

DOI: https://doi.org/10.54393/pjhs.v6i1.2411

These strategies helped the study maintain high levels of accuracy and reliability between the outcome measurements of the two tested groups. TBL Group Intervention: Students needed to complete advanced individual studies before commencing the lecture phases. Group activities combined individual assessment with team discussions where students collaborated to solve application-related questions. The facilitators followed each segment with real-time feedback to clarify confusion while strengthening comprehension. During SGD sessions students participated in instructor-guided group discussions about TBL-normative subject material. Students shared their comprehension by engaging in group discussions yet the instructor did not evaluate separate student quizzes. The research procedure was initiated with numerical assessments that were combined with human feedback methods. Students underwent both pre-test and post-test assessments through a special-purpose multiple-choice test instrument designed for this research project. The pre-test was conducted at the beginning of the year to assess baseline knowledge, while the post-test was administered at the end of the year to measure knowledge gains. Students answered multiple-choice questions about fundamental curriculum material to demonstrate their understanding of how previously learned information applies to professional scenarios. Multiple precautions were established to validate and ensure the accuracy of all assessments. The assessment established construct validity by measuring the intended cognitive domains, which included knowledge retention, critical thinking, and application skills. The evaluation of MCQ reliability used Cronbach's alpha to determine internal consistency among items. The pilot test involved students who participated in the study (n=30), during which Cronbach's alpha value of 0.82 confirmed good reliability in the MCQ test. Obtaining test consistency involved both evenly distributing questions across difficulty levels and implementing a standardized scoring system. A systematic approach was implemented to prove the reliability and validity of MCQ assessments and satisfaction survey tools, which enabled proper assessment of the intended outcome measure. In the end, a satisfaction survey was distributed to participants after completing the interventions. The survey included Likert-scale questions assessing different aspects of the learning experience: perceived effectiveness, engagement, and overall satisfaction with the learning method. The survey was unidentified to ensure honest feedback, and the data were aggregated for analysis. The survey's satisfaction level scoring was designed on the Likert scale, which typically ranges from 1 to 5, with 1: Strongly Disagree, 2: Disagree, 3: Neutral, 4: Agree, and 5: Strongly Agree. For the scoring process, each student responds to the survey by selecting a number on the Likert scale that best represents their opinion for each statement. The scores for each item were recorded, allowing for quantification of satisfaction levels. Data analysis was performed using SPSS version 22.0 (Statistical Package for the Social Sciences). Descriptive statistics (means and standard deviations) were calculated for all variables. Independent t-tests were employed to compare the two groups' pre-test and post-test scores, change in scores, and satisfaction levels. A p-value of <0.05 was considered statistically significant.

RESULTS

Results show the participants were evenly distributed between the TBL and SGD groups, with 49% male and 51% female students. Most students (90%) were between 18 and 23 years old, with an equal distribution of those above 23 years in both groups. The mean high school science grade point average (GPA) was similar across groups (TBL: 3.8 ± 0.4; SGD: 3.7 ± 0.5). Prior exposure to active learning methods was reported by 22% of participants, slightly higher in the SGD group (24%) compared to the TBL group (20%) (Table 1).

Table 1 : Demographic and Academic Characteristics of Participants

Characteristics	TBL Group (n=50)	SGD Group (n= 50)	Total (n=100)
Gender			
Male	25 (50%)	24 (48%)	49 (49%)
Female	25 (50%)	26 (52%)	51 (51%)
Age (Years)			
18–20	20 (40%)	22 (44%)	42 (42%)
21–23	25 (50%)	23 (46%)	48 (48%)
>23	5 (10%)	5 (10%)	10 (10%)
Academic Background			
GPA (Mean ± SD)	20 (40%)	22 (44%)	42 (42%)
Prior Exposure to Active Learning	25 (50%)	23 (46%)	48 (48%)

Research shows the TBL group (59.86) had a slightly higher pre-test score than the SGD group (58.76), indicating a comparable baseline knowledge level. The TBL group outperformed the SGD group significantly, with a mean score of 76.42 versus 68.00, highlighting the effectiveness of TBL in improving knowledge retention. The TBL group's change in score (16.56) was nearly double that of the SGD group (9.24), emphasising the impact of TBL on learning gains. Students in the TBL group reported higher satisfaction (4.14) than the SGD group (2.94), suggesting that TBL enhances academic performance and improves student engagement and enjoyment of the learning process (Table 2).

DOI: https://doi.org/10.54393/pjhs.v6i1.2411

Table 2: Descriptive Statistics for TBL and SGD Groups

Groups	Pre-Test Score (Mean ± SD)	Post-Test Score (Mean ± SD)	Change in Score (Mean ± SD)	Satisfaction Level (Mean ± SD)
TBL (n=50)	59.86 ± 5.79	76.42 ± 9.14	16.56 ± 7.50	49 (49%)
SGD (n=50)	58.76 ± 6.37	68.00 ± 9.45	9.24 ± 6.50	2.94 ± 0.79

Analysis shows the means and standard deviations for pre-test scores, post-test scores, change in scores, and satisfaction levels. The t-test results show no significant difference ($p = 0.368$), indicating that both groups started at similar knowledge levels. An important difference was observed ($t=-4.528$, $p<0.0001$), confirming that TBL leads to higher post-test scores than SGD. The significant t-value ($t=-5.215$, $p<0.0001$) highlights that TBL substantially impacts student learning, resulting in greater knowledge gains. The significant positive t-value ($t=7.159$, $p<0.0001$) indicates that TBL is significantly more satisfying for students than SGD (Table 3).

Table 3: Independent t-test Results Comparing TBL and SGD Groups

Comparisons	T-Statistic	p-value
Pre-Test Scores	-0.904	0.368
Post-Test Scores	-4.528	<0.0001
Change in Scores	-5.215	<0.0001
Satisfaction Levels	7.159	<0.0001

The analysis of demographic subgroups Table 4 revealed that the TBL group consistently demonstrated greater improvements in test scores and higher satisfaction levels compared to the SGD group. Both male and female students in the TBL group showed significantly higher academic gains and satisfaction scores, with no major differences between genders. Younger students (18–20 years) achieved slightly higher improvements and satisfaction compared to older participants, indicating that TBL may particularly benefit this age group. Students with higher academic backgrounds (GPA >3.5) reported better outcomes with TBL in both test score improvements and satisfaction, suggesting that the structured nature of TBL aligns well with high-achieving students. However, the positive impact of TBL was consistent across all subgroups, emphasising its effectiveness as a universally applicable teaching method in medical education (Table 4).

Table 4: Change in Test Scores and Satisfaction Levels by Demographics

Variables	TBL - Test Score Change (Mean ± SD)	SGD - Test Score Change (Mean ± SD)	p-value (Scores)	TBL - Satisfaction (Mean ± SD)	SGD - Satisfaction (Mean ± SD)	p-value (Satisfaction)
Gender						
Male	16.8 ± 7.2	9.5 ± 6.1	< 0.001	4.12 ± 0.82	2.89 ± 0.78	<0.001
Female	16.3 ± 7.8	8.9 ± 6.7	< 0.001	4.15 ± 0.90	3.01 ± 0.79	<0.001
Age (Years)						
18–20	17.2 ± 7.5	9.0 ± 6.3	< 0.001	4.20 ± 0.85	2.91 ± 0.80	<0.001
21–23	16.5 ± 7.1	9.4 ± 6.5	< 0.001	4.10 ± 0.90	2.97 ± 0.77	<0.001
>23	15.8 ± 6.9	9.2 ± 6.2	< 0.001	4.08 ± 0.88	2.90 ± 0.79	<0.001
High School GPA						
Above 3.5	16.9 ± 7.4	9.7 ± 6.4	< 0.001	4.18 ± 0.86	2.95 ± 0.78	<0.001
3.0–3.5	16.0 ± 6.8	9.4 ± 6.5	< 0.001	4.07 ± 0.89	2.92 ± 0.80	<0.001

DISCUSSION

This study revealed valuable insights into the impact of TBL compared to SGD on medical students' academic performance and satisfaction levels. The results suggest that TBL significantly enhances post-test scores and overall satisfaction than SGD, highlighting the effectiveness of the educational strategy. The post-test score showed a significant difference between groups. Post-testing revealed that the TBL group earned a mean score of 76.42, and the SGD group obtained 68.00 as their mean. A substantial p-value of 0.0001 indicates that TBL reduces student confusion while ensuring deeper academic understanding. TBL's adoption of an active learning environment represents one possible reason for successful implementation. According to Børte *et al.*, and Owens *et al.*, active learning methods produce lasting student learning outcomes and academic achievement improvements [14, 15]. Data supported our findings through score change analysis because the TBL group demonstrated 16.56 points of improvement compared to 9.24 points for the SGD group. The improvement in student performance was demonstrated as statistically significant at p less than 0.0001, indicating that TBL enhances both content comprehension and deep engagement with educational material. A study by Burgess, in 2020 proved that the collaborative aspect of TBL where students explain concepts to peers, leads to better retention and comprehension of information [16]. The TBL educational method yielded better satisfaction levels in comparison to SGD ($p<0.0001$) as students achieved a mean satisfaction score of 4.14 versus 2.94. Student opinion indicates that

DOI: https://doi.org/10.54393/pjhs.v6i1.2411

TBL meets their satisfaction expectations. A study by Charalambous *et al.*, observed that the structured feedback provided during TBL sessions contributes to satisfaction. It helps students clarify misunderstandings and feel supported in their learning journey [17]. The satisfaction survey also showed that students in the TBL group appreciated the opportunity for peer interaction and the collaborative learning environment. Following the study, Sannathimmappa *et al.*, reported that students value active participation and collaboration in the learning process, leading to a more enjoyable and effective educational experience [18]. Our results are consistent with the development of literature that supports TBL as an effective educational approach in medical education [19]. Ainsworth *et al.*, Nawabi *et al.*, and Mansoor *et al.*, have shown that TBL enhances academic performance and improves student engagement and satisfaction [20-22]. A meta-analysis by Parappilly *et al.*, found that TBL was associated with better academic outcomes in different disciplines, including health sciences [23]. The findings of this study add to this literature by specifically focusing on medical students, demonstrating that TBL can be a superior alternative to traditional SGD methods. The implications of our study were significant for medical educators seeking to enhance learning outcomes and student satisfaction. Implementing TBL could improve academic performance, enhance engagement, and increase student satisfaction. As medical education progressively underlines the need for collaborative skills and critical thinking, TBL supports these educational goals well.

CONCLUSIONS

It was concluded that TBL significantly enhances academic performance and satisfaction levels among medical students compared to SGD, indicating that TBL promotes an interactive and collaborative learning environment, leading to better engagement and understanding of the material. As medical education progresses, integrating TBL into curricula could improve educational outcomes and prepare students for future clinical practice. It emphasises the importance of adopting innovative teaching strategies that promote active learning and collaboration, ultimately benefiting students' educational skills.

Authors Contribution

Conceptualization: ZA
Methodology: MK, AA, KA, SH
Formal analysis: ZA, BA
Writing review and editing: ZA, MK, AA, KA, SH

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2209

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Association of Age Shock Index with Mortality among Trauma Patients in the Emergency Department

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ARTICLE INFO

Keywords:
Age Shock Index (ASI), Mortality Rate, Emergency Department(ED), Trauma

How to Cite:
Zehra, A., Khan, I. A., Khan, M., Shaikh, S. P., Rathore, P., & Irfan, G. (2025). Association of Age Shock Index with Mortality among Trauma Patients in the Emergency Department: Association of Age Shock Index with Mortality. Pakistan Journal of Health Sciences, 6(1), 209-213. https://doi.org/10.54393/pjhs.v6i1.2209

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Received date: 4th September, 2024
Acceptance date: 17th January, 2025
Published date: 31st January , 2025

ABSTRACT

Trauma injuries cause significant global morbidity and mortality. While current scoring systems like ISS and TRISS are complex, the Age Shock Index (ASI) offers a simpler, potentially more effective method for estimating patient outcomes. **Objective:** To evaluate the association of Age Shock Index with 48-hour in-hospital mortality in a trauma population in an Emergency Department (ED). **Methods:** A comparative cross-sectional study was conducted over eight months in the Emergency Department of Ziauddin University, focusing on pre-selected trauma patients aged 18-65 years. Patients were divided into two groups: the exposed group and non-exposed group, with an Age Shock Index (ASI) ≥ 50, and < 50 respectively. Data analysis was carried out using descriptive statistics, the chi-square test, and independent t-tests with the Statistical Package for Social Sciences (SPSS) version 21.0. **Results:** Patients with an Age Shock Index (ASI) ≥ 50 had significantly higher 48-hour in-hospital mortality (72%) compared to those with an ASI < 50 (12%) ($p < 0.001$). The exposed group also received more intravenous fluids, inotropic support, and blood products. No deaths occurred in the emergency room among the exposed group, but a trend towards higher overall mortality was observed (hazard ratio 48.584, 95% CI: 0.511 - 4622.17, $p = 0.095$). **Conclusions:** The Age Shock Index (ASI) ≥ 50 is associated with significantly higher 48-hour in-hospital mortality in trauma patients. The exposed group required more intensive interventions, indicating a higher severity of injury. ASI may serve as an effective predictor of patient outcomes in emergency settings.

INTRODUCTION

Trauma-related injuries are the leading cause of fatalities and disabilities, resulting in a significant amount of the global health burden . Medical technicians and doctors must rapidly recognize trauma patients who are at a significant risk of death . Despite being a well-known and critical issue, the rapid mortality rate following injury has not altered much over the past few years . Several methodologies have been used in past research to assess the severity and predict the death of people with serious injuries. However, traditional approaches such as the Injury Severity Score (ISS), Trauma Score (TRISS), and New Injury Severity Score (NISS) are regularly used, but they frequently require complicated computations or the need for extensive clinical and laboratory data. Many of these scoring techniques are challenging for their initial implementation in an emergency department (ED) . Currently, a variety of clinical measures, including heart rate (HR), respiration rate/pulse rate (PR), blood pressure (BP), shock index (SI), and age shock index, are used to assess the severity of patients who are seen in the emergency room . Recent study data indicates that ASI is an useful measures for assessing outcomes for patients in

DOI: https://doi.org/10.54393/pjhs.v6i1.2209

emergency situations . The Age Shock Index (ASI) appears to have the potential of becoming a more precise predictor for patient outcome emergencies. The ASI is calculated by taking the product of age with the Shock Index, making this measure a much better reflection because it includes the factors of age and physiological variation with respect to the age. Higher studies show at the ASI; thus, it was known to be related to mortality and further intervention, making it a pertinent point for treatment modalities in various patients.Consequently, the study aimed to compare the relationship of ASI with 48h in-hospital mortality in trauma patients at the ED.

METHODS

The current research was conducted on the trauma cases managed at the Emergency Department at Ziauddin University. Informed consent was obtained from the parents or guardians of the patient. The trauma patients were categorized into two groups with Shock indices into exposed and non-exposed. This study used a non-probability sequential sampling approach and took place over a duration of 6 months period, from April, 2019 to September, 2019. The Ethical Approval was obtained from the Ethical Review Committee of Ziauddin University (Reference Code: 0591118AZEMD). Patients of both genders between the ages of 18 and 65 who had experienced trauma were eligible. The exceptions were isolated traumatic brain injuries, patients who died on presentation, individuals with metabolic disorders or hypertension, pregnant women, and those who were in shock because of non-trauma reasons such as burns, food poisoning, or drug toxicity. The sample size for this study was calculated using WHO sample size calculator, based on statistics from an article that showed a 59.5% mortality rate in the group that was exposed and a 3.1% death rate in the non-exposed group.The computed sample size for each group was 13 people, for a total of 26, with a 95% confidence interval and 80% study power. In order to compensate for probable data loss, the sample size was expanded to 25 in each group, for a total of 50 participants. Data collected included patients' Age, Sex, Intravenous fluids, inotropic support, Blood product, Death in emergency room, and Age Shock Index (ASI) recorded on a pre-designed form. The Age Shock Index (Age SI) was calculated using the initial vital signs recorded in the emergency department. This index, determined as the product of age and the Shock Index (SI), incorporates both the patient's age and physiological parameters. An Age SI value exceeding 50 has been strongly associated with increased mortality rates in trauma patients, highlighting its utility in accurately predicting outcomes.The various hemodynamic instability cut-off values for Age Shock Index was determine the various hemodynamic stability based on other study . Patients with ASI > 50 were classified as the Exposed Group, while those with ASI < 50 were classified as the Non-Exposed Group. Patients were monitored for 48 hours, with all variables measured hourly. Any parameter exceeding its cut-off limits during monitoring was recorded for further evaluation. Admitted patients were tracked for 48 hours using their medical record or reference number, while discharged patients were followed up via the contact number provided on the emergency form. Data were collected using a pre-designed form, and confounders and biases were minimized by adhering strictly to the study protocols. SPSS version 21.0 was used for data analysis. Quantitative parameters, such as age, were calculated as mean ± SD, while qualitative factors, including sex, intravenous fluid administration, inotropic support, use of blood products, death in the emergency room, and 48-hour in-hospital mortality, were assessed for frequency and percentage. Post stratification was identified by applying chi-square test. Probability ratio was determined by Cox regression with a significance level set at $p < 0.05$.

RESULTS

All 50 patients either male or female having age in between 18 to 65 years who meets the inclusion standard for research was incorporate in research for the evaluation of associated 48 hours mortality people with Age SI in traumatic patients admitted at emergency department of hospital. People categorized into two classes according to treatment, in first group 25 patients who Exposed to medicines whereas, in second group 25 patients those were Unexposed to medicines. The age distribution between the exposed and unexposed groups showed a statistically significant difference, with mean ages of 48.32 and 38.44 years, respectively ($p = 0.016$). Gender distribution was similar across both groups, with no significant difference ($p = 0.774$) (Table 1).

Table 1: Age and Gender Distribution of Patients

Variable	Exposed (n=25)	Unexposed (n=25)	p-value
Gender Distribution			
Male	14 (56%)	13 (52%)	0.774
Female	11 (44%)	12 (48%)	
Age (Years)			
Mean ± SD	48.32 ± 10.89	38.44 ± 13.61	0.016

Gender distribution was assessed using chi-square test; age was analyzed using independent t-test.

Table 2 shows significantly higher proportion of exposed patients received intravenous fluids (96%) and inotropic support (96%) compared to the unexposed group (36% and 20%, respectively). Blood product usage was also more common among the exposed group (56%) compared to the unexposed group (8%). No deaths occurred in the emergency room among the exposed group, while one

DOI: https://doi.org/10.54393/pjhs.v6i1.2209

death occurred in the unexposed group (4%). However, 48-hour in-hospital mortality was significantly higher in the exposed group (72%) compared to the unexposed group (12%).

Table 2: Frequency Distributions of Clinical Variables among Trauma Patients

Variable	Exposed	Unexposed	p-value
Intravenous Fluid			
Yes	24 (96%)	9 (36%)	<0.001
No	1 (4%)	16 (64%)	
Inotropic Support			
Yes	24 (96%)	5 (20%)	<0.001
No	1 (4%)	20 (80%)	
Blood Products			
Yes	14 (56%)	2 (8%)	<0.001
No	11 (44%)	23 (92%)	
Death in Emergency Room			
Yes	0 (0%)	1 (4%)	0.13
No	25 (100%)	24 (96%)	
48 Hour In-Hospital Mortality			
Yes	18 (72%)	3 (12%)	<0.001
No	7 (28%)	22 (88%)	

p-values were calculated using chi-square tests to determine the statistical significance of differences between exposed and unexposed groups

Patients with an Age Shock Index (ASI) ≥ 50 had a higher mortality rate (72%) compared to those with an ASI < 50 (12%)(p = 0.000)(Table 3).

Table 3: Impact of Age Shock Index on 48-Hour In-Hospital Mortality

Index	Category	Exposed	Non-Exposed	Total	Chi-Square P-Value
Age Shock Index	< 50	3 (12%)	22 (88%)	25	0.000*
	≥ 50	13 (72%)	7 (22%)	25	
	Total	21	29	50	

Percentages are calculated based on the total number of individuals in each category. Chi-square p-values indicate statistical significance. An asterisk (*) denotes a statistically significant result (p < 0.05).

Table 4 showed hazard ratio for mortality among the exposed group was 48.584, with a 95% confidence interval of 0.511 to 4622.17, and a Cox regression p-value of 0.095. This indicates a trend towards significance, suggesting a higher mortality risk in the exposed group compared to the unexposed group.

Table 4: Hazard Ratios for Mortality among Exposed versus Unexposed Groups

Group	Hazard Ratio	95% Confidence Interval (CI)	Cox Regression P-Value
Exposed	48.584	0.511 - 4622.17	0.095
Unexposed	1.000	-	-

Hazard ratio for the exposed group compared to the unexposed group. The p-value indicates the statistical significance of the difference in mortality risk.

DISCUSSION

It is commonly known that as patients ages, their physiological compensatory systems decrease and their baseline vital sign features change. Elderly people typically have worse outcomes following injury, a lower physiological tolerance, and a higher frequency of complications.15 Given how aging affects vital signs and results, it makes sense that the SI's effectiveness as a predictor would vary with age. The study found that higher ASI values were associated with increased mortality and a higher need for intensive interventions. This aligns with previous research indicating that ASI accounts for age-related physiological variations, offering a more nuanced assessment compared to traditional scoring systems. A recent study revealed a strong positive correlation between mortality in the hospital and the Age Shock Index (ASI) with patients with stroke.In another study, it was observed that the value of the Age Shock Index (ASI) in patients older than 55 years may be useful for early mortality prediction.In addition, elevated ASI score was correlated with the odds of having blood transfusions, suggesting its value as a predictor in the identification of patients who would require more extensive medical intervention. The significant correlation established in the current research has applied better classification of such indices for risk groups and the creation of the triage and therapeutic paradigms. Another study mentioned that, age SI alone predicts a worse outcome for AMI patients receiving PCI.Current study aligns with these findings, showing that ASI is significantly associated with mortality rates in trauma patients. Particularly, the patients which were having elevated ASI values were found to have increased mortality. Earlier studies have proven that these indices can evaluate the severity of trauma and predict outcomes.The ASI, which is the result of adding age to the shock index, seems to increase the mortality prediction accuracy.This is consistent with recent research indicating that SI × age is a highly significant variable that adds more data to the usual prognostic factors and helps predict death in Acute heart Failure patients . Kim *et al.*, applied the Age Shock Index (SI) in projecting fatality risks for older people through cross-sectional data from a nationwide injury surveillance system. The findings showed that Age SI increase in non-survivor patients than in survivors. In particularly, out of all the subjects, 69.4% of high-risk or insecure according to Age SI died. Moreover, the incorporation of ASI into clinical practice could improve triage and promote further and more specific interventions at the ED. The study noted that using age adjusted parameters in the assessment of trauma risk leads to more effective identification of patients with a high risk of deterioration and such patient

DOI: https://doi.org/10.54393/pjhs.v6i1.2209

receiving treatments quicker leading to an improvement in the general prognosis of the disease. In our study, a significantly higher proportion of exposed patients received intravenous fluids and inotropic support compared to the unexposed group. Blood product usage was also more common among the exposed group compared to the unexposed group. This trend highlights the increased need for intensive medical interventions in patients with elevated ASI, reflecting the severity of their hemodynamic compromise and the urgency of their clinical condition. A study on Elevated Shock Index, Pediatric Age-Adjusted (SIPA) demonstrated its association with higher rates of hospital admissions, prolonged lengths of stay, and increased critical interventions such as ventilatory support, fluid boluses, and intravenous medications. These findings emphasize SIPA's utility in identifying high-risk pediatric patients requiring intensive medical care . Moreover, the international guidelines have been developed for the management of shock that emphasize on the importance of prompt initiation of IV fluids, and inotropes .

CONCLUSIONS

The use of ASI as the tools for predicting mortality in trauma patients is evident from the study. Findings of this study support their use in the ED in order to improve risk assessment and management. Future studies should persist in refining these indices and expand their application to patients of different types and in the course of different kinds of treatment. The study was carried out at a single hospital with a relatively small sample in an urban region, which limits the findings' application to larger populations.

Authors Contribution

Conceptualization: AZ
Methodology: IAK, MK, PR, GI
Formal analysis: SPS
Writing, review and editing: AZ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI:https://doi.org/10.54393/pjhs.v6i1.2464

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Correlation of Clinical Frailty Scale Assessment and in-Hospital Mortality in Elderly Critically Ill Patients Admitted to Intensive Care Units of Private Sector Tertiary Care Hospital

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ARTICLE INFO

Keywords:
Clinical Frailty Scale, Frailty, Critical Illness, Mortality

How to Cite:
Muzaffar, S., Hashmi , M., Rasheed, G., Jamil, A., Umer, S., & Kamran, A. (2025). Correlation of Clinical Frailty Scale Assessment and in-Hospital Mortality in Elderly Critically Ill Patients Admitted to Intensive Care Units of Private Sector Tertiary Care Hospital: Clinical Frailty Scale in Elderly Critically Ill Patients Admitted to Intensive Care Units . Pakistan Journal of Health Sciences, 6(1), 214-221. https://doi.org/10.54393/pjhs.v6i1.2464

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Received date: 22nd October, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

Frailty is a complex geriatric condition marked by increased vulnerability to adverse health events. In intensive care unit patients, there is a clear correlation between the Clinical Frailty Scale and higher short- and long-term mortality rates. **Objectives:** To evaluate the prognostic importance of frailty, measure the risk of death in the Intensive Care Unit for all Clinical Frailty Scale scores, and methodically evaluate the association between frailty and Intensive Care Unit mortality. **Methods:** This cross-sectional study was conducted over 1 year (Jan 2023 to July 2023) at the Department of Medical Intensive Care Unit of Ziauddin University Hospital, Karachi Pakistan. Irrespective of gender, all patients of age more than 60 years admitted to the Medical Intensive Care Unit were included. In this study, individuals ≥60 years of age had their pre-admission frailty and hospital mortality compared using the Clinical Frailty Scale. **Results:** The median age was 75 years. The overall mortality rate was 9.9%. The Clinical Frailty Scale score indicated that 29.7% of patients were classified as non-fragile, 18.7% as vulnerable or pre-fragile, and 51.6% as frail. A significant association of Clinical Frailty Scale assessment was observed with gender, age, outcome, Acute Physiology and Chronic Health Evaluation score and invasive (mechanical ventilation). According to multivariate logistic regression, patients on mechanical ventilators have a higher mortality rate. **Conclusions:** It was concluded that the findings demonstrated a strong correlation between mortality and the Clinical Frailty Scale among critically sick patients admitted to the intensive care unit.

INTRODUCTION

As individuals advance in age, they exhibit an increasing susceptibility to adverse outcomes, including mortality. The condition known as frailty is characterized by a diminished capacity to recover from stressors, resulting from declines in physiological reserves and dysfunction across multiple organ systems [1]. Frailty constitutes a complex geriatric condition marked by heightened vulnerability to detrimental health events, including an elevated incidence of falls, nursing home placements, and an increased risk of mortality [2]. The incidence of intensive care unit (ICU) admissions among older adults is substantial, with 41.3% of individuals aged 65 and older, and 65.2% of those aged 80 and above, being admitted to the ICU [3]. Evidence suggests that while older patients often receive greater relative benefits from intensive care interventions compared to younger patients, these benefits are not uniformly observed across the entire population of elderly ICU patients [4]. Research indicates that patients with elevated Clinical Frailty Scale (CFS) score significantly increase their likelihood of dying within 30

DOI:https://doi.org/10.54393/pjhs.v6i1.2464

days and requiring intensive care services. For instance, a prospective cohort study identified that the 30-day survival rates of older ICU patients were independently predicted by their level of frailty, defined as a CFS score of ≥5, with frail patients demonstrating considerably poorer outcomes than their non-frail counterparts [5]. Furthermore, the CFS has been shown to provide additional prognostic value beyond traditional severity scores, such as the Acute Physiology and Chronic Health Evaluation (APACHE) II, in predicting in-hospital mortality [6]. According to a large ecological study conducted in 21 European countries, frailty is identified as an independent predictor of both ICU mortality and 30-day mortality among older patients, with frail individuals exhibiting markedly lower survival rates [7]. Moreover, frailty's predictive power is comparable to, and at times exceeds, that of traditional ICU severity scores like APACHE II and SOFA [8]. Research indicates that frail ICU survivors are more likely to experience functional decline and increased mortality within six months' post-discharge [6]. A study conducted by Baldwin et al. revealed that among ICU survivors aged 65 and older, pre-discharge frailty was associated with a threefold increase in six-month mortality and a higher prevalence of disability [10]. Similarly, Cuenca *et al.* demonstrated that frail ICU patients experienced significantly higher mortality rates at one and six months following discharge compared to their non-frail peers [11]. Moreover, research by Geense *et al.*, indicated that frailty levels varied in the year following ICU admission, with a considerable proportion of unplanned ICU survivors becoming progressively frail by the one-year mark [12].

This study aims to investigate the relationship between pre-admission frailty, as measured by the CFS, and hospital mortality in patients aged 60 and older. The primary objectives comprise evaluating the predictive significance of frailty, assessing ICU mortality risk across the complete range of CFS scores, and systematically examining the association between frailty and ICU mortality. By incorporating frailty into existing risk stratification models, this study aims to mitigate the potential costs of over-medicalization while improving morbidity and mortality outcomes for this vulnerable population.

METHODS

This cross-sectional study was conducted over one year, with a data collection period spanning six months, from January 2023 to July 2023, at the Medical Intensive Care Unit (MICU) of Ziauddin University Hospital in Karachi, Pakistan. The study commenced following the receipt of ethical approval from the Ziauddin University Hospital Research and Ethics Committee (Reference No: 5750722SMCCM). Utilizing a prevalence estimate of 65% [3], a confidence level of 95%, and a margin of error of 5%, a required sample size of 283 was determined using the WHO sample size calculation software. Data were collected through a convenient sampling method. Following an explanation of the study's objectives and clarification that it was non-interventional, informed consent (both written and verbal) was secured from participants or their family representatives. Inclusion criteria encompassed all patients aged over 60 years who were admitted to the MICU. To maintain a focused and homogeneous study population, specific exclusion criteria were implemented. Patients with a duration of hospitalization of fewer than 24 hours were excluded, as their limited stay did not yield adequate clinical data or meaningful outcomes for analysis. Additionally, individuals with neurological conditions such as advanced dementia or those in a vegetative state were excluded due to the significant impact of these conditions on prognosis, which could potentially confound the study's results. Patients admitted for surgical reasons, including trauma, surgical procedures, or accidents unrelated to chronic medical conditions, were similarly excluded. Their outcomes are predominantly influenced by acute surgical interventions rather than the medical factors central to this investigation. Furthermore, individuals with a history of significant organ transplantation were excluded, as their outcomes are substantially affected by transplantation-related factors such as immunosuppression and post-transplant care, which diverge from the general population being examined. These exclusions were intended to minimize confounding variables and reduce selection bias, thereby ensuring a more accurate analysis of the targeted medical conditions. Data collected included demographic information such as age, gender, and the reason for ICU admission. The severity of organ dysfunction was assessed within the initial 24 hours of ICU admission using the cumulative Sequential Organ Failure Assessment (SOFA) score, which ranges from 0 to 24, with higher scores indicating greater dysfunction. Frailty was characterized as a condition marked by reduced physical and psychological reserves, which leads to increased clinical vulnerability. The Clinical Frailty Scale (CFS), a judgment-based assessment tool originally developed for the Canadian Study of Health and Aging, was utilized to evaluate frailty. The 9-point CFS categorizes patients based on their level of physical activity, functional ability, burden of chronic diseases, and cognitive state, with classifications including fit or non-frail (scores 1–3), vulnerable or pre-frail (score 4), frail (scores 5–8), and terminally ill but not otherwise frail (score 9). The necessary data for this assessment were collected from patient records, proxies, or directly from the patients themselves. Follow-up measures were established to

DOI:https://doi.org/10.54393/pjhs.v6i1.2464

document in-hospital mortality as the primary outcome. Secondary outcomes included severity of illness, which was assessed using the SOFA and APACHE-II scores, as well as the need for organ support during the hospital stay. All data were gathered by the principal investigator utilizing a pre-designed proforma. To mitigate confounding variables and bias, there was strict adherence to inclusion and exclusion criteria, along with appropriate stratification procedures. Patient information was securely stored and made accessible exclusively to authorized personnel. The statistical analysis was performed using IBM SPSS Statistics version 27.0. The Shapiro-Wilk test was employed to assess the normality of the data. Qualitative data were expressed as frequencies and percentages, while quantitative variables were analyzed as mean ± standard deviation or median with interquartile range. Relationships between qualitative variables were examined using the chi-square test or Fisher's exact test. Odds ratios were computed through univariate and multivariate binary logistic regression models, with a p-value of less than 0.05 considered statistically significant.

RESULTS

The study involved 283 patients in total among which 154 (45.6%) patients were male and 129 (54.4%) of whom were female. The median age of patients was 75 years with the majority (54.4%) being older than 75 years. The mean length of stay at MICU was 3.37 ± 2.796 days (Table 1).

Table 1: Gender-Based Study (n=283)

Variables	Frequency (%)
Male	154 (45.6%)
Female	129 (54.4%)
Patients Older Than 75 Years	(54.4%)
Median	75 Years
Mean	3.37 ± 2.796 Days

Electrolyte imbalance is the most common diagnosis, accounting for 35.3% of the patients, emphasizing the critical need for managing electrolyte disturbances in this population. Acute Kidney Injury (AKI) follows, affecting 16.6% of the patients, while aspiration pneumonia accounts for 15.5%, highlighting the frequent occurrence of renal impairment and respiratory complications. Congestive cardiac failure (CCF) and community-acquired pneumonia (CAP) affect 13.8% and 13.4% of patients, respectively, underscoring the burden of cardiovascular and respiratory diseases. Diabetic ketoacidosis (DKA) represents 11.7% of diagnoses, with atrial fibrillation affecting 8.5%. The remaining diagnoses, such as metabolic acidosis (6.0%), hypernatremia (5.7%), and ischemic stroke (5.3%), along with others, reflect less frequent yet significant conditions (Figure 1).

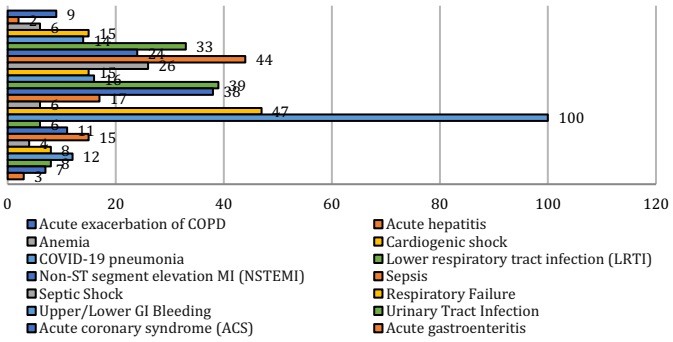


Figure 1: Diagnosis of Patients with Different Diseases

Hypertension is the most common condition, affecting 219 individuals, followed by chronic pulmonary disease with 168 cases. Congestive heart failure is the third most prevalent, with 80 individuals affected. Conditions such as asthma, depression, and Type II diabetes show moderate prevalence, ranging from 15 to 28 cases each. On the other hand, chronic kidney disease (CKD) requiring dialysis, dyslipidemia, and hyperthyroidism have the lowest occurrence, with only 3 to 4 cases reported for each. Overall, cardiovascular and pulmonary conditions appear to have the highest impact on this population (Figure 2).

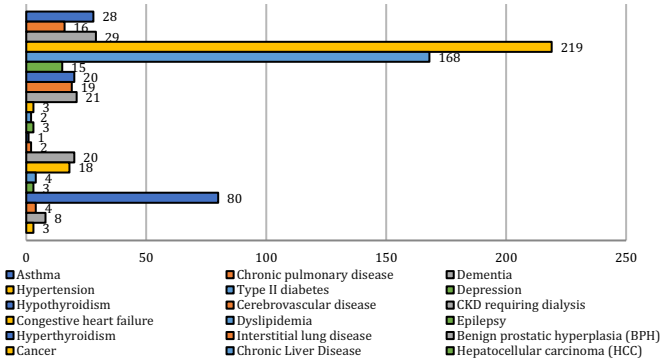
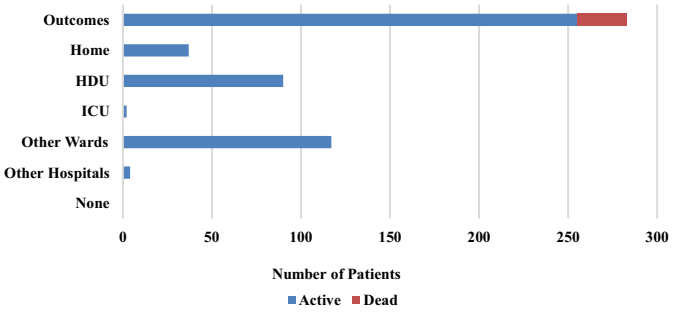


Figure 2: Comorbid Patients with Different Diseases

Among 283 patients, the overall death rate was 9.9%. Among 255 patients who were survived, 14.9% were discharged and transferred to home. The rest of the patients were transferred to other wards of the hospital. Among patients who were transferred to the ward, 27.5% were transferred to HDU, 0.8% were transferred to the ICU, 45.9% were transferred to a non-critical care ward, and 1.6% were transferred to another hospital (Figure 3).



DOI:https://doi.org/10.54393/pjhs.v6i1.2464

Figure 3: Outcome of Patients Based on Home, HDU, OCU

The most crucial finding is the strong association between younger age (≤75 years) and a significantly lower likelihood of frailty, as measured by the CFS ≥5. Patients aged 75 years or younger were found to be markedly less frail compared to older patients but have high significance, with an adjusted odd ratio (AOR) of 0.227 (95% CI: 0.124-0.415, p<0.001). This indicates that younger patients have about one-quarter the risk of frailty as those over 75, emphasizing the profound influence of age on frailty status in clinical settings. Additionally, gender played a role, with males showing lower adjusted odds of frailty compared to females is highly significant (AOR=0.371, 95% CI: 0.207-0.664, p=0.009), and other factors like lower APACHE scores and the absence of mechanical ventilation were also associated with reduced frailty, though age remained the most pronounced determinant of frailty across the cohort (Table 2).

Table 2: Association of CFS, Odds Ratio for CFS score (CFS)≥5

Variables	CFS			p-value	Odds ratio			
	Non-Frail	Vulnerable or Pre-Frail	Frail		Un-Adjusted	(95% CI)	Adjusted	(95% CI)
Gender								
Male	56 (66.7)	31 (58.5)	67 (45.9)	0.008*	9.826	0.485 (0.285-0.826)	0.009	0.371 (0.207-0.664)
Female[R]	28 (33.3)	22 (41.5)	79 (54.1)					
Age Group								
≤75 Years	64 (76.2)	32 (60.4)	58 (39.7)	0.000*	30.535	0.258 (0.145-0.458)	1.667	0.227 (0.124-0.415)
>75 Years[R]	20 (23.8)	21 (39.6)	8 8(60.3)					
APACHE Score								
<15	52 (61.9)	25 (47.2)	63 (43.2)	0.021*	17.462	0.000 (0.0000)	-	-
15-19	22 (26.2)	18 (34)	41 (28.1)					
20-28	10 (11.9)	9 (17)	32 (21.9)					
>28[R]	0 (0)	1 (1.9)	10 (6.8)					
SOFA Score								
<6	67 (79.8)	34 (64.2)	97 (66.4)	0.062	5.809	0.489 (0.266-0.897)	0.058	0.516 (0.261-1.023)
>10[R]	17 (20.2)	19 (35.8)	49 (33.6)					
Invasive (Mechanical Ventilation)								
Mechanical vent	9 (10.7)	12 (22.6)	36(24.7)	0.035*	7.335	2.649 (1.234-5.686)	21.197	1.956 (0.837-4.569)
Self-vent[R]	75 (89.3)	41 (77.4)	110(75.3)					
Vasopressors Support								
Yes	16 (19)	10 (18.9)	31 (21.2)	0.894	0.224	1.103 (0.579-2.100)	- -	- -
No[R]	68 (81)	43 (81.1)	115 (78.8)					
Hemodialysis								
Yes	5 (6)	0 (0)	5 (3.4)	0.191	5.021	0.407 (0.115-1.446)	- -	- -
No[R]	79 (94)	53 (100)	141 (96.6)					
Outcome								
Alive	80 (95.2)	50 (94.3)	125 (85.6)	0.033*	7.191	0.365 (0.122-1.086)	- -	- -
Expired[R]	4 (4.8)	3 (5.7)	2 1(14.4)					

"Chi-Square/Fisher exact test was applied". "Binary logistic regression was applied". "®Reference group". "p-value≤0.05 were considered significant". "*Significant at 0.05 levels"

The most salient finding is the significant association between elevated SOFA scores and increased mortality. Patients with SOFA scores exceeding 10 had substantially higher odds of death with high clinical significance, with an adjusted odd ratio (AOR) of 0.192 (95% CI: 0.069-0.533, p=0.002). This underscores the importance of SOFA scores as a critical prognostic indicator of mortality, reflecting the severity of organ dysfunction. Additionally, the requirement for mechanical ventilation emerged as another significant predictor of mortality. Patients who required invasive mechanical ventilation exhibited a markedly increased risk of death with high clinical significance, with an AOR of 3.680 (95% CI: 1.506-8.995, p=0.004). These findings emphasize that advanced organ failure, as measured by high SOFA scores, and the necessity for mechanical ventilation are the most powerful determinants of poor outcomes in this cohort. While factors such as age and the use of vasopressor support also indicated higher mortality risks, SOFA scores and mechanical ventilation remain the most definitive predictors of mortality in critically ill patients (Table 3).

DOI:https://doi.org/10.54393/pjhs.v6i1.2464

Table 3: Association of Outcome Along with Odds for Expired Patients

Variables	Outcome			Odds ratio		Odds ratio	
	Alive	Expired	p-value	Un-Adjusted	(95% CI)	Adjusted	(95% CI)
Gender							
Male	139 (54.5)	15 (53.6)	0.925	0.925	0.963 (0.440-2.106)	--	--
Female[R]	116 (45.5)	13 (46.4)					
Age Group							
≤75 Years	142 (55.7)	12 (42.9)	0.196	0.199	0.597 (0.271-1.313)	--	--
>75 Years®	113 (44.3)	16 (57.1)					
APACHE Score							
<15	136 (53.3)	4 (14.3)	0.000*	0.003*	0.078 (0.015-0.412)	--	--
15-19	76 (29.8)	5 (17.9)		0.034*	0.175 (0.035-0.874)		
20-28	35 (13.7)	16 (57.1)		0.789	1.219 (0.285-5.211)		
>28®	8 (3.1)	3 (10.7)		--	--		
SOFA Score							
<6	191 (74.9)	7 (25)	0.000*	0.000*	0.112 (0.045-0.275)	0.002*	0.192 (0.069-0.533)
>10®	64 (25.1)	21 (75)					
Invasive (Mechanical Ventilation)							
Mechanical Vent	41 (16.1)	16 (57.1)	0.000*	0.000*	6.959 (3.066-15.796)	0.004*	3.680 (1.506-8.995)
Self-Vent®	214 (83.9)	12 (42.9)					
Vasopressors Support							
Yes	45 (17.6)	12 (42.9)	0.002*	0.003*	3.500 (1.550-7.905)	0.522	1.364 (0.528-3.521)
No®	210 (82.4)	16 (57.1)					
Hemodialysis							
Yes	10 (3.9)	0 (0)	0.286	0.999	0.000 (0.000-0.000)	-	-
No®	245 (96.1)	28 (100)					

The Chi-Square/Fisher exact test was applied. Binary logistic regression was applied. ®Reference group. p-value≤0.05 was considered significant. *Significant at 0.05 levels

DISCUSSION

Frailty, as measured by the Clinical Frailty Scale (CFS), has emerged as a significant predictor of adverse outcomes in critically ill patients. The prevalence of frailty among elderly patients in the Intensive Care Unit (ICU) corroborates the findings of Arias-Rivera *et al.*, who observed a higher prevalence in individuals aged over 70, thereby establishing age as a critical risk factor for frailty within critical care environments [13]. Similarly, Wozniak *et al.*, identified that nearly 40% of long-stay ICU patients aged beyond 65 were classified as frail [14]. Furthermore, this study indicated that males exhibited lower odds of frailty in comparison to females. This observation aligns with the research conducted by Georgakopoulou *et al.*, which noted gender disparities in frailty, with females typically displaying higher frailty scores due to longer life expectancy and greater exposure to chronic diseases [15]. Additionally, Silva-Obregón *et al.*, reported a frailty prevalence of 18.6% in their study cohort, with a notably higher incidence among women [16]. Patients with elevated frailty scores were more likely to present with comorbidities such as hypertension and chronic pulmonary disease. The robust association between frailty and comorbidities is further supported by Öner *et al.*, who found that frailty, assessed using both the Edmonton Frailty Scale and the CFS, was significantly linked to malnutrition and chronic illnesses in elderly ICU patients [17]. Variations in age demographics across studies, particularly those involving a greater proportion of very elderly patients (over 80 years old), tend to report increased frailty rates, as indicated in the literature [18]. Consistently, this study revealed that older patients, particularly those aged 75 and older, were more likely to exhibit enhanced frailty scores. Additionally, frail patients demonstrated a decreased likelihood of being discharged home and an increased probability of requiring long-term care. Sankar *et al.*, observed similar results, noting that critically ill frail patients exhibited diminished functional recovery and a greater likelihood of transfer to nursing facilities [19]. The death rates recorded for frail patients in the hospital, in the ICU, and 30 days' post-discharge were found to be 56.6%,

DOI:https://doi.org/10.54393/pjhs.v6i1.2464

37.7%, and 52.8%, respectively. Such rates are comparatively higher than those reported in prior studies with similar objectives, which indicated ranges of 5% to 36.9%, 10.7% to 50%, and 40.7%, respectively [18]. The current study established a strong correlation between frailty and mortality, with patients categorized as frail (CFS ≥5) experiencing markedly worse outcomes. This finding aligns with the research conducted by Wozniak *et al.*, who identified frailty as an independent predictor of mortality among ICU patients, particularly those with prolonged stays [14]. Moreover, patients aged 75 and older exhibited a significantly elevated risk of frailty and poorer outcomes, which is consistent with the findings of Ryan *et al.*, who documented that frail patients, primarily among the elderly, faced considerably higher mortality rates and observed lower functional recovery [20]. Kroken *et al.*, reinforced the predictive value of frailty in older ICU patients, revealing that frailty scores serve as strong indicators of survival [21]. Furthermore, the Sequential Organ Failure Assessment (SOFA) score, a commonly utilized assessment tool in ICUs for evaluating organ failure, was identified as a complementary predictor alongside frailty. The current study demonstrated that patients with SOFA scores exceeding 10 had significantly higher odds of mortality, supported by an adjusted odd ratio (AOR) of 0.192 (95% CI: 0.069–0.533, p = 0.002). Theodorakis *et al.*, confirmed that the integration of SOFA with frailty assessments provides a comprehensive framework for predicting mortality in ICU settings [22]. Additionally, it was noted that frail patients admitted to the ICU faced a greater likelihood of having life-sustaining treatments halted or withheld (47.2% compared to 20.7%) [23]. The prevalence of frailty reported by Silva-Obregón *et al.*, [16] stood at 18.6%, which is slightly lower than earlier findings that employed the CFS, documenting rates between 23.5% and 43% [24]. In a study conducted within a Pakistani population involving 377 patients, Ali *et al.*, found no correlations between frailty and obesity [25]. A further study from Lahore reported that 64.9% of frail participants and 2.1% of pre-frail participants exhibited impaired functional activities. Moreover, it was found that 56.7% of participants held a fitness level scored between 0 and 6 out of 10, while 22.7% achieved fitness levels ranging from 7 to 10 (p=0.047) [26].

CONCLUSIONS

It was concluded that frailty, as measured by the CFS, is strongly associated with higher mortality, increased dependence post-discharge, and the need for long-term care. Integrating comprehensive frailty evaluations into ICU protocols can enhance patient management by enabling tailored treatment plans, setting realistic care goals, and facilitating informed discussions with patients and families about prognosis. These measures can improve resource allocation and contribute to better overall outcomes for this vulnerable population.

Authors Contribution

Conceptualization: SM, AJ
Methodology: SM, MH, AJ, AK
Formal analysis: SM, MH, GR, AK
Writing review and editing: GR, AJ, SU, AK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2371

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Prevalence of Medicolegal Cases During Covid-19 Pandemic Lockdown; A Local Experience

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ARTICLE INFO

Keywords:
Medicolegal Cases, COVID-19 Pandemic, Physical Assault, Sexual Assault, Trauma

How to Cite:
Murad, T., Ahmad, S., Ramzan, R., Ali, F., Masood, R., & Sana, S. G. (2025). Prevalence of Medicolegal Cases During Covid-19 Pandemic Lockdown; A Local Experience : Medicolegal Cases During Covid-19. Pakistan Journal of Health Sciences, 6(1), 222-227. https://doi.org/10.54393/pjhs.v6i1.2371

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Received date: 22nd October, 2024
Acceptance date: 21st January, 2025
Published date: 31st January, 2025

ABSTRACT

Medical examinations are essential in legal cases, providing critical evidence that influences judicial outcomes. The COVID-19 pandemic impacted various societal aspects, including the nature and frequency of medical examinations. **Objective:** To compare the prevalence and types of medicolegal cases reported at District Headquarters Hospital, Rawalpindi, during the pre-pandemic and pandemic periods. **Methods:** A retrospective comparative cross-sectional study was conducted using data from March 2019 to August 2019 (pre-pandemic) and March 2020 to August 2020 (pandemic). Demographic details, including age and gender, as well as the types of cases (e.g., physical assault, sexual assault, trauma), were analyzed using SPSS version 24.0. **Results:** The total number of cases increased significantly from 389 in the pre-pandemic period to 441 during the pandemic ($P < 0.01$). During the pandemic, physical assault cases increased from 122 (31.36%) to 151 (34.24%), and sexual assault cases rose from 39 (10.02%) to 54 (12.24%) ($P = 0.013$). Blunt trauma cases increased from 79 (20.31%) to 101 (22.9%) and sharp trauma cases from 67 (17.22%) to 89 (20.18%). However, cases involving road traffic accidents (RTA) decreased significantly from 41 (10.54%) to 16 (3.63%) ($P = 0.04$). Poisoning incidents saw slight changes and the occurrence of burns, particularly chemical burns, increased from 3 (0.77%) to 5 (1.13). **Conclusions:** The COVID-19 pandemic lockdown has had a profound impact on the prevalence and nature of medicolegal cases. These findings emphasized the need for targeted interventions to address the specific medicolegal challenges exacerbated by pandemic conditions and to support vulnerable populations, particularly in urban areas and among women.

INTRODUCTION

Medical examinations play a crucial role in various legal cases, providing critical evidence that can influence the outcomes of judicial proceedings. When carrying out these evaluations, healthcare professionals use their medical expertise to look into crimes and determine the legal consequences of injuries and loss of lives. Forensic examination by the medical practitioner is vital to gather and examination of proof concerning injuries on one's body or sexually assaulted persons as well as alcohol/drug abuse cases alongside sanity investigation [1]. The COVID-19 pandemic has severely affected numerous parts of human life such as law and health. The introduction of confinement and other control-related strategies for the disease's spread has led to social and economic disruption that was never witnessed before. This has affected the global occurrence and type of medicolegal cases [2]. The COVID-19 pandemic has led to increased stress, isolation, and job losses, making children and their mothers particularly vulnerable to the risk of domestic violence. Multiple studies have reported a significant rise in domestic violence cases during lockdown periods [3]. The COVID-19 pandemic led to a 10.2% increase in domestic

DOI: https://doi.org/10.54393/pjhs.v6i1.2371

violence calls, driven by households without a prior history of violence [4]. This pandemic has increased domestic violence cases worldwide, but decreased child maltreatment and abuse reports due to home confinement. Studies have shown that the COVID-19 pandemic has led to a decrease in police reports and referrals to child and women protective services, mixed results in calls to police or domestic violence helplines, and an increase in women and child abuse-related injuries treated in hospitals [5]. In addition, firearm injuries also witnessed a sudden rise mostly targeting women and the elderly population. During the COVID-19 pandemic, the incidence of gunshot wounds to the head and neck increased by 10.4%, with alcohol abuse being the most common cause [6]. Lockdown measures decreased some types of crimes, such as street crimes and burglaries, due to increased police presence and reduced opportunities for criminal activities. Conversely, there was a notable increase in cybercrimes, including online fraud, phishing scams, and cyberbullying [7]. The pandemic led to significant job losses and financial insecurity, increasing stress and desperation among individuals. Areas with pre-existing poverty and inequality saw more pronounced increases in crime rates. The uncertainty and fear caused by the pandemic increased stress and anxiety levels across populations [8]. Social isolation due to lockdowns and restrictions exacerbated feelings of loneliness and depression, contributing to violent behavior in some individuals. The global prevalence of mental health issues during the COVID-19 pandemic was 28.0% for depression, 26.9% for anxiety, 24.1% for post-traumatic stress symptoms, 36.5% for stress, 50.0% for psychological distress, and 27.6% for sleep problems [9]. The pandemic also saw a rise in substance abuse as people coped with stress and isolation. Substance abuse is a significant risk factor for violent behavior, including gun violence. Study has shown that During the COVID-19 pandemic, 13.3% of respondents started or increased substance use to cope with stress [10]. Study of literature has highlighted certain gaps. While there are numerous studies examining the prevalence of medicolegal cases at a national or international level, there is a lack of detailed local studies. The literature often generalizes medicolegal cases without breaking down the types of cases (e.g., domestic violence, accidental injuries, suicides, homicides) [11]. A detailed analysis of how different types of cases have been affected by the lockdown is lacking. The pandemic strained healthcare systems, leading to delays in routine medical and forensic examinations [12]. There is insufficient research on how these delays impacted the quality and outcomes of medicolegal investigations. The research investigated whether the prevalence and nature of medicolegal cases at District Headquarters Hospital, Rawalpindi, varied between the pre-pandemic and pandemic periods. The study focused on analyzing the frequency, characteristics, and types of medicolegal cases before and during the COVID-19 lockdown within a specific local context.

It aimed to identify the primary types of medicolegal issues, compare their prevalence between the two periods, and examine any distinctive trends or patterns that emerged during the lockdown. This analysis seeked to enhance understanding of the medicolegal landscape during public health emergencies. The null hypothesis posits no significant difference in the prevalence and types of medicolegal cases between the two periods. In contrast, the alternative hypothesis suggested a significant difference in both prevalence and types of medicolegal cases between the pre-pandemic and pandemic periods.

METHODS

This study was a retrospective comparative cross-sectional study aimed at analyzing the prevalence and characteristics of medicolegal cases across two distinct periods: the pre-pandemic period (March 2019 to August 2019) and the pandemic period (March 2020 to August 2020), after approval from the ethical review committee of DHQ Hospital Rawalpindi, letter No 799/DHQ Hospital Rawalpindi. Data were collected from different sources including hospital records and databases, medicolegal reports and documentation, emergency department logs, and police and forensic reports. A sample size of 150 was determined using G*Power, with an effect size of 0.41, a significance level (α) of 0.05, and a statistical power of 80% ($1-\beta$). The allocation ratio was set to 1, resulting in equal group sizes of 75 participants each for Group 1 and Group 2. These parameters were chosen to ensure the study is adequately powered to detect a medium effect size while minimizing the risk of Type I and Type II errors. Sample size calculation is based on a 95% confidence level, 5% margin of error, and 50% population proportion, but justification for the proportion is missing. The study included all civil and criminal medicolegal cases reported during the specified timeframes: pre-pandemic period (March 2019–August 2019) and pandemic period (March 2020–August 2020). Only cases with complete records, including police reports, medical records, and forensic reports, were considered. Cases were excluded if they had incomplete records, an uncertain cause of death, originated outside the region, or fell under administrative exclusions. A structured data extraction form was developed to ensure uniformity in data collection. Cases with incomplete or missing records and cases in which the determination of the cause of death is kept under observation were excluded from this study. The date and time of the incident to analyze temporal patterns, location of the Incident including urban versus rural

DOI: https://doi.org/10.54393/pjhs.v6i1.2371

distribution, type of medicolegal case, circumstances of the incident (e.g., domestic violence, road traffic accident), medical findings, and forensic details were noted. Demographic data including the age and gender of the medicolegal examinee was noted. The number and type of medicolegal cases in the pre-pandemic and pandemic era was noted and the results were compared to assess any change in the prevalence of medicolegal cases after the pandemic sets it. A team of trained researchers and medical professionals were responsible for data extraction. Each team member was briefed to ensure consistency and accuracy in data collection. The confidentiality of the patient and victim was protected throughout the study. Data analysis was performed using SPSS (Statistical Package for the Social Sciences) version 24.0. Descriptive statistics were used to summarize demographic data, including means, standard deviations, and percentages. Inferential statistics, such as chi-square tests, were applied to compare the frequencies of different types of medicolegal cases between the pre-pandemic and pandemic periods. A P-value of ≤0.05 was considered statistically significant. These findings underscore the pandemic's impact on the nature and frequency of various medicolegal cases, with notable increases in assault, specific trauma categories, and changes in demographic patterns.

RESULTS

The study analyzed the prevalence and characteristics of medicolegal cases during the pre-pandemic and pandemic periods. The total number of cases increased significantly from 389 in the pre-pandemic period to 441 during the pandemic (P < 0.01). The average age of individuals involved in these cases showed a slight, non-significant decrease from 29.6 ± 12.9 years to 28.6 ± 11.5 years (P = 0.065). Gender distribution revealed a significant shift, with the proportion of male cases decreasing from 67.35% to 60.01% (P = 0.04) and female cases increasing from 32.65% to 39.99% (P = 0.03). Additionally, there was a notable change in the location of incidents, with rural cases decreasing from 58.34% to 53.97% (P < 0.01) and urban cases increasing from 43.18% to 46.03% (P < 0.01). These findings highlight the impact of the pandemic on the distribution and demographics of medicolegal cases (Table 1).

Table 1: Number and Distribution of Medicolegal Cases

Variables	Pre-Pandemic Period Mean ± SD/ Frequency (%)	Pandemic Period Mean ± SD/ Frequency (%)	p-value
Number of Cases	389	441	<0.01
Age	29.6 ± 12.9	28.6 ± 11.5	0.065
Gender			
Male	262 (67.35%)	265 (60.01%)	0.04
Female	127 (32.65%)	176 (39.99%)	0.03
Location			
Rural	227 (58.34%)	238 (53.97%)	<0.01
Urban	168 (43.18%)	203 (46.03%)	<0.01

Figure 1 depicted the distribution and comparison of medicolegal cases reported during the pre-pandemic period (March 2019–August 2019) and the pandemic period (March 2020–August 2020), categorizing the data by frequency and types of cases to highlight significant changes or trends between the two periods.

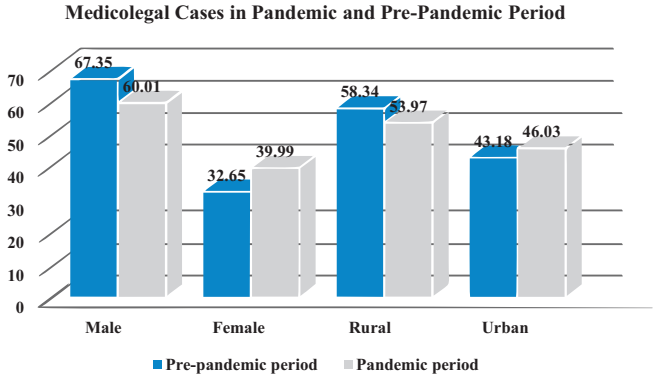

Figure 1: Medicolegal Cases in Pandemic and Pre-Pandemic Period

The study examined various types of medicolegal cases before and during the pandemic periods, revealing significant changes in their prevalence. During the pandemic, physical assault cases increased from 122 (31.36%) to 151 (34.24%), and sexual assault cases rose from 39 (10.02%) to 54 (12.24%), with both showing significant differences (P = 0.013). The trauma category also saw notable shifts, with blunt trauma cases increasing from 79 (20.31%) to 101 (22.9%) and sharp trauma cases from 67 (17.22%) to 89 (20.18%). However, cases involving Road Traffic Accidents (RTA) decreased significantly from 41 (10.54%) to 16 (3.63%) (P = 0.04). Poisoning incidents saw slight changes, with corrosive poisonings decreasing from 12 (3.01%) to 7 (1.58%), and other poisonings, such as the intake of rat poison and wheat pills, slightly increasing from 13 (3.34%) to 15 (3.4%) (P = 0.04). The occurrence of burns, particularly chemical burns, increased from 3 (0.77%) to 5 (1.13%), while electrical burns decreased from 6 (1.54%) to 4 (0.91%) (P = 0.03). These findings underscore the pandemic's influence on the nature and frequency of various medicolegal cases, highlighting shifts in assault, trauma, poisoning, and burn incidents (Table 2).

Table 2: Types of Medicolegal Cases in Pandemic and Pre-Pandemic Period (n=830)

Variables	Pre-Pandemic Period Frequency (%)	Pandemic Period Mean ± SD/ Frequency (%)	p-value
Assault	122 (31.36%)	151 (34.24%)	0.013
Physical	39 (10.02%)	54 (12.24%)	
Sexual	83 (21.34%)	97 (21.99%)	

DOI: https://doi.org/10.54393/pjhs.v6i1.2371

Trauma	224 (57.58%)	247 (56.01%)	0.04
Blunt	79 (20.31%)	101 (22.9%)	
Sharp	67 (17.22%)	89 (20.18%)	
Firearm	37 (9.51%)	41 (9.29%)	
RTA	41 (10.54%)	16 (3.63%)	
Poisoning	33 (8.48%)	31 (7.03%)	0.04
Corrosive	12 (3.01%)	7 (1.58%)	
Alcohol	8 (2.01%)	9 (2.04%)	
Intake of rat poison, wheat pills	13 (3.34%)	15 (3.4%)	
Burns	10 (2.57%)	12 (2.72%)	0.03
Chemical	3 (0.77%)	5 (1.13%)	
Electrical	6 (1.54%)	4 (0.91%)	
Dry	1 (0.26%)	3 (0.68%)	

Figure 2 compared the frequency and types of medicolegal cases reported during the pre-pandemic period (March 2019–August 2019) and the pandemic period (March 2020–August 2020). The figure highlighted variations and trends, providing a visual analysis of how the pandemic influenced the nature and prevalence of these cases.

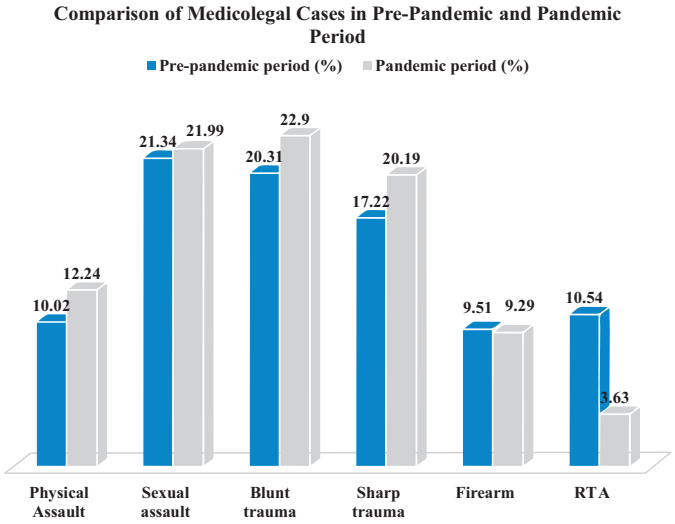

Figure 2: Comparison of Medicolegal Cases in the Pre-pandemic and Pandemic Period

DISCUSSION

The study's analysis of medicolegal cases during the COVID-19 pandemic lockdown compared to the pre-pandemic period reveals significant changes in the frequency and nature of these cases. The overall number of cases increased from 389 to 441, indicating a heightened incidence of medicolegal issues during the lockdown. There was a notable increase in physical assault cases, rising from 122 (31.36%) pre-pandemic to 151 (34.24%) during the pandemic, and in sexual assault cases, which increased from 39 (10.02%) to 54 (12.24%) (P = 0.013). This rise could be attributed to increased stress, economic hardship, and social isolation during the lockdown, which may have exacerbated interpersonal conflicts and domestic violence [13]. These findings correlated with the findings of Shahid E *et al.*, which reported 34.3% increase in cases of assault with ocular injury during COVID-19 lockdown, with most of the injuries being superficial with majority of the cases attributed to intimate partner violence, posing challenges to health care providers in managing sexual assault patients [14]. The COVID-19 lockdown increased the vulnerabilities of women to sexual victimization, creating opportunities for motivated offenders and promoting sexual violence. Moreover, policies such as social distancing, self-isolation, and lockdown policies added fuel to fire [15]. The overall trauma cases showed a slight decrease in blunt trauma cases from 79 (20.31%) to 101 (22.9%) and in sharp trauma cases from 67 (17.22%) to 89 (20.18%). However, there was a significant reduction in road traffic accident (RTA) cases, from 41 (10.54%) to 16 (3.63%) (P = 0.04). This decrease is likely due to reduced vehicular movement and travel restrictions during the lockdown period, leading to fewer traffic-related incidents. These findings correlate with the study of Chodos M *et al.*, that reported 22.6% cases of penetrating injuries during pandemic as compared to 15.1% in pre-pandemic period. Similarly, the firearm injuries during pandemic increased to 11.8% from 6.8% in pre-pandemic period [16]. The decrease in corrosive poisoning might be linked to reduced access to such substances during the lockdown, while the slight increase in other poisonings could reflect increased mental health issues and suicide attempts during the pandemic. Study conducted by Farooq S *et al.*, has also shown relevant findings with increase in suicidal ideation during pandemic to 12.1% [17]. Moreover, studies have shown that increased event rates for suicide ideation (10.81%), suicide attempts (4.68%), and self-harm (9.63%) during the COVID-19 pandemic when considered against event rates from pre-pandemic studies [18]. This study has provided data to inform policies related to public health emergencies, such as pandemic lockdowns, by highlighting trends and types of medicolegal cases that emerged during such periods in local context. It has stimulated further research into specific aspects identified in the study and the effectiveness of interventions during lockdowns. This study also has certain limitations. The study's scope may be limited to a specific period during the pandemic lockdown, which might not capture changes or trends outside of this timeframe [19]. The retrospective design relies on the accuracy and completeness of hospital records, which may introduce bias due to missing or incomplete data. As a single-center study, the findings are specific to District Headquarters Hospital, Rawalpindi, and may not be generalizable to other regions or healthcare settings. Furthermore, external factors such as changes in law enforcement policies, socio-economic conditions, and public awareness during the pandemic were not accounted for and may have

DOI: https://doi.org/10.54393/pjhs.v6i1.2371

influenced case patterns. While the study analyzed demographic and case-type data, it lacked an exploration of psychological and social factors, such as mental health impacts and domestic dynamics, which may have contributed to observed changes. Additionally, the absence of post-pandemic data limits understanding of the pandemic's long-term effects on medicolegal trends [20, 21].

CONCLUSIONS

The Covid-19 pandemic lockdown has had a profound impact on the prevalence and nature of medicolegal cases. The increase in assault and certain types of trauma cases underscores the social and psychological stresses induced by the lockdown. Reduced mobility has led to a decrease in road traffic accidents. This information makes it even more necessary to come up with certain measures that can be used to deal with the particular medicolegal problems worsened by the same factors, while at the same time aiding those members of society who need help most especially in towns where they live or women. Future research should address these limitations by including multi-center data, extending the timeframe of analysis, and incorporating qualitative assessments to explore underlying socio-economic and psychological factors. These enhancements would provide a more comprehensive understanding of the pandemic's impact on medicolegal cases.

Authors Contribution

Conceptualization: TM, SGS
Methodology: TM, SA, SGS
Formal analysis: FA
Writing, review and editing: RR, RM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2655

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Association of Plateletcrit Value with Gestational Diabetes Mellitus: A Case Control Study in A Tertiary Care Setting

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ARTICLE INFO

Keywords:
Gestational Diabetes Mellitus, Platelet Count, Plateletcrit, Glucose Tolerance Test

How to Cite:
Chaudhary, S., Kausar, Z., Khan, R., & Farhan, E. (2025). Association of Plateletcrit Value with Gestational Diabetes Mellitus: A Case Control Study in A Tertiary Care Setting : Plateletcrit Value with Gestational Diabetes Mellitus. Pakistan Journal of Health Sciences, 6(1), 228-232. https://doi.org/10.54393/pjhs.v6i1.2655

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Received Date: 5th December, 2024
Acceptance Date: 22nd January, 2025
Published Date: 31st January, 2025

ABSTRACT

Gestational Diabetes Mellitus (GDM) is linked to numerous maternal and fetal complications. Typically diagnosed in the third trimester with OGTT, early detection could prevent many adverse outcomes. Emerging evidence highlights the role of platelets in GDM pathogenesis, suggesting platelet indices, including plateletcrit, might aid early diagnosis. **Objective:** To determine the association between GDM and elevated plateletcrit levels. **Methods:** A case-control study was conducted over six months (May - October 2024) in Gynaecology and Obstetrics Unit 1, Sir Ganga Ram Hospital, Lahore. After ethical approval, 100 pregnant women meeting the inclusion criteria were enrolled. At 24-28 weeks' gestation, all participants underwent a 75g OGTT. Based on results, they were divided into Group A (controls with normal OGTT) and Group B (cases with deranged OGTT). Plateletcrit values from the second trimester were obtained retrospectively from medical records. Quantitative variables were analyzed using Student's t-test ($P \leq 0.05$ deemed significant), while qualitative variables were expressed as percentages. **Results:** Group B (GDM patients) had significantly higher mean plateletcrit values (0.24 ± 0.08) compared to Group A (non-GDM) (0.14 ± 0.03) ($P = 0.000$). Conversely, the mean platelet count was higher in Group A than Group B ($P = 0.000$). **Conclusion:** Pregnant women with GDM exhibited higher plateletcrit values and lower platelet counts compared to non-GDM women, suggesting plateletcrit as a potential marker for early GDM diagnosis.

INTRODUCTION

Gestational Diabetes Mellitus (GDM) refers to glucose intolerance that develops or is recognized for the first time during pregnancy [1]. It affects approximately 4-8% of pregnant women, out of which 10-15% women develop complications. GDM increases the risk of feto-maternal and neonatal complications such as macrosomia, polyhydramnios, intrauterine death, instrumental delivery, caesarean section, respiratory distress syndrome, perinatal morbidity and mortality. Complications related to GDM can be prevented by early diagnosis [2]. In pregnant women having genetic predisposition, placental hormones like growth hormone, placental lactogen, progesterone and cortisol cause increase in insulin resistance which ultimately leads to GDM. Under the effect of placental lactogen lipolysis increases which increase the free fatty acid level in the body. These free fatty acids further enhance insulin resistance, which causes acceleration of sub-chronic inflammation. The pro-inflammatory cytokines in sub-chronic inflammation contribute to causation of GDM [3]. It is suggested that in gestational diabetes mellitus, there is platelet activation as a result vascular endothelial injury caused by sub-chronic inflammation and insulin resistance [4]. Due to increased platelet turnover and platelet production in bone marrow, younger platelets are released into circulation. These younger platelets are larger and more reactive than smaller ones due to enhanced enzymatic and metabolic activity. This leads to increase in platelet count and platelet indices

DOI: https://doi.org/10.54393/pjhs.v6i1.2655

(including Platelet distribution width (PDW), plateletcrit (PCT), and Mean platelet volume (MPV) [5]. Plateletcrit (PCT), a parameter calculated as the product of mean platelet volume (MPV) and platelet count, indicates the total platelet mass in volume of blood circulation. It is suggested to be one of the best indicators reflecting platelet function [3]. The normal plateletcrit during pregnancy is reduced due to expanded plasma volume (0.17) [6]. These pathophysiological changes are suggested to occur weeks or months before GDM is diagnosed. GDM is screened at 28 weeks' gestation using screening tools like glucose challenge test (GCT) or Oral glucose tolerance test (OGTT). Literature have documented the potential role of platelets in pathological mechanism of development of diabetes. High plateletcrit value has the potential of being used as a screening test to know the risk of GDM. Fashami *et al.*, found statistically significant association of platelet indices with gestational diabetes mellitus ($p<0.001$). The sensitivity and specificity of plateletcrit has been found to be higher than other platelet indices [2]. Chandra and Shetty, reported significantly higher platelet count ($p <0.01$) and lesser mean platelet volume (MPV) ($p <0.001$), but he found no difference in plateletcrit value ($p= 0.75$) in women with GDM. Khan and Ashraf, observed mean platelet volume (MPV) ($p=0.002$*) and platelet distribution width (PDW) ($p=0.010$*) to be significantly increased in pregnant women with GDM compared to the apparent healthy pregnant women ($p<0.05$). they did not study the plateletcrit value [7, 8]. Many other researches also studied MPV and PWD in GDM, although plateletcrit is a better parameter reflecting platelet function. Current study was conducted with the objective of determining the association of higher plateletcrit with GDM. Association of high plateletcrit value with GDM, if proven may help us detecting probable risk of the disease long before the clinical diagnosis or abnormality of OGTT or GCT. An additional benefit is the low cost and wide availability of CBC, making it a convenient screening option. Early positive screening with CBC may warn the patient and help initiate lifestyle modifications and planning a diagnostic test for GDM for better pregnancy outcome [9].

Considering the conflicting findings in the literature, this study was carefully planned and designed.

METHODS

This was a case control study conducted over 6 months' period (May 2024 to October 2024) at Obstetrics and gynaecology Unit 1, Sir Ganga Ram Hospital, Lahore. Blood samples were collected from all participants at the time of the screening (24–28 weeks of gestation). The blood was processed as follows: after collection, samples were immediately analyzed for Complete Blood Count (CBC) and plateletcrit, with the results being retrospectively reviewed from the patients' medical records. The sample size was calculated using mean Platelet count in controls group (193.0 ± 55.06) and cases is (144.5 ± 61.9) by taking 80% power of test, 5% margin of Error and 20% drop out rate was 100 (50%) in each group [10]. After permission of Institutional Ethical Committee (No.81-Gynea/Synopsis/ERC), 100 pregnant patients, 20-35 year-old, with singleton pregnancy (confirmed on ultrasound), gestational age 24 -28 weeks (calculated from LMP OR first trimester ultrasound) were enrolled in the study. The age range was kept as 20-35 years as after age of 35 many of patients diagnosed as GDM are known diabetics. The gestation was chosen to be around 28 weeks as OGTT is done at this gestation, and patients were grouped based on OGTT results. To enroll the patients, non-probability consecutive sampling technique was used. Potential confounders, including medical history and concurrent conditions, were minimized by applying strict exclusion criteria. Patients with prior history of GDM, overt diabetes mellitus, alcohol intake, smoking, and any medical or obstetrical disorders (e.g., hypertension, thyroid disease, autoimmune disorders, or polycystic ovarian syndrome) were excluded from the study. Before enrollment written informed consent from was taken from the patients to fulfill the selection criteria. The patients were screened at 24-28 weeks' gestation with 75gm Oral Glucose Tolerance Test (OGTT). To diagnose GDM International Diabetes Federation guidelines was used stating fasting blood glucose level >92mg/dl, glucose level 1-hour post glucose administration>180mg/dl or glucose level 2 hour after glucose administration >153mg/dl [11]. On the basis of result of OGTT the patients were divided into two groups, each group comprising of 50 participants. Women having normal OGTT were enrolled in Group A (Controls) whereas, those having deranged OGTT, diagnosed as GDM were included in Group B (Cases). Patient's CBC with plateletcrit during second trimester was retrospectively taken from her medical record. Data including patients age, parity, gestational age, platelet count and plateletcrit were recorded on preformed proforma. Confounding variables were controlled by exclusion criteria. SPSS version 26.0 was used to analyzed the research data. The quantitative variables i.e. age, gestational age, platelet count and plateletcrit were presented as mean ± SD. The qualitative variables i.e. parity was presented as frequency and percentage. Data were stratified for age to address the confounding variable. After stratification Independent sample t-test was applied. P-value was considered as statistically significant if ≤0.05.

DOI: https://doi.org/10.54393/pjhs.v6i1.2655

RESULTS

In Group A (controls) the mean age of patients was 29.4 ± 3.55 years, (range 22-35 years) in comparison to 26.43 ± 4.82 years (range 20-35 years) in group B (cases with GDM). The mean gestational age in Group A was 25.8 ± 1.41 weeks (range 24-28 weeks) as compared to 25.82 ± 1.52 weeks (range 24-28 weeks) in group B. Group A included 56% primigravida and 44% multigravida compared to 60% primigravida and 40% multigravida in Group B. The mean platelet count was found to be 359.31 ± 27.12 (range of 398-313 × 109/L) in Group A, which was higher than mean platelet count in Group B 225.09 ± 49.51 (range 308-146 × 109/L) (P value 0.000). The mean plateletcrit value was significantly higher in Group B pregnant women with GDM (mean ± SD: 0.24 ± 0.08) as compared to Group A non-GDM pregnant women (mean ± SD: 0.14 ± 0.03) (P value=0.000) (Table 1).

Table 1: Comparison of Clinical Factors, Platelet Count and Plateletcrit % Among Groups (n=50)

Variables	Categories	Group A (Controls) Frequency (%) /Mean ± SD	Group B (Cases with GDM) Frequency (%) /Mean ± SD	p-Value
Age (Years)	Mean ± SD	29.4 ± 3.55	26.43 ± 4.82	0.002
	Max	35	35	
	Min	22	20	
Parity	Primigravida	28 (56%)	30 (60%)	0.039
	Multigravida	22 (44%)	20 (40%)	
Gestational Age (Weeks)	Mean ± SD	25.8 ± 1.41	25.82 ± 1.52	0.916
	Max	28	28	
	Min	24	24	
Plateletcrit (%)	Mean ± SD	0.14 ± 0.03	0.24 ± 0.08	0.000
	Max	0.21	0.6	
	Min	0.06	0.18	
Platelet Count × 109/L	Mean ± SD	359.31 ± 27.12	225.09 ± 49.51	0.000
	Max	398	308	
	Min	313	146	

In figure 1, plateletcrit (%) was compared among groups to assess variations in platelet mass, reflecting potential differences in hematological responses. Statistical analysis determined significant differences across study groups.

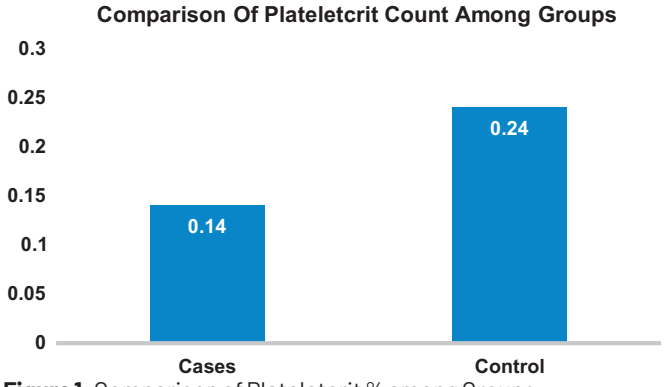

Figure 1: Comparison of Plateletcrit % among Groups

Figure 2 illustrated the comparison of platelet count among groups, highlighted variations in platelet levels. Statistical analysis was performed to assess significant differences across the study groups.

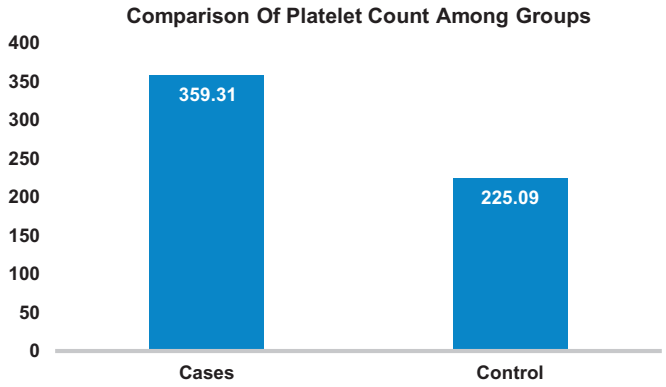

Figure 2: Comparison of Platelet Count Among Groups

The mean plateletcrit value for the <30 group is 0.199 ± 0.062, while for the >30 group, it is 0.217 ± 0.108. Similarly, the mean platelet count is 274.095 ± 68.865 for the <30 group and 257.902 ± 84.624 for the >30 group. In both cases, the p-values 0.266 for plateletcrit and 0.287 for platelet count indicated no statistically significant differences between the two age groups (Table 2).

Table 2: Effect of Age on Plateletcrit and Platelet count

Variables	Age	Mean ± S.D	p-Value
Plateletcrit	<30	0.199 ± 0.062	0.266
	>30	0.217 ± 0.108	
Platelet Count	<30	274.095 ± 68.865	0.287
	>30	257.902 ± 84.624	

DISCUSSION

The prevalence of Gestational Diabetes Mellitus (GDM), a common obstetrical complication, is reported to be 9.3% to 25.5% of pregnancies, depending on the used diagnostic criteria and ethnicity of population [12]. In Pakistan the reported prevalence of GDM in a metanalysis ranged between 8.42% and 35.80%, with overall pooled estimate of 16.7% [13]. Gestational Diabetes Mellitus (GDM) is a chronic inflammatory condition. Numerous factors including hyperlipidemia, insulin resistance, hyperglycemia, inflammatory process, endothelial dysfunction and oxidative stress lead to platelet activation. Platelet interaction with endothelium by producing Reactive Oxygen Species (ROS) causes initiation of endothelial dysfunction in GDM [14]. Endothelial dysfunction characterized by altered balance of vasodilators, such as nitric oxide and vasoconstrictors lead to impaired vascular response. Endothelial dysfunction causes pro-inflammatory and pro-coagulatory vascular environment favoring thrombus formation [15]. Platelet

DOI: https://doi.org/10.54393/pjhs.v6i1.2655

reactivity and aggregation is caused by Reactive Oxygen Species (ROS). Due to this there is accumulation of Advanced Glycation End products (AGEs) in plasma that interact with specific receptors on the endothelium to cause endothelial dysfunction. This leads to reduction in the production of Nitric Oxide (NO) and PGI2. All these mechanisms are suggested to contribute to complications of GDM [16]. Activated platelets have larger MPV and higher plateletcrit, which may cause hypercoagulability in the placental bed leading to vascular events. These events can be responsible for feto-maternal complications in GDM patients. Platelet activation may be detected by platelet parameters like MPV, platelet count, plateletcrit and PDW [17]. Amongst these, MPV and plateletcrit are emerging as a potential predictor or a cheap, easily available, screening tool for early detection of GDM in numerous studies. Contradictory results have been reported on the positive association and potential screening role of platelet indices. In current study the association of plateletcrit was determined with GDM. Current GDM pregnant patients were younger than healthy pregnant patients. There was also significant difference in parity between both groups. This is a limitation of study. As ideally both groups should have similar age and parity. Gestational age was similar in both groups. Platelet count was found to be significantly lower in GDM patients as compared to healthy pregnant controls (p value=0.000). This finding is consistent with results of Khan and Ashraf, [8]. Fashami MA *et al.*, reported higher count in GDM pregnant patients 233.0 ± 62.6 compared to 193.3 ± 49.5 [2]. Similarly, Xiang LL *et al.*, also reported higher platelet count in GDM group 221.27 ± 43.04 vs 218.95 ± 45.27 [18]. Simsek and Altekin, and Baldane S *et al.*, found no difference in platelet count between patients with GDM and healthy pregnant women [19, 20]. Main outcome of current study parameter was plateletcrit, which was significantly higher in patients with GDM as compared to healthy controls. However, in another study reported results were consistent with current study, reporting lower platelet count and higher plateletcrit and MPV in women with GDM [20]. Liu G *et al.*, observed contradictory findings reporting no difference in platelet count, MPV and plateletcrit between GDM and normal pregnancy groups [21]. The size of platelet is related to platelet activity and is reflected by MPV, plateletcrit and PWD. Chronic low-grade inflammation in GDM leads to platelet activation and ultimately change in platelet indices. GDM develops when pancreatic function changes due to placental hormones during the second trimester may surpass the body's coping mechanisms. A study on platelet indices in healthy pregnancies and GDM found no difference in inflammatory markers during the first trimester. However, there was an inverse relationship between increasing MPV values and the likelihood of GDM. The analysis showed that while MPV has association with GDM, it is not sufficient as a standalone diagnostic marker [21].

CONCLUSIONS

Pregnant patients with GDM had higher mean plateletcrit values and lower platelet count as compared to non GDM pregnant patients indicating their potential role in its pathophysiology and prediction. Future prospective cohort studies of changes in inflammatory factors and platelet indices during first trimester followed-up to the end of pregnancy are suggested to establish its role as an early screening test to diagnose gestational diabetes mellitus. This study's single-center design, small sample size and retrospective nature may limit the generalizability of its findings.

Authors Contribution

Conceptualization: SC
Methodology: SC, RK, EF
Formal analysis: SC, ZK
Writing, review and editing: SC, ZK

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2742

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Impact of Dengue Fever on Pregnancy Outcomes: A Prospective Observational Study

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ARTICLE INFO

Keywords:
Pregnancy, Dengue Fever, Maternal outcome, Fetal outcome, Preterm delivery, Fetal growth restriction, Stillbirth

How to Cite:
Zubair, M., Azmat, S., Malik, M. K., Khan, R. A., Asghar, S., & Shahwar, D. (2025). Impact of Dengue Fever on Pregnancy Outcomes: A Prospective Observational Study: Impact of Dengue Fever on Pregnancy Outcomes . Pakistan Journal of Health Sciences, 6(1), 233-237. https://doi.org/10.54393/pjhs.v6i1.2742

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Received Date: 27th September, 2024
Acceptance Date: 19th January, 2025
Published Date: 31st January, 2025

ABSTRACT

Dengue in pregnancy has a profound negative impact on both maternal and fetal outcomes, leading to increased maternal and neonatal mortality. **Objective:** To evaluate the maternal and fetal outcomes in pregnant women affected by dengue fever. **Methods:** A prospective observational study was carried out at Niazi Welfare Foundation Teaching Hospital, Sargodha. Non probability convenient sampling technique was used to collect data from 36 pregnant women enrolled after confirming dengue infection through NS-1 and IgM/IgG tests. Maternal and fetal outcomes were monitored throughout pregnancy, labor, and the postpartum period. Data was analyzed using SPSS version 26.0 and presented in frequency and percentages. **Results:** Fetal complications observed in this study were, preterm delivery in 16 cases (44.4%), term delivery in 14 cases (39%), fetal growth restriction in 8 cases (22%), and intrauterine death in 6 cases (16.6%). Maternal outcomes included, postpartum hemorrhage in 6 cases (16.6%), 7 infected women (19.4%) were admitted to the ICU, and two mothers (5.5%) died. The frequency of neonatal admission to the NICU was 30.5%. **Conclusions:** Dengue infection in pregnancy is linked to heightened risk of maternal and perinatal morbidity and mortality. Timely clinical interventions are necessary to avoid devastating consequences.

INTRODUCTION

Dengue is a highly prevalent viral vector-borne disease globally, affecting nearly 390 million people annually, with approximately 96 million cases being symptomatic [1]. The dengue virus (DENV) is primarily transmitted by female mosquitoes of the Aedes aegypti species, Aedes albopictus play a secondary role in its transmission [2]. Pregnancy, being an immune-compromised state heightens the risk of dengue fever, particularly in highly endemic regions [3]. Dengue in pregnancy is associated with an increased risk of preterm delivery, low birth weight, and hemorrhage affecting both the mother and fetus [4]. However, timely and adequate rehydration therapy, administered either orally or intravenously, alongside blood and blood product transfusions, has been shown to significantly improve maternal outcomes [5]. Dengue during pregnancy has a profound negative impact on both maternal and fetal outcomes, with maternal mortality rates reaching as high as 15.9% [6]. Complications such as preterm labor and postpartum hemorrhage contribute significantly to maternal and neonatal morbidity [7]. To mitigate these risks, effective vector control strategies should be prioritized [8]. In dengue fever a rapid decline in platelet count is common, active intervention are necessary if the patient is in labor or experiencing a bleeding disorder [9]. Existing literature indicates a higher incidence of preterm deliveries, low birth weight infants,

DOI: https://doi.org/10.54393/pjhs.v6i1.2742

preeclampsia, and increased rates of cesarean sections in cases of dengue fever during pregnancy [10]. A study reported early delivery in 23.5% of cases and postpartum hemorrhage in 17.8% [11]. Among pregnant women infected with the dengue virus, premature birth occurred in approximately 10% of pregnancies, and low birth weight was observed in 18% of cases [12]. Perinatal complications included six neonatal intensive care unit admissions and one neonatal death [13]. Given these poor obstetric outcomes, early admission and prompt management of dengue in pregnancy are essential to mitigate risks [14]. To expand our understanding of the clinical profile, as well as maternal and fetal outcomes of dengue fever in pregnancy, and to investigate these issues in greater depth, a descriptive observational study was conducted.

This study aimed to evaluate the maternal and fetal outcomes of pregnant patients diagnosed with dengue fever.

METHODS

A prospective observational study was conducted at Niazi Welfare Foundation Teaching Hospital, Sargodha, from September 2023 to November 2024. Sample size for study was calculated on open Epi software based on Intrauterine fetal mortality (4%) from a previous research [16] at 95% confidence interval and 6.4% margin of error. Ethical approval for the study was obtained from the Institutional Review Board under approval number NM&DC-IRB-54 and Letter Ref No: IRB/NM&DC/586. A written informed consent was taken from all participants and they were informed about all the risk and benefits. Non probability consecutive sampling technique was used in this study. During study duration, all pregnant women presenting to the OPD, Emergency, and Labor Room with fever were screened for dengue. Those exhibiting dengue symptoms and testing positive through laboratory investigations for dengue NS1 (non-structural protein), IgM, or IgG antibodies were enrolled in the study. Relevant information was collected and documented in a structured Performa and Excel sheet. Symptoms of dengue including fever, myalgia, arthralgia, headache, retro-orbital pain, nausea, vomiting, and abdominal pain were recorded in Performa. Dengue-related parameters, including thrombocytopenia, hemoglobin levels (Hb%), total leukocyte count (TLC), and elevated ALT and AST levels, were recorded for analysis. Maternal outcomes observed included miscarriages, preterm birth, fetal growth restriction, placental abruption, stillbirth, mode of delivery (SVD/LSCS), postpartum hemorrhage (PPH), and the need for blood and platelet transfusions. Additional data such as age, parity, and gestational age were also documented. Pregnant women with known cases of ITP or fever caused by COVID-19, malaria, typhoid, or other infections were excluded from the study. Data were compiled in an Excel sheet and analyzed using SPSS version 26.0 and presented as frequency and percentage.

RESULTS

During the study period, a total of 36 pregnant women diagnosed as dengue positive through either Non-Structural Antigen 1 (NS-1 Ag) or dengue IgM and IgG tests were included. The mean age of the women was 24 ± 5.3 years, with an age range of 18 to 39 years. The majority of the pregnant patients with dengue were multiparous (24 cases) while 12 cases were primigravida. Regarding gestational age, 2 women (5.4%) were in their first trimester, 2 women (5.4%) were in the second trimester, and 32 women (86.4%) presented in the third trimester. The majority of the cases tested positive for dengue NS-1, IgM, and IgG (Table 1).

Table 1: Maternal Characteristics of Dengue Infected Pregnancy

Age	24 ± 5.3 (18-39) Years
Parity	
Primigravida	12 (33%)
Multigravida	24 (67%)
Gestational Age	
1st Trimester	2 (5.4%)
2nd Trimester	2 (5.4%)
3rd Trimester	32 (86.4%)
Dengue serology	
Dengue IgM +VE	27 (75%)
Dengue IgM -VE	9 (25%)
Dengue IgE +VE	31 (86%)
Dengue IgE -VE	5 (14%)
NS-1 Positive	19 (53%)
NS-1 Negative	12 (33.3%)
NS-1 Not Checked	5 (13.7%)

The clinical presentations in dengue patients included fever (92%), myalgia (53%), headache (69%), exanthem/rash (22%), nausea (25%), and vomiting (19.4%). Thrombocytopenia was observed in 30.5% of the pregnant women infected with dengue (Table 2).

Table 2: Clinical Manifestations of Dengue Fever in Pregnant Women

Clinical Manifestations	Frequency (%age)
Fever	33 (92%)
Myalgia	19 (53%)
Headache	25 (69%)
Exanthems	8 (22%)
Vomiting	7 (19.4%)
Nausea	9 (25%)
Conjunctivitis	5 (14%)
Arthritis	4 (11%)
Leucopenia	2 (5.5%)

DOI: https://doi.org/10.54393/pjhs.v6i1.2742

Thrombocytopenia	11 (30.5%)
Retro-orbital pain	2 (5.5%)

The feto-maternal outcomes recorded in the study were as follows: preterm delivery in 16 cases (44.4%), term delivery in 14 cases (39%), fetal growth restriction in 8 cases (22%), and intrauterine death in 6 cases (16.6%). Regarding the mode of delivery, 8 women (22%) had a vaginal birth, while 14 women (39%) underwent a cesarean section (LSCS). Postpartum hemorrhage occurred in 6 cases (16.6%), which was managed with blood transfusions and fresh frozen plasma. Platelet concentrate was administered to those with a platelet count below 50,000/mm^3. 1 pregnant woman with dengue underwent obstetric hysterectomy. Additionally, 7 infected women (19.4%) were admitted to the ICU, and two mothers (5.5%) died. The frequency of neonatal admission to the NICU was 30.5% (Table 3).

Table 3: Feto-Maternal Outcomes in Pregnant Women with Dengue

Variables	Frequency (%)
Preterm Delivery	16 (44.4%)
Term Delivery	14 (39%)
Fetal growth restriction	8 (22%)
Fetal distress	7 (19.4%)
Intra uterine death	16 (16.6%)
SVDs	8 (22%)
LSCS	14 (39%)
Miscarriages	2 (5.5 %)
Ectopic pregnancy	2 (5.5 %)
Postpartum hemorrhage	6 (16.6%)
Obstetric hysterectomy	1 (2.7%)
Maternal admission to ICU	7 (19.4%)
Neonatal admission to NICU	1 (30.5%)
Maternal death	2 (5.5%)

DISCUSSION

Dengue fever and other infections can easily affect pregnant women at any stage of pregnancy, as pregnancy is an immunosuppressive state, making it a significant risk factor for dengue. In this study, 36 pregnant females were diagnosed with dengue, average age of patients in current study was 24 ± 5.3 years, with a range from 18 to 39 years. This age range was lower than that observed in the study [15], but comparable to many studies in the literature, reflecting variations in the age of marriage and childbearing across different countries due to sociocultural and developmental factors. The period of dengue infection during pregnancy plays a crucial role in determining the type and severity of complications. If dengue fever occurs during the first trimester, there is an increased risk of abortion. In contrast, if dengue infection occurs in the third trimester, it is associated with a higher risk of low birth weight, preterm labor, and vertical transmission of the virus. In current study, the frequency of dengue infection was 5.4% in the first trimester, 5.4% in the second trimester, and 86.4% in the third trimester, which is consistent with previous studies [16]. However, some studies have reported a higher frequency of infection in the first trimester [17]. Additionally, another study found a 40.9% dengue infection rate in the second trimester [18]. In present study, the maternal and fetal outcomes of pregnant women suffering from dengue were examined. Preterm delivery occurred in 44.4% (16) of cases, term delivery in 39% (14), fetal growth restriction in 22% (8), fetal distress in 19.4% (7), and intrauterine death in 16.6% of patients. A high frequency of threatened preterm labor was also observed, with similar findings in other studies [19]. Impaired placental circulation, endothelial damage, and increased vascular permeability may contribute to intrauterine death (IUD) and fetal growth restriction. Early diagnosis of dengue infection, along with specific management, especially in the third trimester, can improve outcomes. Timely intervention may help prevent preterm labor, fetal growth restriction, and intrauterine death, ultimately improving maternal and fetal health. Among the 36 pregnant women in the study, 8 (22%) had a vaginal birth, and 14 (39%) underwent a cesarean section. The increased cesarean section rate may be attributed to fetal distress and the acute phase of infection, which aligns with findings from various studies in the literature [20]. In current study, postpartum hemorrhage (PPH) occurred in 16.6% of cases (6 women), with 1case requiring obstetric hysterectomy due to severe PPH. Critical conditions in mothers led to ICU admissions for 7 (19.4%) women, and 2 (5.4%) maternal deaths were recorded. In comparison, the study reported ICU admissions for 32% of mothers and a maternal mortality rate of 14% [16]. A systematic review and meta-analysis found that dengue virus infection in pregnant women was associated with increased maternal mortality and neonatal deaths when compared to pregnant women without dengue [21]. A research study reported perinatal complications, including six nursery admissions and one neonatal death [15], highlighting the need for early admission and prompt management due to poor obstetric outcomes. In current study, most pregnant patients required clinical management during the third trimester and benefited from multidisciplinary care. Similar observations were made in other studies [22]. Current study provides valuable insights for clinical implications because timely intervention along-with proper fluid management and careful monitoring of the disease can significantly enhance maternal and fetal outcomes in pregnancy. Implementation of vector control strategies is crucial to reduce maternal and fetal morbidity and mortality. This was a single center observational study.

DOI: https://doi.org/10.54393/pjhs.v6i1.2742

There is need for large scale studies in other regions to enhance generalizability.

CONCLUSIONS

Dengue fever during pregnancy is linked to adverse outcomes, including stillbirth, preterm delivery, fetal growth restriction, postpartum hemorrhage, maternal ICU admission, and increased maternal and neonatal mortality. Therefore, it is regarded as a high-risk condition requiring specialized management, timely intervention, and vigilant monitoring to prevent complications and achieve better outcomes. Emphasis on early detection and timely management is critical in reducing the morbidity and mortality associated with dengue fever for both mother and fetus.

Authors Contribution

Conceptualization: MZ
Methodology: MZ, RAK, DES
Formal analysis: SA, MKM, SA
Writing, review and editing: MKM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2487

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Preliminary Investigation of AI Adoption among Healthcare Practitioners in Pakistan

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ARTICLE INFO

Keywords:
Artificial Intelligence (AI), Healthcare Professionals, Medical Specialties, Professional Experience

How to Cite:
Habib, S., Khan, Z. U., Nawaz, A., Salman, R., Saeed, U., Saeed, S., & Habib, T. (2025). Preliminary Investigation of AI Adoption among Healthcare Practitioners in Pakistan: AI Adoption among Healthcare Practitioners . Pakistan Journal of Health Sciences, 6(1), 238-243. https://doi.org/10.54393/pjhs.v6i1.2487

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Received Date: 20th November, 2024
Acceptance Date: 17th January, 2025
Published Date: 31st January, 2025

ABSTRACT

Artificial intelligence (AI) is progressively revolutionizing healthcare systems globally, delivering innovative solutions for diagnosis, treatment, and operational efficiency. However, its acceptance among healthcare providers in Pakistan remains unexplored. **Objectives:** To determine the awareness of AI adoption among healthcare practitioners in Pakistan. **Methods:** A cross-sectional survey was conducted from May to July 2024, using Google Surveys to collect data from 321 healthcare professionals across various medical specialties in Pakistan. Structured questionnaires were distributed electronically, and the responses were analyzed using Chi-Square tests to determine associations between AI knowledge, attitudes, and professional characteristics. **Results:** The majority of respondents (61.1%) were female, with 53.6% aged 20-29. Most had 1-5 years of experience (48.3%) and worked in tertiary healthcare institutions, with 52.3% in the public sector and 47.7% in the private sector. Only 7.6% considered AI of no value, while 24.5% saw it greatly improving diagnostic accuracy, 17% aiding patient diagnosis, and 15.2% in treatment planning. **Conclusions:** This study concludes that there is a crucial knowledge gap and poor AI adoption among Pakistan's healthcare practitioners, which is compounded by insufficient training and technological constraints. Addressing these challenges is critical for attaining AI's potential in improving healthcare outcomes.

INTRODUCTION

Applications of Artificial intelligence (AI) in medical field globally have shown diverse horizons for rapid and accurate diagnosis, overall patient management and improved medical teaching [1]. The potential of AI to analyze variety of diverse data pertaining to clinical and medical education, permits rapid evaluation and early diagnosis of underlying disorders [2]. This potential has revolutionized the domain of prompt patient management, prevention protocols in medicine and updated health care provision [3]. AI has readily demonstrated healthy and accurate progress encompassing virtually all domains of health-care provision by introducing innovative technologies, including Internet of Things (IoT), Cloud technologies, and Wearable devices, to fulfil the critical demands in the healthcare field [4]. AI is rapidly being utilized worldwide to enhance medical applications and improve overall patient outcomes especially in developed countries. [5, 6]. On the other hand, in developing countries, the adoption and subsequent implementation of AI in health-care practices is subject to a variety of technical and administrative challenges [7]. In Pakistan, the employment of AI in the healthcare sector appears to be in its embryonic stage,

DOI: https://doi.org/10.54393/pjhs.v6i1.2487

with existing applications being generally targeted for diagnostics and the management of extensive patient data. Although the potential of AI in service delivery is well appreciated by most healthcare workers and physicians, it still faces hindrances, such as infrastructural limitations and a lack of specific AI training among health professionals [8]. The applications of AI in medical education and faculty engagement are equally pivotal [9]. This study also encompasses the adoption of AI among medical faculty in medical colleges in Pakistan, as it explores how AI technologies are integrated into the curriculum and advanced teaching methodologies. Further knowledge of how faculty members adopt and perceive AI can provide insights into the preparedness of future medical practitioners and the potential progress in educational methodologies [10]. Despite its significant potential, the comprehensive integration of AI in healthcare services appears to be an upheaval task. Similar studies have effectively highlighted the new challenges faced by the medical practitioners and faculties in adopting and utilizing AI technologies [11]. Along the same lines, few studies have emphasized the necessity to create developed frameworks to improve the implementation of AI in providing up to mark healthcare services and medical education [12].

This study aims to focus on how healthcare professionals in different hospital settings in Pakistan understand and utilize AI. The study assesses their baseline knowledge of AI, examines current AI applications in patient care, hospital settings, and educational environments, and simultaneously explores their attitudes towards adopting and integrating AI in patient care and medical teaching.

METHODS

A cross-sectional, questionnaire-based survey was conducted to determine the level of AI adoption among healthcare professionals and medical faculty, in Pakistan's private and tertiary care facilities. The study was carried out from May to July 2024. Pertinent data regarding Knowledge, Attitudes, and Practices (KAP) was summated through the survey, disseminated via Google survey forms to gather baseline information from medical specialists, clinical practitioners, and medical faculty regarding knowledge, impact, and practice of AI. The survey questionnaire was distributed through professional networks and social media channels dedicated to a spectrum of medical professionals in Pakistan. All the respondents were preliminarily informed about the anonymity and confidentiality of survey participation. Principles of research ethics and relevant legal requirements were fully complied with, and duly considered during the entire survey, and focused on the baseline knowledge and applications of AI among the given population. The calculated sample size at 50% probability, with 6% margin of error and 95% confidence interval, and 20% non-response rate the sample size was 321. All the results obtained were evaluated using SPSS version 26.0, a bivariate analysis was conducted. Chi-square test was employed for this analysis, including all the completed survey responses. This study adhered to all relevant ethical requirements and approved by the Institutional Review Board (IRB) of RLKU medical and dental college (Ref no: RLKUMC/IRB/0023/24). Prior to their participation in the trial, all subjects provided their informed consents, while the participants were assured about the privacy and confidentiality of their responses, and special information.

RESULTS

Data were obtained from 321 healthcare experts in Pakistan. The majority of responders (61.1%) were female, with 53.6 percent being between the ages of 20 and 29. Almost half of them possessed one to five years of professional experience (48.3%). Most respondents worked in tertiary healthcare institutions, with 22.4% in affiliated teaching hospitals and 17.4% in public healthcare facilities, such as DHQ (District Headquarters Hospital) and THQ (Tehsil Headquarters Hospital). Hospitals in the private sector, which are comprised of clinics and general practitioners, comprise 16.2% of respondents, while an equal number (16.5%) work in rural health centers (RHC) and basic health units (BHU). Medical faculty accounted for 14% of responders while teaching hospitals affiliated with medical colleges contributed about 11.9%. In terms of overall sector distribution, about half of the respondents (52.3%) worked in the public sector, whereas 47.7% worked in the private sector (Table 1).

Table 1: Socio-Demographic Characteristics of Study Participants (n=321)

Variable	Category	Frequency (%)
Gender	Male	122 (38)
	Female	196 (61.1)
	Preferred Not to Say	03 (0.9)
Age	20-29 Years	172 (53.6)
	30-39 Years	104 (32.4)
	40-49 Years	23 (7.2)
	50-59 Years	12 (3.7)
	60-69 Years	10 (3.1)
Medical Specialty	Medicine and Allied	131 (40.8)
	GP and Family Medicine	83 (25.9)
	Surgery and Allied	47 (14.6)
	Medical Faculty	45 (14)
	Public Health and Administration	15 (4.7)
Professional Experience	Less than 1 Year	60 (18.7)
	1-5 Years	155 (48.3)
	6-10 Years	53 (16.5)

DOI: https://doi.org/10.54393/pjhs.v6i1.2487

	11-20 Years	38 (11.8)
	More than 20 Years	15 (4.7)
Professional Experience	Private Sector	153 (47.7)
	Government Sector	168 (52.3)
Professional Setting	Private Care Health Facility (Teaching Hospital)	38 (11.9)
	Private Care Health Facility (Clinic/GP)	52 (16.2)
	University /Medical College	43 (13.4)
	Rural Health Care (RHC)/Basic Health Unit (BHU)	53 (16.5)
	Tertiary Healthcare Facility (DHQ/THQ)	56 (17.4)
	Tertiary Healthcare facility (teaching hospital)	79 (24.6)

The study investigated respondents' awareness and comprehension of AI technology in their respective fields, and it was observed that only 44% had a basic knowledge of AI. These results reveal that while a considerable majority of respondents have at least a basic comprehension of AI, a sizeable proportion of health professionals lack knowledge, with only a handful holding advanced competence in this technology. Respondents were familiar with a variety of AI applications, with diagnostic tools (32.1%), medical teaching (26.4%), patient data management (23.9%), treatment planning (21.8%), robotic procedures (19.1%), and administrative chores (15.5%) being the most well-known. However, 25.5% of respondents had no awareness of it (Figure 1).

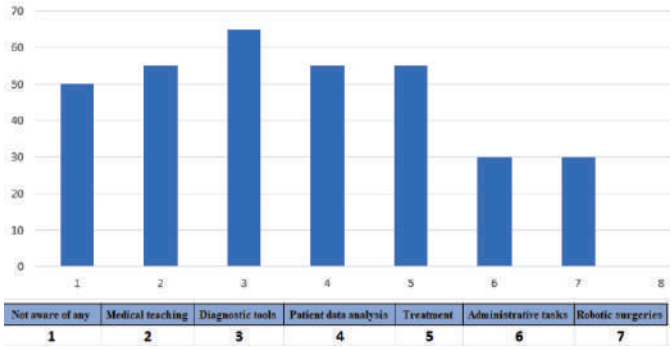

Figure 1: Awareness of AI Applications Among Healthcare Professionals

The study primarily focused on respondents' degree of AI training and found that just 6.3% got considerable formal training. Notably, the majority, 56.6%, had received no training in AI applications in the medical field. Nearly half of the respondents (48.6%) had never utilized any AI application in their medical practice. Among those who had utilized this technology, the most common users were medical teaching (14.5%) and diagnostic tools (14.5%). Other popular applications included AI imaging and patient data management (9.7%) and AI treatment planning (11.8%) (Figure 2).

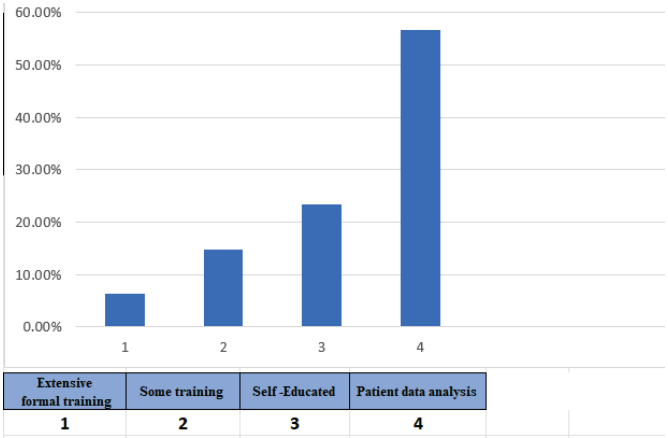

Figure 2: AI Training Status Among Health Professionals

Only 7.6% of respondents considered AI to be of no value in their profession. In contrast, 12.2% saw the effectiveness of AI in medical teaching as pivotal. A larger proportion, 17%, were of the view that AI considerably assists in patient diagnosis, whereas 15% of respondents saw managing patient records as a crucial benefit, while 15.2% viewed AI's role in treatment planning as considerably applicable. A substantial number of respondents (24.5%) stated that AI considerably increases diagnostic accuracy, whereas 38.7% thought it improved accuracy slightly. In addition, 16.9% of interviewees said AI may aid in the development of concepts and learning skills. Healthcare providers' opinions toward AI adoption may be influenced by their working environment. Furthermore, the analysis of AI applications in various professional fields indicating that medical professionals and faculty possessing larger working experience have adopted AI better compared with those having less professional experience in their fields (Table 2).

Table 2: Health Professionals perceptions of AI applications in Medical Practice

AI Application	Percentage of Respondents
AI considered of no value in profession	7.60%
AI effectiveness in medical teaching	12.20%
AI assists in patient diagnosis	17%
AI in managing patient records	15%
AI's role in treatment planning	15.20%
AI considerably increases diagnostic accuracy	24.50%
AI improves diagnostic accuracy slightly	38.70%
AI aids in the development of concepts and learning skills	16.90%

DISCUSSION

Adoption and application of AI in improvising diagnostic and other healthcare benefits are rapidly progressing worldwide, thus positively contributing to effective treatment of the patients [13]. Our study focusses to evaluate the knowledge, attitudes and behaviors of diverse

DOI: https://doi.org/10.54393/pjhs.v6i1.2487

healthcare professionals and medical faculty toward AI in Pakistan. These variable findings are strongly influenced by professional experiences and medical specialties. On the contrary, medical specialists demonstrated better levels of adoption of AI, whereas, general medical practitioners showed broader utilization of AI expertise, which is probably owed to better focused training and exposure in their disciplines. Highly experienced medical professionals mostly remain cautious, probably owing to their established habits and routine, or enduring profound doubts about the efficacy of newer diagnostic and management technologies [14].This generational difference emphasizes the importance of ongoing professional and faculty development programs designed to meet more experienced practitioners' concerns while utilizing the passion and adaptability of younger professionals. Younger professionals' knowledge of developing technology and their more adaptable approach to breakthroughs are likely to contribute to their more positive views of AI. Specific 'mentorship' programs can potentially address the specific hindrances faced by highly experienced medical practitioners, thereby, motivating them to adopt and utilize AI in respective medical fields [15]. On the contrary, a study conducted in Hungary reveals that older individuals have higher digital health literacy than younger individuals [16]. Regarding the attitudes of healthcare professionals about use of AI, majority of healthcare professionals were considerably optimistic about the potential of AI to improve overall patient care, diagnostic accuracy, and better and effective administrative tactics. Similarly, a study conducted in Seoul, South Korea, shows that most medical professionals trust AI devices to aid the healthcare sector [17]. However, these optimistic views were encompassed by considerable concerns about data privacy, job displacement, and reliability of AI in diagnosis of complex clinical disorders [18]. The positive attitudes observed in tertiary care settings were probably influenced by increased exposure to advanced research, better access to AI resources, and frequent backing-up by organizational support for adopting the innovative technologies [19]. On the other hand, in primary care settings, due to lack of required resources and back-up support, there exists a skepticism about the utility and overall benefits of AI in respective domains [20]. Regarding practical applications, the study observed that AI technologies are currently being utilized in a very limited range within private clinical practice. Tertiary care facilities and academic institutions had much better and effective adoption rates compared with private clinics and rural health centers [21]. Routinely scheduled workshops, online training courses on AI, and practical hands-on sessions are effective options for assuring accessibility to healthcare professionals in private sectors or in less privileged areas [22].

CONCLUSIONS

This study concludes that although the basic knowledge and awareness of AI is consistently present among medical professionals and faculty, but considerable lack of expertise exists, which exhibits a major gap in applications of AI in medical practice and teaching. Most of the practitioners are unaware of practical applications of AI in their respective domains, and they remain skeptic about effective applications of AI in diagnosis, patient management, medical teaching and administrative accuracy. To overcome the major knowledge gaps and limitations highlighted in this study, extensive AI training programs for Pakistan's healthcare providers must be implemented. These programs should concentrate on the practical uses of AI in medical practice, diagnosis, and education. Encouraging cooperation between healthcare practitioners and AI developers can help to create user-friendly, effective AI systems.

Authors Contribution

Conceptualization: SH, AN
Methodology: SH, AN
Formal analysis: SH, RS, SS
Writing review and editing: ZUK, RS, TH, US

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2623

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Evaluating the Diagnostic Accuracy of High-Resolution Computed Tomography in Detecting COVID-19: A Comparative Study Using Polymerase Chain Reaction as the Gold Standard

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ARTICLE INFO

Keywords:
High-Resolution Computed Tomography, COVID-19 Diagnosis, Polymerase Chain Reaction, Sensitivity and Specificity, Diagnostic Accuracy

How to Cite:
Saleem, R., Khan, S., Nowsherwan, ., Shuaib, S. L., Syed, R., & Sattar, M. (2025). Evaluating the Diagnostic Accuracy of High-Resolution Computed Tomography in Detecting COVID-19: A Comparative Study Using Polymerase Chain Reaction as the Gold Standard: Diagnostic Accuracy in Detecting COVID-19. Pakistan Journal of Health Sciences, 6(1), 243-248. https://doi.org/10.54393/pjhs.v6i1.2623

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Received date: 1st December, 2024
Acceptance date: 22nd January, 2025
Published date: 31st January, 2025

ABSTRACT

Pakistan has faced three waves of COVID-19, each intensifying the strain on diagnostic resources. Delayed diagnoses during these waves hindered timely treatment and contributed to disease transmission. **Objective:** To evaluate the diagnostic accuracy of High-Resolution Computed Tomography (HRCT) in detecting COVID-19, using Polymerase Chain Reaction (PCR) as the gold standard. **Methods:** A cross-sectional study was conducted from November 26, 2021, to May 26, 2022, at the Department of Radiology, Northwest General Hospital & Research Centre, Peshawar. The study included 234 clinically suspected COVID-19 patients, aged 20–60 years, of both genders. Chest CT scans were performed, and results were compared with PCR. Data were analyzed using SPSS version 20, with $p<0.05$ considered significant. **Results:** Of the 234 patients, 133 tested positive for COVID-19 via PCR, while 101 were negative. HRCT demonstrated an overall accuracy of 73.9%, sensitivity of 72.9%, specificity of 75.2%, positive predictive value of 79.5%, and negative predictive value of 67.8%. Chi-square analysis revealed significant correlations of HRCT accuracy with BMI ($p=0.004$) and illness duration ($p=0.010$) but not with age ($p=0.956$) or gender ($p=0.113$). **Conclusions:** HRCT shows reasonable sensitivity, specificity, and overall accuracy as a diagnostic tool for COVID-19. Its performance improves in women, those with higher BMI, and longer illness duration but should not replace PCR testing due to its modest negative predictive value.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of COVID-19, a highly contagious and pathogenic viral infection initially identified in Wuhan, China [1]. COVID-19 quickly spread to 213 nations, severely impacting the United States, Italy, Spain, and the United Kingdom. Pakistan reported its first case in Karachi in February 2020, ranking among the top 20 most affected nations [2]. On March 12, 2020, the World Health Organization declared the outbreak a pandemic [3]. By April 20, 2020, over 2.4 million cases had been confirmed in 205 countries [4]. SARS-CoV-2 infections range from asymptomatic to severe, with severe cases associated with high viral loads, inflammation, and immunological dysregulation, often worsened by aging or comorbidities like diabetes and hypertension [5, 6]. Chronic complications such as fatigue and cognitive dysfunction are also recognized [7]. High-Resolution Chest Computed Tomography (HRCT) has demonstrated excellent sensitivity and specificity in detecting lung involvement and diagnosing COVID-19 [8]. With a

DOI: https://doi.org/10.54393/pjhs.v6i1.2623

sensitivity of 97% in identifying COVID-19, HRCT aids early detection, especially in cases presenting before clinical symptoms [9]. Its diagnostic patterns, including Ground-Glass Opacities (GGO), consolidation, and pleural effusions, are critical in managing the disease [10, 11]. However, the American College of Radiology advises caution in using HRCT routinely for diagnosis [4]. Pakistan's healthcare system, burdened during COVID-19 waves, faced limited diagnostic resources. While PCR remains the gold standard, HRCT offers quick results, aiding timely clinical decisions [12, 13].

This study evaluated HRCT's diagnostic accuracy using PCR as the gold standard in Peshawar, Khyber Pakhtunkhwa, providing insights for regions with limited PCR access.

METHODS

A cross-sectional study was conducted between November, 2021, and May, 2022, in the Radiology Department of Northwest General Hospital and Research Centre, Peshawar. The sample size was determined to include 234 participants, calculated based on assumptions of HRCT sensitivity at 92%, specificity at 23%, and a prevalence rate of 40.4%, using a 95% confidence level and a 7% margin of error [14]. Non-probability sequential sampling was employed to select participants. Patients aged 20–60 years, irrespective of gender, were eligible if they met the operational definition of COVID-19 infection. Exclusion criteria included individuals who had undergone chest surgery within six months or were unwilling to undergo PCR testing. Approval for the study was granted by the Institutional Review Board of Northwest General Hospital and Research Centre, Peshawar (Ref. No: NWGH/Res/Ethical approval/1724). All participants provided informed written consent after the study's purpose, methods, and data usage were explained to them. A standardized proforma was used to record demographic data such as age and gender. Chest HRCT scans were conducted by a radiologist with over five years of expertise, following international guidelines. Blood samples measuring five microliters were collected post-HRCT and sent for PCR testing to confirm COVID-19 infection. Data analysis was performed using SPSS version 20.0. Descriptive statistics were computed for demographic and clinical variables. Continuous variables such as age, BMI, and symptom duration were expressed as means with standard deviations, while categorical variables including gender, HRCT findings, and PCR results were presented as frequencies and percentages. The diagnostic accuracy of HRCT was calculated using the formula: Accuracy = (a+d)/(a+b+c+d), where "a" represents true positives, "b" false positives, "c" false negatives, and "d" true negatives. Stratification by variables such as age, gender, BMI, and symptom duration was conducted, with correlations assessed through chi-square testing ($p<0.05$ considered statistically significant).

RESULTS

There were 234 people who signed up for the study, and their average age was 52.80 years±5.30 years. The average height of the participants was 170.46 ± 8.00 cm, and their average weight was 71.85 kg±6.45 kg. The BMI was 24.82 kg/m^2 ±2.74 kg/m^2 on average. Furthermore, the illness lasted an average of 5.07 days ±1.03 days. Table 1 provides a summary of the study participants' clinical and demographic traits.

Table 1: Demographic characteristics of the Participants

Variables	Mean ± SD
Age (Years)	52.80 ± 5.298
Weight (Kg)	71.85 ± 6.454
Height (cm)	170.46 ± 8.003
BMI (Kg/m^2)	24.822 ± 2.742
Duration of Disease (Days)	5.07 ± 1.029

According to the age group distribution, 33.3% of the participants (n=78) were over 40, while the majority (66.7%, n=156) were 40 years of age or younger. Women made up 26.5% (n=62) of the sample, while men made up 73.5% (n=172). Of the individuals, 83.8% (n=196) had a BMI of more than 22 kg/m^2, while 16.2% (n=38) had a BMI of less than 22 kg/m^2. In terms of symptom duration, Figure 1 shows that 41.5% (n=97) experienced symptoms that lasted less than five days, whereas 58.5% (n=137) had symptoms that lasted five days or more.

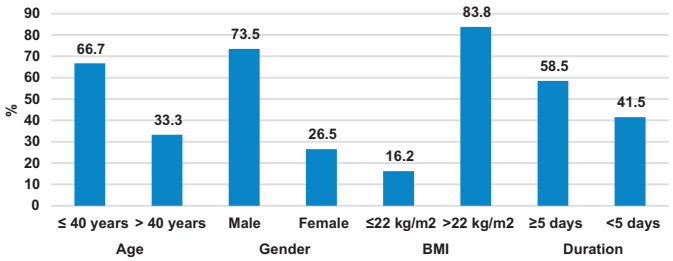

Figure 1: Demographic and Clinical Characteristics of the Participants Distribution

Using Polymerase Chain Reaction (PCR) as the gold standard, table 2 shows the diagnostic performance of High-Resolution Computed Tomography (HRCT) in detecting COVID-19. With a sensitivity of 72.9%, HRCT detected 122 cases as positive out of the 234 participants, 97 of which were true positives. HRCT had a specificity of 75.2%, properly identifying 76 of 101 negative cases. Comparatively speaking, 43.2% of participants were PCR-negative and 56.8% of participants were PCR-positive. Twenty-five percent of HRCT-positive cases were PCR-negative, while 79.5% were PCR-positive. In contrast,

DOI: https://doi.org/10.54393/pjhs.v6i1.2623

32.1% and 67.9% of HRCT-negative cases were PCR-positive and PCR-negative, respectively. The probability that a positive HRCT result would translate into a true positive is known as the Positive Predictive Value (PPV), and it was 79.5%. The likelihood that a negative HRCT result is actually negative, or the Negative Predictive Value (NPV), was 67.8%. HRCT has a 73.9% overall diagnostic accuracy.

Table 2: Diagnostic Accuracy of High-resolution Computed Tomography vs PCR as Gold Standard

Variables	HRCT Result	PCR Positive Frequency (%)	PCR Negative Frequency (%)	Total	Diagnostic Metrics
Overall	Positive	97 (79.5%)	25 (20.5%)	122	Sensitivity: 72.9% (65.5–79.4%)
	Negative	36 (32.1%)	76 (67.9%)	112	Specificity: 75.2% (66.5–82.6%)
	Total	133	101	234	PPV: 79.5% (71.7–85.8%)

Across various age ranges, the diagnostic accuracy of HRCT in identifying COVID-19 was evaluated. HRCT had a sensitivity of 73.6%, specificity of 70.7%, positive predictive value (PPV) of 77.9%, Negative Predictive Value (NPV) of 65.7%, and overall accuracy of 72.4% in patients aged 40 years or younger (n=156). Of the people who tested positive for HRCT, 22.1% were false positives and 77.9% were real positives. Of those who tested negative for HRCT, 65.7% were real negatives and 34.3% were false negatives. HRCT showed a sensitivity of 71.4%, specificity of 83.3%, PPV of 83.3%, NPV of 71.4%, and accuracy of 76.9% in people over 40 (n=78). 83.3% of those who tested positive for HRCT were true positives, whereas 16.7% were false positives. Of those who tested negative for HRCT, 71.4% were real negatives and 28.6% were false negatives. Male and female HRCT diagnostic accuracy in identifying COVID-19 was assessed independently. The HRCT's sensitivity, specificity, and positive predictive value (PPV) were 69.2%, 69.1%, 77.4%, and 59.5%, respectively, for males (n=172). In males, the overall accuracy was 69.2%. 22.6% of the male HRCT-positive individuals were false positives, whereas 77.4% were real positives. Of the guys who tested negative for HRCT, 40.5% had true negative results and 59.5% had false negative results. The HRCT demonstrated superior diagnostic performance in females (n=62), with 86.2% sensitivity, 87.9% specificity, 86.2% PPV, and 87.9% NPV. For females, the overall accuracy was 87.1%. Of the females who tested positive for HRCT, 13.8% were false positives and 86.2% were real positives. Among HRCT-negative females, 12.1% were true positives, andwere true negatives. A chi-square test was performed to evaluate the association between HRCT diagnostic outcomes and the variables of age and gender. For age, the analysis yielded a p-value of 0.956, indicating no statistically significant correlation between age groups (≤40 years and >40 years) and HRCT results. Similarly, for gender, the p-value was 0.113, suggesting no statistically significant relationship between gender (male and female) and HRCT results. These findings imply that neither age nor gender had a significant impact on the diagnostic performance of HRCT in this study, as shown in table 3.

Table 3: Comparative Analysis of Diagnostic accuracy of HR-CT among the Age and Gender Groups

Variables		HRCT	PCR				p-Value
			Positive Frequency (%)	Negative Frequency (%)	Total Frequency (%)	Diagnostic Performance Metrics	
Age	≤40 Years	Positive	67 (77.9%)	19 (22.1%)	86 (100%)	Sensitivity= 73.6%	0.956
						Specificity = 70.7%	
		Negative	24 (34.3%)	46 (65.7%)	70 (100%)	PPV= 77.9%	
		Total	91 (58.3%)	65 (41.7%)	156 (100%)	NPV= 65.7%	
						Accuracy=72.4%	
	>40 Years	Positive	30 (83.3%)	6 (16.7%)	36 (100%)	Sensitivity= 71.4%	
						Specificity = 83.3%	
		Negative	12 (28.6%)	30 (71.4%)	42 (100%)	PPV= 83.3%	
		Total	42 (53.8%)	36 (46.2%)	78 (100%)	NPV= 71.4%	
						Accuracy= 76.9%	
Gender	Male	Positive	72 (77.4%)	21 (22.6%)	93 (100%)	Sensitivity= 69.2%	0.113
						Specificity =69.1%	
		Negative	32 (40.5%)	47 (59.5%)	79 (100%)	PPV= 77.4%	
						NPV=59.5%	
						Accuracy=69.2%	
		Total	104 (60.5%)	68 (39.5%)	172 (100%)	Sensitivity= 86.2%	
	Female	Positive	25 (86.2%)	4 (13.8%)	29 (100%)	Specificity =87.9%	
		Negative	4 (12.1%)	29 (87.9%)	33 (100%)	PPV= 86.2%	
		Total	29 (46.8%)	33 (53.2%)	62 (100%)	NPV=87.9%	
						Accuracy=87.1%	

DOI: https://doi.org/10.54393/pjhs.v6i1.2623

When stratified by BMI, the diagnostic accuracy of HRCT varied significantly. For individuals with a BMI of ≤22.0 kg/m^2 (n=38), HRCT demonstrated a sensitivity of 33.3%, specificity of 100.0%, PPV of 100.0%, and NPV of 76.5%, with an overall accuracy of 78.9%. In this group, all HRCT-positive individuals were true positives (100%), while 23.5% of HRCT-negative individuals were false negatives. In contrast, for individuals with a BMI >22.0 kg/m^2 (n=196), HRCT sensitivity increased to 76.8%, and specificity was 66.7%, with a PPV of 78.8% and NPV of 64.1%. The overall accuracy was slightly lower at 72.9%, with 78.8% of HRCT-positive individuals being true positives and 21.2% being false positives. Among HRCT-negative individuals, 35.9% were false negatives, and 64.1% were true negatives. Similarly, disease duration influenced HRCT diagnostic performance. For individuals with a disease duration ≤5 days (n=137), HRCT sensitivity was 65.5%, specificity was 82.9%, with a PPV of 88.0% and an NPV of 55.7%. Overall accuracy in this group was 71.5%. Among HRCT-positive individuals, 88.1% were true positives, and 11.9% were false positives, while 44.3% of HRCT-negative individuals were false negatives, and 55.7% were true negatives. For disease duration >5 days (n=97), HRCT sensitivity increased to 88.4%, while specificity decreased to 68.5%. The PPV was 69.1%, and the NPV was 88.0%, with an overall accuracy of 77.3%. In this group, 69.1% of HRCT-positive individuals were true positives, and 30.9% were false positives. Among HRCT-negative individuals, 11.9% were false negatives, and 88.1% were true negatives. A chi-square test revealed statistically significant associations between HRCT diagnostic outcomes and BMI categories (p=0.004) as well as disease duration (p=0.010). These findings suggest that BMI and disease duration are important factors influencing HRCT's diagnostic efficacy in detecting COVID-19 (Table 4).

Table 4: Comparative Evaluation of HR-CT Diagnostic accuracy across BMI and Disease Duration

Variables		Diagnostic Performance Metrics	HRCT	PCR			p-Value
				Positive Frequency (%)	Negative Frequency (%)	Total Frequency (%)	
BMI (kg/m^2)	≤22.0	Sensitivity= 33.3%	Positive	4 (100%)	0 (0.0%)	4 (100%)	0.004
		Specificity=100.0%	Negative	8 (23.5%)	26 (76.5%)	34 (100%)	
		PPV=100.0%	Total	12 (31.6%)	26 (68.4%)	38 (100%)	
		NPV= 76.5%					
		Accuracy=78.9%					
	>22.0	Sensitivity =76.8%	Positive	93 (78.8%)	25 (21.2%)	118 (100%)	
		Specificity= 66.7%	Negative	28 (35.9%)	50 (64.1%)	78 (100%)	
		PPV= 78.8%					
		NPV= 64.1%	Total	75 (38.3%)	196 (100%)	75 (38.3%)	
		Accuracy= 72.9%					
Duration of Disease	≤5 Days	Sensitivity= 65.5%	Positive	59 (88.1%)	8 (11.9%)	67 (100%)	0.010
		Specificity= 82.9%	Negative	31 (44.3%)	39 (55.7%)	70 (100%)	
		PPV= 88.0%					
		NPV= 55.7%	Total	90 (65.7%)	47 (34.3%)	137 (100%)	
		Accuracy=71.5%					
	>5 Days	Sensitivity= 88.4%	Positive	38 (69.1%)	17 (30.9%)	55 (100%)	
		Specificity= 68.5%	Negative	5 (11.9%)	37 (88.1%)	42 (100%)	
		PPV= 69.1%					
		NPV= 88.0%,	Total	43 (44.3%)	(55.7%)	97 (100%)	
		Accuracy= 77.3%					

DISCUSSION

The gold standard for evaluating the diagnostic precision of High-Resolution Computed Tomography (HRCT) in identifying COVID-19 is Polymerase Chain Reaction (PCR). HRCT showed sensitivity, specificity, PPV, NPV, and accuracy of 72.9%, 75.2%, 79.5%, 67.8%, and 73.9%, respectively. These results suggest HRCT is a reliable diagnostic tool, especially where PCR testing is unavailable. Most participants were middle-aged, with a mean age of 52.8 ± 5.3 years, BMI of 24.8 ± 2.7 kg/m^2, and illness duration of 5.1 ± 1.0 days [15]. A total of 74% of patients showed the crazy-paving pattern on HRCT scans, consistent with prevalence rates of 12.5–36% reported in the literature [16, 17]. Pleural and pericardial effusions were observed in 10% and 5% of cases, aligning with reported rates of 4.8–8.4% [16, 18]. The posterior segments of the right upper lobe and posterior basal segments of both lungs were most affected, consistent with findings from previous studies [14, 16, 19]. Comparisons with studies by Hanif N *et*

DOI: https://doi.org/10.54393/pjhs.v6i1.2623

al., revealed similarities and discrepancies in diagnostic performance. Hanif N *et al.*, reported lower specificity (23%) but higher sensitivity (92%) compared to these findings [2]. This may have indicated challenges in distinguishing COVID-19 from other conditions, leading to more false positives in their study [20]. Fang Y *et al.*, reported higher sensitivity (97%) but lower specificity (25%) than these results, indicating HRCT's strong detection capabilities but limited specificity in their study [8]. Deng *et al.*, reported sensitivity, specificity, and accuracy of 85.71%, 60.94%, and 65.38%, respectively, showing variability in diagnostic metrics [21]. These findings demonstrated that females had higher diagnostic accuracy (87.1%) than males (69.2%), with females showing greater sensitivity (86.2%) and specificity (87.9%). Hanif N *et al.*, reported higher sensitivity (100%) in males, highlighting demographic differences [2]. We observed significant associations between HRCT accuracy and BMI (p=0.004) and disease duration (p=0.010), which Hanif N *et al.*, did not address [2]. The sensitivity (72.9%) and PPV (79.5%) in this study highlight HRCT's utility in identifying true positives but were lower than metrics reported by Ali *et al.*, (91% sensitivity, 83% PPV) [22]. Ali *et al.*, also reported higher specificity (90%) and NPV (84%), surpassing these findings of 75.2% and 67.8%, respectively [22]. Differences in population demographics, imaging protocols, and diagnostic criteria likely contribute to these variations [22]. This study underscored HRCT's value as a complementary diagnostic tool for COVID-19, particularly in resource-constrained settings. However, the lower specificity and NPV emphasize the importance of confirmatory PCR testing. Limitations include the single-center design, small sample size, and potential observer bias. Future research with larger multicenter cohorts and multiple radiologists could enhance generalizability and reliability. Additionally, studies exploring HRCT's role in predicting disease severity and outcomes could further establish its clinical utility.

CONCLUSIONS

With an overall accuracy of 73.9%, a sensitivity of 72.9%, and a specificity of 75.2%, HRCT proves to be a valuable diagnostic tool for COVID-19. Its diagnostic performance is significantly influenced by gender, BMI, and disease duration. Higher accuracy was observed in females, individuals with a BMI over 22 kg/m^2, and those with a disease duration longer than five days, while age showed no significant impact. HRCT plays a complementary role in resource-limited settings, particularly when PCR testing is unavailable. However, confirmatory PCR testing remains essential due to HRCT's moderate negative predictive value. Future studies with larger and more diverse populations are needed to validate these findings and explore additional factors affecting diagnostic performance.

Authors Contribution

Conceptualization: RS
Methodology: RS, SK, N, SLS, MS
Formal analysis: RS, SK, N, RS, MS
Writing, review and editing: RS, SK, N, SLS, RS, MS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2165

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Prevalence of Nonalcoholic Fatty Liver Disease among Obese Patients Presented in Liaquat University Hospital Hyderabad/Jamshoro

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ARTICLE INFO

Keywords:
NAFLD, Non-Alcoholic Fatty Liver Disease, Obesity, BMI, Fatty Liver, Prevalence, Pakistan

How to Cite:
Memon, Y., Fareed, G., Shaikh, T. Z., Ali Qureshi, K., Karim, I., & Memon, Z. H. (2025). Prevalence of Nonalcoholic Fatty Liver Disease among Obese Patients Presented in Liaquat University Hospital Hyderabad/Jamshoro : Nonalcoholic Fatty Liver Disease among Obese Patients. Pakistan Journal of Health Sciences, 6(1), 249-253. https://doi.org/10.54393/pjhs.v6i1.2165

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Received Date: 23rd November, 2024
Acceptance Date: 21st January, 2025
Published Date: 31st January, 2025

ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a common liver disorder strongly linked to obesity and metabolic syndromes. Its identification in obese patients is critical for early management and prevention of complications. **Objective:** To evaluate the prevalence of NAFLD in obese patients presenting to a tertiary care hospital in Hyderabad, Pakistan. **Methods:** A cross-sectional study was conducted in Liaquat University Hospital Hyderabad and Jamshoro, over six months. Initially, 78 obese patients (BMI>30) were included through convenience sampling but after weight adjustment (IPW) it became 500 Patients. Demographic, anthropometric, and clinical data were collected. NAFLD diagnosis was based on ultrasound findings. Data were analyzed using SPSS version 22.0. **Results:** The prevalence of NAFLD was 41% in obese patients presented to hospital. In the adjusted model, BMI was the strongest predictor of NAFLD (OR = 1.205, 95% CI: 1.165–1.246, p<0.001), with each unit increase in BMI increasing the odds of NAFLD by 20.5%. Male had significantly lower odds of NAFLD compared to female (OR = 0.644, 95% CI: 0.540–0.767, p<0.001). Waist circumference (OR = 0.981, p=0.017p) and weight (OR = 0.969, p<0.001) were negatively associated with NAFLD, likely reflecting residual effects after adjusting for BMI. **Conclusions:** NAFLD is prevalent among obese patients in Pakistan, with Body Mass Index as the primary risk factor. Adjusting for sampling biases via IPW provided more accurate and generalizable findings. Routine screening for NAFLD and targeted interventions for weight management, particularly in female, are essential to mitigate disease progression.

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is rapidly emerging as one of the most significant public health challenges worldwide, particularly in developing countries such as Pakistan [1]. NAFLD encompasses a spectrum of liver abnormalities, ranging from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and even hepatocellular carcinoma [2]. Unlike liver damage caused by excessive alcohol consumption, NAFLD occurs in individuals with little to no history of alcohol intake and is strongly associated with metabolic risk factors, including obesity, type 2 diabetes mellitus (T2DM), dyslipidemia, and hypertension [3]. The global prevalence of NAFLD has been estimated to be around 25%, with significant variation between regions more in China and lowest in Japan, driven by the prevalence of obesity and metabolic syndrome in different populations [4, 5]. Obesity is a significant contributor to the prevalence of Non-Alcoholic Fatty Liver Disease (NAFLD) in Pakistan. According to the Global Nutrition Report, 13.4% of adult women and 7.5% of adult men in Pakistan are living with obesity [6]. This prevalence is influenced by factors such as poor dietary habits, sedentary lifestyles, and limited access to preventive healthcare services. The World Obesity Federation's Global Obesity Observatory assigns Pakistan a national obesity

DOI: https://doi.org/10.54393/pjhs.v6i1.2165

risk score of 6.5 out of 10, indicating a high risk based on obesity prevalence and related factors [7]. In Pakistan, the prevalence of NAFLD is becoming a critical health concern due to the rising rates of obesity and metabolic disorders [1]. Studies conducted in the region highlight that the pooled prevalence of NAFLD in the general population is approximately 29.82% (95% CI: 21.39–39.01%), with a disproportionately higher prevalence observed in specific high-risk groups [5]. The pooled NAFLD prevalence in the general population was 29.82% (95% CI 21.39–39.01%; prediction interval: 2.98–68.92%) based on 13 studies. In individuals with metabolic disorders, the prevalence of NAFLD in patients with diabetes, hypertension, and obesity, was 58.47% (95% CI 54.23–62.64%; prediction interval: 38.16–77.40%), 74.08% (95% CI 60.50–85.70%), and 47.43% (95% CI 30.49–64.66%), respectively. The role of tertiary care hospitals in addressing NAFLD is not addressed in above-described studies and most of the populations have associated metabolic syndrome, but this study will highlight the prevalence in obese without metabolic syndrome and presented toward tertiary care hospital. Understanding the prevalence of NAFLD in this high-risk group is crucial for several reasons. Firstly, it provides insights into the magnitude of the problem within a clinical setting, facilitating the allocation of resources for screening and management. Secondly, it highlights the need for multidisciplinary interventions involving hepatologists, endocrinologists, dietitians, and primary care physicians to address the underlying risk factors comprehensively.

The study was conducted to evaluate the prevalence of NAFLD in obese patients that are presenting to Tertiary care hospital in Hyderabad and Jamshoro.

METHODS

This is the prospective cross-sectional study was conducted at the Department of Medicine, Liaquat University Hospital, Hyderabad, over a six-month period (March 2024 to August 2024). Convenience sampling was employed to recruit patients presenting to the outpatient and inpatient departments of Liaquat University Hospital. Convenience sampling was chosen due to logistical constraints and the limited timeframe of the study with efforts to enhance the representation of sample to some extent. The challenges with other sampling techniques include the lack of a comprehensive sampling frame of all eligible patients, resource constraints, and time limitations. The sample size was determined using OpenEpi, based on a Brazilian study reporting a 32.7% NAFLD prevalence in the obese population presenting to Tertiary care hospital [8]. Parameters included a 95% confidence level, 80% power, an odds ratio of 9, and a prevalence difference of 27%, yielding a required sample size of 78 (Fleiss with continuity correction). The study included 78 participants aged 18–65 years with a BMI ≥30 kg/m^2. Exclusion criteria were a history of alcohol consumption, pregnancy, prior liver transplant, or metabolic conditions like diabetes or hypertension. Approved by the Institutional Review Board of Liaquat University , the study obtained written informed consent from all participants. Data collection involved demographic, anthropometric, and clinical assessments, with BMI calculated as weight (kg)/height (m^2). NAFLD was diagnosed via abdominal ultrasound, conducted independently by two blinded radiologists based on hepatic steatosis findings. Analysis was performed using SPSS version 22.0. Descriptive statistics summarized continuous and categorical variables, while the Shapiro-Wilk test assessed data normality. Statistical tests included the t-test, Mann-Whitney U test, and chi-square test, with p-values and confidence intervals reported for precision. Logistic regression analysis was used to identify predictors of NAFLD, employing two models: an unadjusted model to estimate crude associations and an adjusted model using inverse probability weighting (IPW) with BMI as weighting variable to account for sampling biases. Predictors included BMI, weight, waist circumference, age, and gender, with odds ratios (ORs) and 95% confidence intervals (CIs) calculated for associations. Statistical significance was set at $p<0.05$. Multi-collinearity was ruled out (VIF <5), and model fit was confirmed with the Hosmer-Lemeshow test. Comparison of models showed the adjusted model to be more reliable and generalizable.

RESULTS

The total patients in study were 78 in number out of them 35.9% (n=28) are male and 64.1% (n=50) were female (Figure 1). The mean age, and BMI of the patients was 49.38 ± 7.81 and 35.79 ± 2.50 respectively. The waist circumference of the patient was found to be 94.39 ± 5.24 and wight of the patients was 85.62 ± 6.95, and their distribution is evaluated using Shapiro-Wilk test for normality (table 1).

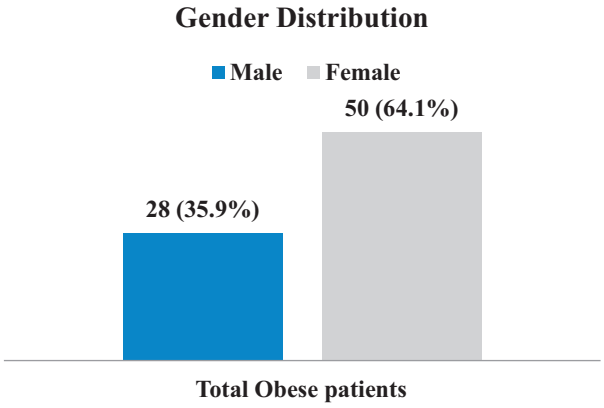

Figure 1: Gender Distribution

DOI: https://doi.org/10.54393/pjhs.v6i1.2165

Table 1: Descriptive Analysis

Variables	Mean ± SD	Distribution
Age	49.38 ± 7.81	Non-parametric
BMI	35.79 ± 2.50	Parametric
Waist Circumference (cm)	94.3 ± 5.24	Parametric
Weight	85.62 ± 6.95	Non-Parametric

Total number of 32 (41%) obese patients has positive findings of non-alcoholic fatty liver disease (95% CI: 30.1%–51.9%) with mean age of 49.84 ± 1.13, the female (56.25%) were more, and the mean BMI, Waist Circumference and weight was 35.15 ± 1.04, 94.56 ± 0.81, 85.37 ± 1.04 respectively. For the comparison between the ultrasound negative patients see table 2. The data were not found to be significant in relation to comparison. For parametric data independent T test performed, for non-parametric data Mann Whitney U test performed and for categorical data; chi; square test was performed.

Table 2: Analysis of Obese Patients with or Without Ultrasound Findings of NAFLD

Variables		Ultrasound Positive	Ultrasound Negative	p-value
Age (Mean ± SD)		49.84 ± 1.13	49.05 ± 1.28	0.704[1]
Gender	Male	14 (43.75%)	14 (30.43%)	0.167[3]
	Female	18 (56.25%)	32 (69.6%)	
BMI (Mean ± SD)		35.15 ± 0.41	36.23 ± 0.37	0.060[2]
Waist Circumference (Mean ± SD)		94.56 ± 0.81	94.28 ± 0.84	0.81(4)9[2]
Weight		86.37 ± 1.04	85.01 ± 1.12	0.661[1]

1: Calculated Via Man Whitney U Test, 2: Independent T Test, 3: Chi Square Test

For adjustment of sampling biases and cofounding variables using inverse probability weighting (IPW) was applied which increases the sample size from 78 to 500 patients with similar distribution and then logistic regression applied which identified BMI as a significant predictor of NAFLD (OR = 1.205, 95% CI: 1.165-1.246, p<0.001). For every one unit increase in BMI, the odds of NAFLD increased by 20.5%. Gender also significantly influenced NAFLD prevalence with male having lower odds of NAFLD than female (OR = 0.644, 95% CI: 0.540-0.787, p<0.001). Additionally, waist Circumference (OR = 0.981, 95% CI: 0.966-0.997, p=0.017) and weight (OR = 0.969, 95% CI: 0.958- 0.980, p<0.001) were negatively associated with NAFLD, it could be due to reflection of dominance of BMI as an obesity related risk factor for NAFLD, with waist and weight showing residual effect in adjusted model. Age showed a minor but statistically significant association with each additional year decreasing the odds NAFLD by 1.5% (OR = 0.985, 95% CI: 0.974 -0.996, p= 0.007). On comparison to unadjusted results, the adjusted analysis showed a stronger association between BMI and NAFLD, while accounting for sampling biases. Adjusting for sampling biases revealed that gender and waist circumference were also significant predictors which were less evident in the unadjusted model. This method reduced the impact of sampling bias and provided a more representative estimate of the association between predictors and NAFLD prevalence (Table 3)

Table 3: Comparison of Unadjusted and Adjusted Logistic Regression Model for Association between Variables and NAFLD

Variables	Un adjusted Model (OR, 95% CI, p-value)*	Adjusted Model (OR, 95% CI, p-value)+
BMI	1.205 (0.985 – 1.473), p=0.069	1.205 (1.165 – 1-246), p=0.001
Waist circumference	0.973 (0.885 – 1.070), p=0.574	0.981 (0.966 – 0.997), p=0.17
Weight	0.971 (0.906 – 1.040), p=0.402	0.969 (0.958 – 0.980), p=0.001
Age	0.981 (0.919 – 1.047), p=0.563	0.985 (0.974 – 0.996), p=0.007
Gender (Male versus Female)	0.660 (0.232 – 1.883), p=0.438	0.644 (0.540 – 0.767), p=0.001

*Calculated via logistic regression analysis
+ Adjusted using inverse probability weighting to account for sampling biases and logistic regression analysis

The adjusted model provides more reliable estimates of the predictors of NAFLD. BMI emerged as the strongest risk factor, with a 20.5% increase in odds per unit increase. Gender, weight, waist circumference, and age also showed significant associations after adjustment, highlighting the importance of controlling for sampling biases and confounding variables in logistic regression analysis.

DISCUSSION

NAFLD prevalence among obese patients was 41%, consistent with global estimates (36–80%) but mostly with metabolic syndrome [1]. Obesity remains a critical factor for NAFLD, underscoring the need for heightened clinical focus in Pakistan, where sedentary lifestyles and dietary changes exacerbate obesity rates [9]. A higher prevalence in female (56.25%) vs. male (43.75%) may reflect sociocultural norms limiting female activity and hormonal/metabolic differences [5, 10-12]. Adjusted analysis showed that male had 35.6% lower odds of NAFLD (OR=0.644, p<0.001), suggesting gender-specific risk profiles influenced by local factors. Age significantly influences NAFLD prevalence and progression. In this study, the mean age among NAFLD-positive patients was 49.84 ± 6.44 years, aligning with global data showing increased NAFLD prevalence in middle-aged adults due to cumulative metabolic risk factors (e.g., obesity, insulin resistance and hypertension) [4]. Large-scale studies confirm the highest prevalence in the 40–59-year age group, reflecting the natural accumulation of metabolic derangements over time, Asia study found that individuals aged 40–59 years exhibited highest prevalence of NAFLD [13]. The mean BMI of NAFLD patients was 35.15 ± 1.04, with BMI emerging as the strongest independent predictor after

DOI: https://doi.org/10.54393/pjhs.v6i1.2165

adjustment (OR=1.205, p<0.001). Despite initially non-significant findings, each unit increase in BMI raised NAFLD odds by 20.5%. Central obesity, indicated by a mean waist circumference of 94.56 ± 0.81 cm, also played a role. However, after adjusting for BMI, weight (OR=0.96, p<0.001) and waist circumference (OR=0.98, p=0.017) showed inverse associations, highlighting BMI's overriding influence [14]. These results underscore the importance of targeted interventions focusing on weight reduction and visceral fat control [15]. However, the lean patient with metabolic syndrome is also a risk factor for developing NAFLD [16]. Ultrasound is a widely used as a non-invasive and cost-effective modality but its sensitivity and specificity vary depending on the degree of hepatic steatosis [17]. A total of 41% of obese patients found to have ultrasound positive findings for NAFLD, however in this study there is no significant differences in demographic and anthropometric variables. The mean age in ultrasound positive is slightly higher, this finding aligned with studies suggesting the older individuals are more likely to develop detectable liver changes [18]. Female are more in ultrasound positive group; it could be due to postmenopausal effect, due estrogen withdrawal and central fat distribution [19]. While BMI and waist circumferences are slightly lower in ultrasound positive group, which was not statistically significant. It could be suggestive of concurrence of higher BMI and central obesity could be associated with metabolic factors such as insulin resistance and lipid profiles changes, but these patients were excluded from study [20]. The prevalence of NAFLD in this cohort underscores significant public health challenges in Pakistan, where limited resources exacerbate the disease burden. NAFLD elevates the risk of liver-related morbidity and cardiovascular disease, a leading cause of death in the country [21]. Accordingly, routine screening for NAFLD should be integrated into healthcare for obese individuals. The hospital-based sampling may not fully represent the broader obese population, and ultrasound potentially underestimates mild hepatic steatosis. Moreover, the cross-sectional design precludes causal inferences, and confounding variables (e.g., diet, physical activity) were not examined. Negative associations for weight and waist circumference warrant further investigation for possible multi-collinearity or population-specific factors.

CONCLUSIONS

In conclusion this study reveals significant NAFLD burden among obese Pakistanis. The study also highlights BMI's role, IPW-adjusted model nuances, and the necessity of targeted screening and weight management programs for mitigating progression in resource-limited settings.

Authors Contribution

Conceptualization: YM
Methodology: YM, IK
Formal analysis: TZS, KAQ
Writing review and editing: GF, ZHM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2124

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

The Impact of Education on Knowledge and Use of Contraceptive Methods: A Comparative Analysis of Educated and under educated Populations

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ARTICLE INFO

Keywords:
Contraceptive Knowledge, Education Impact, Usage Disparities, Reproductive Health

How to Cite:
Suhail, Z., Hussain, M., Hasan, S. U., Huda, A., Raza, T., & Javaid, A. (2025). The Impact of Education on Knowledge and Use of Contraceptive Methods: A Comparative Analysis of Educated and Under educated Populations. Pakistan Journal of Health Sciences, 6(1), 254-259. https://doi.org/10.54393/pjhs.v6i1.2124

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Received date: 2nd November, 2024
Acceptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

Education enhances knowledge and decision-making regarding contraceptive methods, thus playing an important role in the public health and reproductive outcomes. **Objective:** To evaluate the impact of education on knowledge and use of contraceptive methods by comparing educated and undereducated populations. **Methods:** This was a descriptive comparative cross-sectional study conducted among 400 participants in Lahore using simple random sampling. Chi-square test were applied by using SPSS version 23. **Results:** The Chi-square tests showed notable disparities in both the understanding and application of contraceptive methods among educated and uneducated groups. Knowledgeable individuals showed greater awareness of techniques like oral contraceptive pills (81.5% versus 34.4%, $p < 0.001$) and condoms (86.5% versus 60.5%, $p < 0.001$). Usage rates were also skewed towards the educated group, showed notable differences in methods such as IUCDs (21.5% versus 6.3%, $p = 0.005$) and injectable (24.7% versus 9.5%, $p = 0.003$). These results highlighted the essential importance of education in improving both awareness and the practical use of contraceptive methods to achieve better reproductive health results. This study highlighted notable differences in contraceptive knowledge and usage between educated and undereducated populations. **Conclusions:** In conclusion, the results emphasize the critical role of education in enlightening knowledge and the use of contraceptive methods, also mentioning the urgent need for targeted public health interventions to address the unmet contraceptive needs of undereducated populations.

INTRODUCTION

Contraception is an important module of public health, playing a crucial role in population management, family planning and the well-being of individuals, particularly women [1]. The effectiveness and widespread use of contraceptive methods are influenced by several factors, among which education stands out as a significant determinant [2]. Both formal and informal education are instrumental in shaping individual's knowledge, practices and attitudes regarding contraception [3]. It not only authorizes individuals (particularly women) but also improves awareness about the various contraceptive methods, to make informed decisions about their reproductive health. This study tries to examine the impact of education on the knowledge and the use of contraceptive methods by leading a comparative analysis between educated and undereducated populations. Altogether, the use of contraceptive methods has been steadily increasing, so far significant disparities persist between different populations, particularly between those with different levels of education [4]. According to the

DOI: https://doi.org/10.54393/pjhs.v6i1.2124

World Health Organization (WHO), almost 214 million women of reproductive age in developing countries want to avoid pregnancy but are not with any form of contraception [5]. This unmet need for contraception is often higher among women with lower levels of education, contributing to higher rates of maternal mortality and morbidity and unintended pregnancies in this group. The lack of knowledge and access to contraceptive methods among undereducated populations is an important public health concern that highlights the importance and understanding the role of education in promoting the use of contraception. Through several mechanisms education influences the use of contraceptives. Firstly, education helps to access information about reproductive health, allowing individuals to understand the several contraceptive methods available, their appropriate use, benefits and side effects [6]. Educated individuals are more likely to be exposed to sexual and reproductive health education through formal prospectuses, healthcare services and public health campaigns [7]. This exposure adopts a better understanding of the importance of family planning and the role of contraception in preventing Sexually Transmitted Infections (STIs) and unwanted pregnancies. Secondly, education fosters decision-making skills and critical thinking, which are essential for making informed choices about contraception [8]. Educated women are more likely to question traditional beliefs and social norms that may discourage the use of contraception. They are also more likely to consult healthcare providers, use modern contraceptive methods and seek out information effectively [9]. Moreover, education is often associated with greater autonomy and empowerment, enabling women to negotiate contraceptive use with their partners and assert control over their reproductive choices. In contrast, undereducated populations are often at a disadvantage when it comes to accessing and utilizing contraceptive methods. A lack of education can limit individuals' understanding of reproductive health, leading to misconceptions and myths about contraception that discourage its use. For instance, some women may believe that certain contraceptive methods cause infertility or other serious health problems, deterring them from using these methods [10]. Additionally, undereducated women are less likely to have access to healthcare services where they can receive accurate information and guidance on contraception. This lack of access is combined by socio-economic factors such as cultural norms, gender inequality and poverty which further limit their ability to make up-to-date reproductive choices [11]. The relationship between education and contraceptive use is complex and influenced by a myriad of factors, including socio-economic status, cultural beliefs, and access to healthcare services [12]. In many societies, education serves as a pathway to greater socio-economic opportunities, which in turn can influence reproductive health behaviors. Educated women are more likely to be working, have higher incomes and enjoy better living style, all of which are related with higher contraceptive use [13]. Furthermore, education can play a transformative role in stimulating and changing cultural and religious norms, that may discourage the use of contraception. Nevertheless, the impact of education on the use of contraceptives is not even across all populations. In a few cases, the mere provision of educational facilities may not be sufficient to overcome societal and deeply entrenched cultural barriers to contraceptive use [14]. One of the previous studies showed that, in some cultures, there may be strong opposition to contraception based on religious beliefs or traditional practices, which can persist even among educated individuals [15]. In such contexts, all-inclusive reproductive and sexual health education that reports the cultural barriers is essential to encouraging the contraceptive use. The current study objectives were to explore these problems by comparing the knowledge and the use of contraceptive methods among educated and undereducated populations. The differences in the use of contraceptive between these groups is determined by investigation, this research pursues to provide insights into how education can be used to improve the outcomes of reproductive health. Precisely, the study analyzed how educational achievement influences knowledge about different contraceptive methods, the probability of using modern contraceptives and the factors that may facilitate or hinder contraceptive use in both educated and undereducated populations. The understanding of the impact of education on the use of contraceptive is crucial for emerging effective public health interventions that address the unmet need for contraception. Through highlighting the role of education in promoting contraceptive use, the current study aims to contribute to the broader discourse on reproductive rights and health, mainly in low- and middle-income countries where educational disparities are most distinct. The results of current research will have important suggestions for healthcare providers, policymakers and educators who are working to improve access to contraception and encourage reproductive health equity.

The aim of this study was to assess the impact of education on contraceptive knowledge and usage between educated and undereducated populations.

METHODS

This was the descriptive comparative observational study, conducted from August 2022 to July 2023, among a population of two types, undereducated (primary and

DOI: https://doi.org/10.54393/pjhs.v6i1.2124

matric) and educated (intermediate, graduated, etc.) populations living in different areas of Lahore city. The sample size calculation was done by using Cochran's sample size formula, in which, the Z-score for a 95% confidence interval was 1.96, the proportion of estimation was 0.5, and the margin of error was 0.05 (5%). Through calculation, the approximate sample size calculated was 385, so the current study sample size was 400 as the study by Fred Yao Gbagbo used the sample size related to the current study [16]. This study was approved by the Institutional Review Board of the University of Lahore with Ref No. CRiMM/22/Research/005. The data was collected after taking informed consent from the participants using a simple random sampling technique. The data were collected using a questionnaire divided into three sections (demographics, knowledge, and usage of contraceptive methods). Data were entered and analyzed in SPSS version 23.0. Frequency and percentages were used for categorical variables. Mean and standard deviation were calculated for continuous variables. Chi-square was applied to determine the knowledge and usage of contraceptive methods between education groups. The inclusion criteria for the study consisted of participants aged 18 years and older, encompassing both genders to capture diverse perspectives. Individuals from various socio-economic backgrounds were included to ensure a comprehensive analysis. The undereducated group comprised individuals with at least a high school/matric diploma or equivalent, while the educated group included those with a graduation or higher diploma or equivalent. Additionally, only participants capable of providing informed consent were included. The exclusion criteria excluded individuals with cognitive impairments and pregnant individuals from the study.

RESULTS

The demographic characteristics of the study participants reveal significant insights into the population being studied. The majority of participants are between 31-45 years of age (49.5%), with a smaller proportion under 30 (42.5%) and even fewer over 45 years (8.0%). Education levels vary, with 21.8% of participants being uneducated, 15.8% having completed matric education, 25.7% having finished college, and 36.7% holding a university degree. The employment status showed that a substantial 69.3% are unemployed, indicating potential socioeconomic challenges that may influence health behaviors, including contraceptive use. Additionally, the majority of participants reside in urban (42.7%) and rural areas (39.7%), with a smaller group from semi-urban areas (17.6%) as shown in Table 1.

Table 1: Demographic Characteristics of Study Participants

Variables	Categories	Frequency (%)
Age	18-30	171 (42.5%)
	31-45	198 (49.5%)
	>45	31 (8.0%)
Under Education	Uneducated	87 (21.8%)
	Matric	63 (15.8%)
Educated	College	103 (25.7%)
	University	147 (36.7%)
Occupation	Employed	123 (30.7%)
	Unemployed	277 (69.3%)
Area of Residence	Rural	159 (39.7%)
	Urban	171 (42.7%)
	Semi-Urban	70 (17.6%)

The findings from the Chi-square test indicate a significant difference in the knowledge of various contraceptive methods between educated and undereducated populations, emphasizing the vital role that education plays in increasing awareness. Such as, 86.5% of educated participants reported knowledge of condoms, in contrast to only 60.5% of those in the undereducated group (24.00, $p < 0.001$). Similarly, awareness of oral contraceptive pills was markedly higher among educated individuals, with rates of 81.5% compared to 34.4% in the undereducated group (30.00, $p < 0.001$). This pattern of disparity was consistent across all contraceptive methods evaluated, including IUCDs, injectable, and tubal ligation, with most comparisons yielding p-values that indicate strong statistical significance. These results underscore the pressing need for targeted educational initiatives aimed at undereducated populations to enhance their understanding and use of effective contraceptive methods, which could lead to improved reproductive health outcomes within these communities as shown in Table 2.

Table 2: Comparison Between Education Groups and Contraceptive Methods to assess participants' knowledge about Contraceptive Methods

Contraceptive Methods Knowledge	Undereducated Group Frequency (%)	Educated Group Frequency (%)	Chi-Square	p-Value
Withdrawal	93 (46.5%)	155 (77.5%)	22.50	<0.001
Condoms	121 (60.5%)	173 (86.5%)	24.00	<0.001
Safe Periods	39 (19.4%)	97 (48.6%)	18.00	<0.001
Oral Contraceptive Pills	69 (34.4%)	163 (81.5%)	30.00	<0.001
Diaphragm	11 (5.4%)	45 (22.3%)	10.00	0.002
Vaginal Cream	30 (15.0%)	71 (35.6%)	8.00	0.005
IUCD	29 (14.5%)	89 (44.4%)	15.00	<0.001
Implants	23 (11.4%)	80 (40.0%)	12.50	<0.001
Injectable	19 (9.6%)	73 (36.6%)	10.00	0.002
Vasectomy	3 (1.6%)	27 (13.4%)	6.00	0.014
Tubal Ligation	9 (4.8%)	44 (22.0%)	8.00	0.005

DOI: https://doi.org/10.54393/pjhs.v6i1.2124

Breast Feeding	86 (43.2%)	113 (56.6%)	3.60	0.0058

The Chi-square test results concerning the usage of contraceptive methods indicate notable disparities between educated and undereducated populations, highlighting the influence of education on contraceptive behaviors. For example, 61.0% of educated participants reported using condoms, compared to only 40.6% of those who were undereducated (12.56, $p < 0.001$). This suggests that education significantly contributes to the adoption of safer contraceptive practices. Similarly, the use of oral contraceptive pills was reported by 43.7% of educated individuals, in contrast to just 14.7% among the undereducated group (16.78, $p < 0.001$), revealing a substantial gap in the uptake of modern contraceptive methods. Other contraceptive options, such as IUCDs (21.5% versus 6.3%, $p = 0.005$) and injectables (24.7% versus 9.5%, $p = 0.003$), also demonstrated significant differences, further supporting the idea that education enhances both awareness and the use of effective contraceptive choices. While some methods, like breastfeeding, did not show a significant difference in usage ($p = 0.206$), the overall findings strongly indicate that educated individuals are more likely to engage in a variety of contraceptive practices as shown in table 3.

Table 3: Comparison of Under Educated and Educated Participants with the Use of Contraceptive Methods

Contraceptive Methods Usage	Undereducated Group Frequency (%)	Educated Group Frequency (%)	Chi-Square	p-Value
Withdrawal	45 (22.4%)	67 (33.6%)	6.45	0.011
Condoms	81 (40.6%)	122 (61.0%)	12.56	<0.001
Safe Periods	10 (5.0%)	30 (15.0%)	7.21	0.007
Oral Contraceptive Pills	29 (14.7%)	87 (43.7%)	16.78	<0.001
Diaphragm	5 (2.3%)	17 (8.3%)	3.84	0.050
Vaginal Cream	11 (5.7%)	25 (12.5%)	4.00	0.045
IUCD	13 (6.3%)	43 (21.5%)	8.00	0.005
Implants	11 (5.4%)	36 (18.0%)	6.75	0.009
Injectable	19 (9.5%)	49 (24.7%)	8.57	0.003
Vasectomy	1 (0.5%)	5 (2.5%)	-	-
Tubal Ligation	3 (1.5%)	19 (9.5%)	6.00	0.014
Breast Feeding	33 (16.6%)	53 (26.7%)	1.60	0.206

DISCUSSION

Previous studies have consistently shown that the level of education is a vital factor influencing contraceptive knowledge and use in different areas. One of the previous researches in sub-Saharan Africa indicates that women who possess higher education are more inclined to use modern contraceptive methods than those with lower education levels (Cleland *et al.*, in 2012, Ahinkora *et al.*, in 2021) [17, 12]. Likewise, in South Asia, variations in education have been associated with marked differences in reproductive health results, as educated women showed higher awareness and utilization of contraceptives (Memon *et al.*, in 2024; Kabir *et al.*, in 2024) [18, 19]. Through exploring these worldwide patterns, the analysis can emphasize the commonality of the connection between education and contraceptive methods, while also pinpointing successful strategies and interventions effective in different situations. This comparative method enhances the conversation and offers essential insights for policymakers and practitioners seeking to tackle unmet contraceptive requirements in less-educated groups. This research showed several significant strengths, especially the large sample size of 400 participants, enhancing the reliability and generalizability of the results. Incorporating individuals with diverse educational experiences from those without formal schooling to those who possess college diplomas provides a broad perspective on how education influences knowledge and the application of contraceptive methods. This variety is crucial, as it reflects the actual differences in knowledge and actions related to contraception. Moreover, the significant unemployment rate among participants (69.3%) emphasizes the socioeconomic difficulties that could affect health behaviors, such as contraceptive use, thus reinforcing the need for focused interventions in economically disadvantaged areas. These results supported the recognized association between education and awareness of contraceptives, aligning with earlier research by Beyene KM *et al.*, in 2023 and Rana MS *et al.*, in 2024, which showed that increased educational levels correlate with enhanced knowledge of modern contraceptive methods [20, 21]. Significantly, this study provides a distinct viewpoint by exploring the differences in contraceptive awareness between educated and less educated groups. Nevertheless, this research has limitations that could influence the wider relevance of its findings. Cultural attitudes unique to Lahore or Pakistan might restrict the applicability of the findings to other areas since local family planning norms can greatly impact contraceptive acceptance and use. Moreover, the study's cross-sectional design limits the capability to make causal inferences; although the connection between education and contraceptive knowledge is evident, it cannot be conclusively stated that higher education directly results in better contraceptive practices without taking into account other possible confounding factors. Given these findings, there is an immediate necessity for focused educational initiatives directed at undereducated groups to improve their knowledge and use of effective contraceptive techniques. These interventions must directly target the socio-economic and cultural obstacles that hinder access to contraception. These obstacles, such as gender disparity, cultural misunderstandings about

DOI: https://doi.org/10.54393/pjhs.v6i1.2124

contraception, and poverty, have been noted in earlier research but frequently lack a concentrated analysis of undereducated populations.

CONCLUSIONS

This study emphasized the critical importance of educational achievements to influence contraceptive awareness and practices among women showed that greater educational levels were consistently linked to enhanced understanding and use of modern contraceptive techniques. This research uncovers notable differences in contraceptive usage among various regions, especially in sub-Saharan Africa and South Asia, where educational programs can enhance reproductive health results. The placement of these findings in a global framework, the research highlighted the importance of specific educational initiatives to meet unmet contraceptive demands, thereby, enhancing reproductive autonomy and promoting health equity.

Authors Contribution

Conceptualization: ZS
Methodology: MH
Formal analysis: MH
Writing, review and editing: SH, AH, TR, AJ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2124

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DOI: https://doi.org/10.54393/pjhs.v6i1.2614

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

High Mortality Rate Due to Inflated Prevalence of Drowning Cases; An Observational Study Reflecting Regional Trends and Factors Affecting Asphyxial Deaths Due to Drowning in District Muzaffargarh

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ARTICLE INFO

Keywords:
Drowning, Accidental Drowning, Asphyxia, River Chenab

How to Cite:
Sana, S. G., Ashraf, R., Zahra, S. H., Murad, T., Ahmed, I., & Javed, S. (2025). High Mortality Rate Due to Inflated Prevalence of Drowning Cases; An Observational Study Reflecting Regional Trends and Factors Affecting Asphyxial Deaths Due to Drowning in District Muzaffargarh: Regional Trends and Factors Affecting Asphyxia Deaths Due to Drowning in Muzaffargarh. Pakistan Journal of Health Sciences, 6(1), 260-264. https://doi.org/10.54393/pjhs.v6i1.2614

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Received date: 1st November, 2024
Acceptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

Asphyxia deaths due to drowning, especially accidental deaths are soaring daily in many areas of Pakistan. This fact led us to conduct this study on prime areas of Muzaffargarh on the bank of River Chenab. **Objectives:** To determine the frequency of drowning cases and factors affecting their high prevalence. **Methods:** A retrospective study comprising 5 years (2019-2023), including both genders and age groups, asphyxia deaths particularly due to drowning but excluding unidentified bodies and other modes of asphyxia deaths. All variables are analyzed through SPSS-27. **Results:** Out of 412 drowning cases, 309 cases belong to accidental drowning (75%) with a predominance of the male population, almost 68.68%. The most prevalent age group involved is 11-20 years (31.31%). The majority of cases happen in the monsoon and summer seasons, 28.88% and 26.45% respectively. **Conclusions:** It was concluded that asphyxia deaths due to drowning are rising day by day, especially the cases involving accidental deaths. This showed the lack of proper preventive strategies in areas of Chenab River in District Muzaffargarh.

INTRODUCTION

The Drowning Debacle, creeping engulfing innocent lives daily, making it the third leading cause of unintentional deaths globally. According to WHO, low and middle-income countries account for 90% of unintentional drowning deaths [1]. WHO estimated that nearly 263000 drowning deaths occur globally annually [2] and the most affected population belongs to low and middle-income countries like Pakistan, amounting to almost 82000 fatalities including the precious lives of children aged 1 to 14 years [3]. Loss of many precious lives is underestimated in terms of data gathering by authorities which snubs the actual need for help [4]. According to a study conducted in Tanzania, children aged less than 14 and older people are the most vulnerable population group [5]. In another study, homicidal deaths due to drowning also escalated daily, especially when we talked about child homicide [6]. In

DOI: https://doi.org/10.54393/pjhs.v6i1.2614

consonance with research done in Australia, suicidal deaths due to drowning are soaring day by day and the most endangered people are women and older [7]. According to another significant study, the majority of cases of drowning deaths are accidental and involve young men, going on excursion trips and there they meet their unfortunate fate [8]. Another noticeable reason is drug and alcohol intoxication which leads to increasing cases of drowning deaths in coastal areas [9]. A greater number of children are affected daily, which highlights the need for assessing the risk and developing its managing strategies on the local level [10]. The rate of hospitalization due to drowning cases is inflated as compared to previous years [11]. All over the world, especially in high-income countries, prioritizing the need for proper infrastructure for the collection of legit data and also constructing a proper management system for drowning death cases, is being initialized already [12]. Among other countries, Pakistan is another underdeveloped country, that faces an enormous number of accidental deaths due to drowning. Changing climate, excessive flooding and lack of protected excursion spots near lakes and rivers, make it very easy to be engulfed by unintentional drowning death. Another important factor is the lack of a proper management system for dealing with drowning deaths, which also correlates directly to the lack of people awareness, lack of people education and lack of preventive measures. Muzaffargarh district lies on the bank of the Chenab River, a major agricultural land with many industrial zones, contributing greatly to the economy of Pakistan, yet highly underprivileged and ignored in terms of basic life facilities, education and health opportunities. Being on the bank of the Chenab River, a huge number of accidental cases appear in the locality, which marks the highest rate of mortality due to drowning in this district. Development of water safety measures, preventive strategies, training of the local population awareness programs and a proper management system is the actual need of the hour so that the mortality rate could be minimalized in this underestimated and ignored area.

That is why, this study aims to highlight the prevalence of drowning cases, with contributing factors, so that proper planning to deal with such cases should be optimized by the authorities.

METHODS

A 5-year retrospective study was conducted at Central Station of District Emergency Service, Rescuee1122. This study duration was January 2019 to December 2023 and comprised 412 cases of deaths due to drowning during this period. After receiving approval from concerned authorities (ref no: 9/19/DEO/MGH/ (PES)), a random sampling Technique was used. Dead bodies of asphyxia deaths due to drowning were included in this study. Dead bodies of other modes of asphyxia deaths like strangulation and hanging and unidentified dead bodies were excluded. Data records were taken. All the variables were collected and analyzed through SPSS version 27.0. The statistical analysis of data was carried out using tables, graphs and percentages.

RESULTS

According to this study, out of 412 drowning cases, 309 include accidental cases (75%), 71 suicidal cases (17.23%) and 32 homicidal cases (7.76%). The majority of cases belong to the male gender (68.68%) and the most prevalent age group is 11-20 (31.31%). Age less than 10 years and from 21-30 years also show a significant number of cases, 23.78% and 18.93% respectively. Almost 28.88% of cases took place during monsoon season, 26.45% in summer and the most happening time of occurrence is morning (48.05%) and afternoon (24.75%). A few eminent reasons for accidental cases were excursion (31.71%), swimming (25.24%) and professional animal caretakers (23.30%) (Table 1).

Table 1: Frequency and Percentages of Different Variables

Variables	Frequency (%)
Gender	
Male	283 (68.68%)
Female	129 (31.31%)
Age (Years)	
<10	98 (23.78%)
11-20	129 (31.31%)
21-30	78 (18.93%)
31-40	56 (13.59%)
41-50	32 (7.76%)
>50	19 (4.61%)
Manner of Death	
Suicide	71 (17.23%)
Homicide	32 (7.76%)
Accident	309 (75%)
Time of Drowning	
Morning	198 (48.05%)
Afternoon	102 (24.75%)
Evening	61 (14.80%)
Night	33 (8.00%)
Season of Drowning	
Spring	78 (18.93)
Summer	109 (26.45)
Monsoon	119 (28.88)
Autumn	62 (15.04)
Winter	44 (10.67)

Results show a correlation between factors affecting accidental drowning. The prominent reason in cases of accidental drowning is excursion (31.71%), as for season, monsoon accounts for the highest frequency, almost

DOI: https://doi.org/10.54393/pjhs.v6i1.2614

29.77% and the most happening time is morning, 39.15% (Table).

Table 2: Inferential Data Regarding Accidental Cases

Accidental Cases (309/75%)		Frequency (%)
Reasons	Excursion	98 (31.71%)
	Bathing/Washing	61 (19.74%)
	Swimming	78 (25.24%)
	Occupational (Animal Caretakers)	72 (23.30%)
Time	Morning	121 (39.15%)
	Afternoon	93 (30.09%)
	Evening	64 (20.71%)
	Night	31 (10.03%)
Seasons	Spring	56 (18.12%)
	Summer	89 (28.80%)
	Monsoon	92 (29.77%)
	Autumn	44 (14.23%)
	Winter	28 (9.06%)

This finding manifests a gradual inflation of accidental cases of drowning, with the escalation of cases in 2023 (Figure 1).

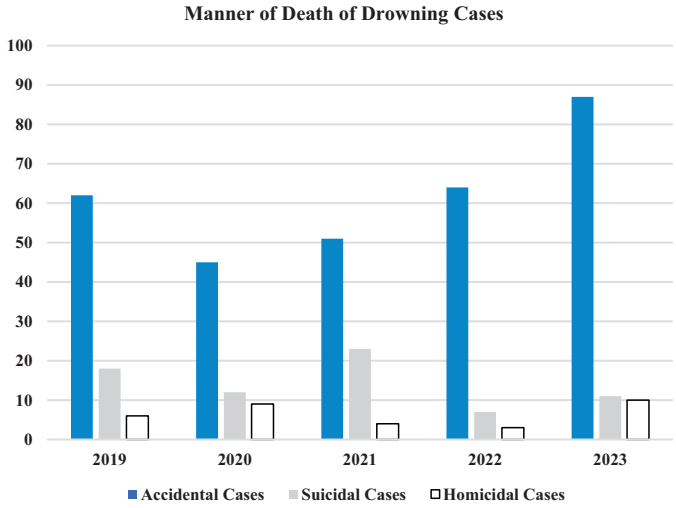

Figure 1: Year Wise Distribution of Drowning Cases According to Manner of Death

DISCUSSION

In this five-year study, a total of 412 cases are encountered, of which 309 cases belong to accidental deaths alone. The majority of cases belong to the male population (68.68%) with the most happening age group of 11-20 years (31.31%). A study conducted in Karachi manifests that there is a high prevalence of the male population, with almost 83.01% involved in drowning cases [13]. Another study done in Hyderabad demonstrates that there is a high prevalence of the male population involved in asphyxia deaths especially cases of drowning [14]. The same fact is interpreted in this current study which shows that males are more prone to face accidental deaths in drowning, as they are the sole bread earners and the majority are involved in professions like animal caretakers, who use canals and river sides to provide water to their animals, also many people wash their clothes and bathe along the riverside. Another astonishing fact is that many people who come for excursions along canal or river sides face a high ratio of accidental deaths due to drowning. A high number of cases belong to people who live in nearby areas of canals and rivers, and they are indulged in swimming, especially in summer. Complementing these facts described in this study, another research elaborated that swimming as an excursion activity leads to a high ratio of accidental deaths due to asphyxia drowning [15]. Another study done in Arkanabad Karachi shows that drowning deaths are becoming as common as natural deaths, highlighting the fact that such cases of deaths due to drowning are spreading day by day [16]. Some risky behavioural factors like intoxication, lack of swimming skills, swimming alone without any protective measures, bathing and playing without considering water levels and some other irresponsible activities lead to the soaring number of accidental drowning cases in broad daylight [17]. The majority of the cases occur in the monsoon season and also in summer, especially the people of flood-prone areas highly affected by seasonal changes, this environmental fact is being elaborated by another study [18]. A frequent number of accidental cases appear mostly in the morning and afternoon as the majority of professional animal caretakers perform their daily activities at that particular time. The same goes for people coming for excursion and enjoyment in broad daylight. In all these scenarios males are mostly involved in accidental deaths due to drowning [19]. The current study reveals that homicidal and suicidal cases are less common, 7.76% and 17.23% respectively. One study elaborated that, homicidal deaths due to drowning are sometimes hard to justify as many other asphyxia factors are involved in the majority of cases [20]. Similarly, suicidal deaths are less prevalent than homicidal deaths in comparison to accidental drowning cases. According to the current study, cases of drowning deaths have not declined over the period, but they are gradually inclining over the years. Hence this study highlights the necessity of implementing prevention strategies, policy-making and advocacy to reduce such traumatic mishaps shortly [21].

CONCLUSIONS

It was concluded that deaths due to drowning, especially accidental deaths, are on the rise in district Muzaffargarh, as the majority of cases occur in the Chenab River. Therefore, proper management systems dealing with prevention programs, techniques and legislation are mandatory to overcome flaws and cons which prevail in those areas and are the main reasons behind such

DOI: https://doi.org/10.54393/pjhs.v6i1.2614

disastrous drowning deaths. There is a dire need for strict policymaking for the prevention of such disastrous accidents shortly.

Authors Contribution

Conceptualization: SGS
Methodology: SHZ, SJ
Formal analysis: TM, IA
Writing review and editing: SGS, RA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2439

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Shovel Shaped Incisors: A Non-Metric Dental Trait in Local Population of Punjab, Pakistan

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ARTICLE INFO

Keywords:
Shovel Incisors, Forensic Dentistry, Maxillary Incisors, Dental Procedures

How to Cite:
Bano, S., Nawaz, R. S., Zafar, R., Hassan, G., Javed, M., & Yasen, A. (2025). Shovel Shaped Incisors: A Non-Metric Dental Trait in Local Population of Punjab, Pakistan: Non-Metric Dental Traits. Pakistan Journal of Health Sciences, 6(1), 265-269. https://doi.org/10.54393/pjhs.v6i1.2439

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Received date: 21st October, 2024
Acceptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

Maxillary Incisors being the anterior teeth hold great importance for function and esthetics. Different morphological traits can affect the shape of incisors. Shoveling is a non-metric morphological trait predominantly seen in maxillary incisors and is characterized by prominent mesial and distal ridges enclosing a central fossa on the lingual surface of incisors. **Objective:** To determine the frequency of shovel shaped Incisors and its distribution according to gender in a local population of Punjab, Pakistan. **Methods:** The study was a cross-sectional study carried out on 176 students of age between 17-23 years. Probability, stratified random sampling technique was employed and the study was conducted from March, 2023 to November, 2023. The participants taken for the study were carefully examined clinically to diagnose the presence or absence of this trait. **Results:** Out of total population of 176, only 55 (31.2%) individuals were positive for shoveling trait. Among the positive individuals, no gender predilection of this trait was observed. **Conclusion:** Non-metric dental traits can be assessed to identify ethnic groups, forensic odontology and inform clinical management in various dental procedures.

INTRODUCTION

Odontogenesis is a complex yet well-regulated process. It is a highly diverse phenomenon which involves molecular factors that interact throughout prenatal and postnatal development. Tooth crown features are a result of this diverse process and is controlled by interaction of chemical signals between neighboring and distant cells. Hence the variation in the normal morphology of a tooth is a result of simultaneously acting genetic as well as environmental factors [1]. The study of dental traits and its relation with human development by linking it to the past and present population is called Dental Anthropology [2]. Trait is defined as a characteristic feature that distinguish an individual and its frequency of occurrence varies in different populations [3]. Study of dental morphology in relation to dental anthropology requires to understand the way in which frequency, sexual dimorphism and symmetrical distribution of tooth crown morphological traits (TMCT) vary in permanent teeth in different populations [4]. Dental traits are broadly classified as metric and non-metric traits. Metric traits are those which can be readily quantified for example, crown height, length and width. While non-metric traits are those which show variation in normal anatomy. These may be present or absent, with a variable frequency in different population in certain period of time. Examples of such traits include labial curvature, Shovel-shaped incisors and Carabelli's

DOI: https://doi.org/10.54393/pjhs.v6i1.2439

cusp [5]. The non-metric dental traits are heritable features that express morphological variation within one population and among different populations as well. Hence, they can be used in comparing the culture, history and biological progress of early and modern humans [6]. These traits are particularly useful in clinical dentistry, oral pathology, tooth morphology, dental anthropology and forensics [7]. Non-metric dental features provide unique insights into the evolutionary history and genetic makeup of the human population [8]. Teeth are having the strongest structure due to its highest mineral content and can serve as excellent source of study material in forensic and genetic as they remain preserved after any disaster or explosion. Due to this, the non-metric dental traits can be used by forensic odontologist to help identify a person or differentiate between races [9, 10]. Among the non-metric traits incisor shoveling has attained high attention for the forensic odontologists and anthropologists [11]. Incisors, being the anterior group of teeth, hold an important position in oral cavity both esthetically and functionally. According to studies incisors have a high tendency of acquiring multiple morphological variations that can be influenced genetically or environmentally. This includes peg shaped incisors, shoveled incisors, dens invaginatus, barrel shaped or cone shaped incisors [12]. Shoveling is a characteristic predominantly seen in maxillary incisors and occasionally in mandibular incisors. It is defined by prominent mesial and distal ridges enclosing a central fossa on the lingual surface of incisors [13]. The prevalence of this feature varies among different population and ethnic groups. Incisors shoveling was reported in 1920 by Hrdlicka and he proposed it as a trait of Mongoloid dentition. High prevalence has been reported in Eskimos, Pima Indians, North American Indians, and Aleuts [3]. Shoveling of teeth has been previously classified in different grades in 1963 by Hanihara and later in 1998 by Sciulli. Following is the grading criteria:

Grade 0: No shovel-shape, lingual surface smooth.
Grade 1: Semi shovel-shape, slight elevation of marginal ridges.
Grade 2: Shovel, marginal ridges easily seen.
Grade 3: Strong or marked shovel when marginal ridges are broad and high [14].

Understanding the prevalence of this morphological trait is essential for dental practitioners to identify and manage it effectively [15]. Pakistan is a diverse nation with a rich blend of ethnic groups. However, data on the prevalence of shovel-shaped incisors within the country remains limited. This study aimed to explore the prevalence of shoveling in a local population from Punjab, Pakistan.

METHODS

The study was designed as a cross-sectional quantitative investigation. The current study was conducted at FMH College of Medicine and Dentistry after taking approval from Institutional Review Board (Ref No. FMH-01-2020-IRB-715-M), Lahore conducted from March, 2023 to November, 2023. The sample size was calculated by the following formula using 6% margin of error and on based of finite population 478.

$$n = \frac{N}{1+Ne^2} \qquad n = 176$$

A total of 176 undergraduate dental students were included in the study after taking their informed consent. Probability Stratified Random sampling was employed to gather participants from the BDS program, encompassing students from the 1st to the final year. The study included Maxillary Incisors in male and female students in the 1st through 4th years of the BDS program, while those with or missing Maxillary Incisors were excluded. Data were collected through visual observations using dental examination sets, following approval by the institutional review board and obtaining informed consent from the students. Participants were briefed on the procedure and assured of sterilization and confidentiality. Observations were made according to the criteria by Sciulli as mentioned above. At least two investigators observed and recorded on the proforma containing a section of gender, age, presence/absence of trait and if present, grades of shovel-shaped Maxillary Incisors. The statistical analysis was done using SPSS version 23.0. Descriptive statistics was applied to have frequency and percentage and Chi-square was applied to compare between two genders. P-value of ≥0.05 was considered statistically significant.

RESULTS

In this study a total sample of n=176 was selected for the estimation of frequency of shovel-shaped incisors out of which 54 were males and 122 were females. The data for number of individuals observed positive for this trait is provided in the Table- 1. Out of total population of 176, only 55 (31.2%) cases were found to be having shovel shaped incisors. Among the 54 males, only 17 (31.4%) had shoveled incisors of varying grades and out of 122 females, 38 (31.1%) had shoveled incisor of varying grades. The results showed almost equal predilection of this trait in both the genders (p=1.000).

Table 1: Number of Individuals for Shovel-Shaped Incisors

Gender	Number of Individual	Frequency of Trait Frequency (%)
Male	54	17 (31.4%)
Female	122	38 (31.1%)
Total	176	55 (31.2%)

*p-value was found to be 1.000

The grades of shoveling were recorded according to the

DOI: https://doi.org/10.54393/pjhs.v6i1.2439

previously published data. The results are shown in the table-2.

Table 2: Frequency of Shovel Grades

Grades	Frequency (%)
Grade 0	122 (69.3%)
Grade 1	19 (10.8%)
Grade 2	30 (17%)
Grade 3	5 (2.8%)
Total	176

Grade 0: No shovel-shape, lingual surface smooth.
Grade 1: Semi shovel-shape, slight elevation of marginal ridges.
Grade 2: Shovel: marginal ridges easily seen.
Grade 3: Strong or marked shovel when marginal ridges are broad and high.

In the study population, grade 2 shoveling was observed with the highest percentage of 17% (figure1). The percentage of grade 1 shoveling was 10.8% while only 2.8% cases showed grade 3 shoveling.

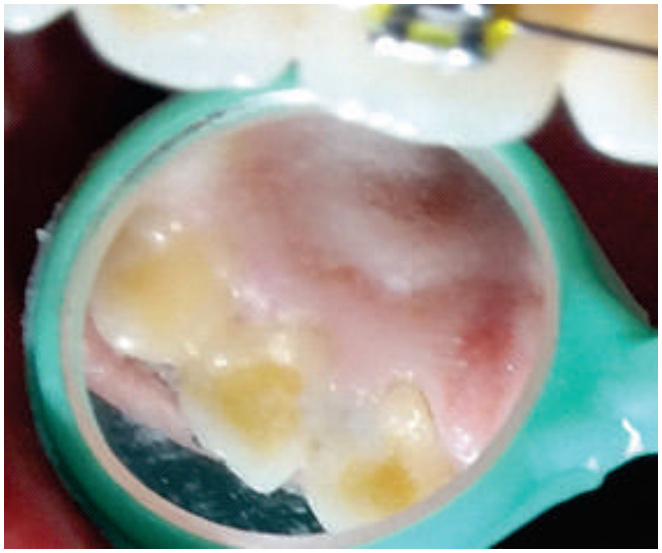

Figure 1: Grade 2 Shovel on Maxillary Left Central Incisor: Elevated and Thick Marginal Ridges with Deep Lingual Fossa

DISCUSSION

Genetics greatly influences the morphology of a tooth, highlighting the importance of studying dental morphology for understanding demographic connections and evolutionary ties. Identification of specific morphological features and bite patterns not only provide valuable insights into dental history but also help dentists in planning optimal treatment for the best outcomes. As due to presence of shoveling, such incisors may develop a room for caries to develop. Very few studies are done in Pakistan to explore such traits as comparative study of different morphological traits provides distinction among populations and may also aid the forensic odontologists to explore specific features in different people to help their identification [16]. Therefore, our study was designed to investigate the frequency of shoveling in a sub population in Punjab, Pakistan. Frequency of shoveling has been investigated in different populations and according to data it was found that this trait is most commonly seen in North American, South American and north Asian populations [5]. The current study showed that only 31% of the sample population had varying grades of shovel-shaped incisors. According to a study in Native Americans some percentage of shoveling is seen in almost every individual [1]. In a local study conducted in Abbottabad among different ethnic groups a lower frequency of shoveling was found [17]. In another study in Odisha and Kerala states of India, a low frequency of shoveling (15%) was found [18]. Contrary to this, another study done in Vidarbha subpopulation showed that 88% of Maxillary Incisors had shoveling that is much higher as compared to the results of present study [9]. Although shoveling do not exhibit sexual dimorphism yet many studies showed a higher female tendency as compared to males. Our findings also indicated no gender predilection regarding the shovel shaped incisors. Contrary to it, a study conducted in Nepal among the Newari children of Bhaktapur, a slightly higher male predilection of shoveling was seen than females. They reported 45.5% shoveling in males and 40.6% in females [19]. Another study of school children from Gujrat state, India also showed more shoveling in males than females [5]. In a previous study conducted in Brazil, shoveling was found to be more prevalent in females (66.7%) than in males (33.3%) in another study conducted among Asian population, females had higher incidence of shoveling as compared to men [20, 21]. These results are contrary to our study where only 31.1% females were found to be positive for this trait as compared to men which were 31.4%. The variation in results may be due to difference in population and area involved along with the genetic factors involved.

CONCLUSIONS

Non-metric morphological traits help in identification of a population and an individual belonging to different ethnicity. In our study shoveling was found in 31.2% of the studied individuals with no gender predilection. As the data regarding this trait in Pakistani population is limited, it should be explored further in detail among more population groups and in other provinces of Pakistan.

Authors Contribution

Conceptualization: SB
Methodology: GH
Formal analysis: SB, RZ, MJ
Writing, review and editing: SB, RSN, RZ, AY

All authors have read and agreed to the published version of the manuscript

DOI: https://doi.org/10.54393/pjhs.v6i1.2439

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2439

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DOI: https://doi.org/10.54393/pjhs.v6i1.2559

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Weight Gain in Severe Acute Malnutrition Children after Discharge from CMC Children's Hospital Larkana Followed-Up for Two Months

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ARTICLE INFO

Keywords:
Severe Acute Malnutrition, Body Weight, Illiterate, Wasting

How to Cite:
Mehak, . ., Shaikh, N. F., Baloch, D., Gemnani, V. K., Ahmed, S. . ., & Jamaro, S. . (2025). Weight Gain in Severe Acute Malnutrition Children after Discharge from CMC Children's Hospital Larkana Followed-Up for Two Months: Weight Gain in Severe Acute Malnutrition Children. Pakistan Journal of Health Sciences, 6(1), 270-275. https://doi.org/10.54393/pjhs.v6i1.2559

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Received date: 14th November, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

Globally, 19 million children under five suffer from severe acute malnutrition, causing 400,000 deaths annually. Early detection is crucial for treatment and reducing consequences in community and healthcare settings. **Objectives:** To assess weight gain in severe acute malnutrition (SAM) children two months after discharge from Children's Hospital. **Methods:** A prospective cohort study was conducted on children with SAM, receiving treatment at the oral therapy program (OTP) clinic at Chandka Medical College, Children Hospital, Larkana. Through consecutive sampling, 99 children aged 6-60 months with SAM and good appetites during discharge were enrolled. Mothers were explained about OTP. Follow-ups were conducted every 15 days up to two months after discharge to assess weight gain. SPSS version 22.0 was used to analyze the data. **Results:** Analysis revealed that 58.6% were male, with a mean age of 16.4 ± 8.2 months, while 52.5% were below 12 months old, mostly in rural areas (58.6%), and (32.3%) had illiterate maternal education status. Mean body weight at discharge was 4100 ± 620 grams. By the end of 2 months, weight gain was noted among 91(91.9%) children. Weight gain was "good" in 51.5% of children, moderate in 34.3%, and poor in 14.2%. The weight gain was significantly associated with younger age groups (p=0.0085), literate mothers (p=0.0071), and increased monthly income families (p= 0.0416). **Conclusions:** The study found a significant association between weight gain and SAM management. Clinical-based treatment is often only the first step; however, sociodemographic factors like age, maternal education, and family income are crucial for sustaining nutritional and medical recovery and reducing morbidity and mortality.

INTRODUCTION

Severe acute malnutrition (SAM) is a major worldwide and national public health concern, especially among children under the age of five [1]. In low- and middle-income countries, an estimated 34.2 million children under the age of five (5) were affected by SAM in 2022, accounting for almost 45% of all child deaths [2, 3]. Severe acute malnutrition (SAM) is defined as "very low weight for height (below -3Z scores of the median WHO growth standards) by apparent severe wasting or the presence of nutritional edema" [4]. According to the report of WHO 2013, SAM is considered to be a major cause of mortality among children. SAM is estimated to affect around 20 million pre-school children who are mainly from African and Southeast Asian countries. In 2022, 45 million children under the age of five, or 6.8% of this age group, were afflicted by wasting. Out of these, 13.7 million (2.1%) experienced severe wasting [5]. Compared to healthy children, the risk of mortality is estimated to increase 9-fold among children who have SAM [6]. SAM affects around 3.1% of children under 5. years old with a weight-for-length or height z-score (WHZ) <-3 criteria, resulting in an estimated 450,000 cases [6]. There is no national evidence on the incidence of SAM by mid-

DOI: https://doi.org/10.54393/pjhs.v6i1.2559

upper arm circumference and the existence of bipedal edema in children below 5 years of age; thus, the actual figures for children having SAM might be much greater than estimated currently [7]. Children with SAM can be effectively treated by WHO recommendations that are practical and maintainable even in small district hospitals with imperfect resources. WHO guidelines are an organized method of care and include 10 steps in two stages, to manage the acute problems and long-term to promote recovery and growth [8]. In 2022, there were 149 million stunted children under the age of five, while 37 million were overweight or obese. Undernutrition is responsible for about half of all fatalities in low- and middle-income countries, and it affects nearly half of these children [9]. A study from Rajasthan, India, evaluating outcomes on follow-up of children after SAM treatment, noted that 51.7% of children had a poor rate of weight gain, 31% had moderate, and 6.89% had a good rate of weight gain on follow-up [10]. Pakistan has the world's third-highest proportion of stunted children, after only Nigeria and India. In Pakistan, the prevalence of stunting was estimated to be 45%, wasting at 10.5%, and underweight at 31.6% [11, 12]. This study will address the gap in the gain among SAM children on follow-up visits after discharge, as well as challenges such as inadequate nutrition, poor access to resources, or lack of monitoring that could hinder their progress. A two-month follow-up will assist in identifying social, environmental, or economic aspects that impact the child's health after being discharged from the hospital and that contribute to a sustained recovery. Although they are counseled about the treatment, nutrition, and preventive measures, the high mortality rate alarms establishing a better follow-up program to identify the actual situation. This study will test the follow-up. treatment and care and will give us insight into the exact picture of follow-up among children with SAM.

In this study, we attempted to determine weight gain in severe acute malnutrition (SAM) children (6 months to 60 months) after discharge from the hospital, followed by weekly follow-up for two months, and the influence of sociodemographic factors such as age, gender, monthly income, and maternal education among these children.

METHODS

A prospective cohort study was conducted at the oral therapeutic program clinic at CMC Children Hospital, Larkana, from August 2021 to February 2022, approved by the CPSP Research Evaluation Unit and authorized by the Hospital's Ethical Review Committee with Reference No. CPSP/REU/PED-2017-221-4562. All participants were informed about the research methodology and acquired written consent. A study of a total of 99 children aged 6-60 months with severe acute malnutrition with good appetite discharged from the hospital was enrolled at the OTP clinic at CMC Children Hospital, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana, Pakistan. Mothers were explained about OTP. All children whose mothers or caretakers were trained about how to feed and how to give complementary locally prepared food at home according to WHO protocol. Children were called in for follow-up every 15 days for up to two months following discharge to see if they had gained weight. The sample size is computed by Rao sample size software to be 99 according to the formula (n = z2 * p *(1 - p)). / e2), assuming the rate of weight gain among SAM children on follow-up (6.89%) [10], with a confidence level of 95% and a margin of error of 0.05 and a consecutive sampling technique applied. This study included both genders, aged 6 to 60 months. discharged children (as per operational definition) with a good appetite. All children who had gained weight for at least 3 days. No sign of active infection. In the study, children with chronic illnesses, congenital heart disease, cerebral palsy, and those who missed or didn't complete a 2-month follow-up period were excluded. All study data such as age, residence, gender, food, and weight (Seca 725 Germany) were entered into a study-specified questionnaire. The study reduced potential bias by excluding caregivers who were unwilling to follow up during selection, using phone reminders to caregivers to reduce the bias, and weight measurement bias was reduced by using a standardized digital scale by trained healthcare staff. However, selection bias may persist due to the exclusion of children unable to attend follow-ups, potentially limiting the generalizability of the findings. SPSS version 26.0 was applied to analyze the data. Mean ± SD was presented for quantitative variables like age, gestational age, and body weight. Frequency and percentage were computed for qualitative variables like age, gender, body weight, maternal education, and monthly income. Effect modifiers like age, gender, body weight, maternal education, and monthly income were controlled by stratification. Post-stratification chi-square test was applied, and p-value ≤ 0.05 was considered statistically significant.

RESULTS

In all, 99 children had a mean age of 16.4 ± 8.2 months, 52 (52.5%) were under 12 months, 40 (40.4%) were between 13 and 36 months, and 7 (7.1%) were between 37 and 60 months (Figure 1).

DOI: https://doi.org/10.54393/pjhs.v6i1.2559

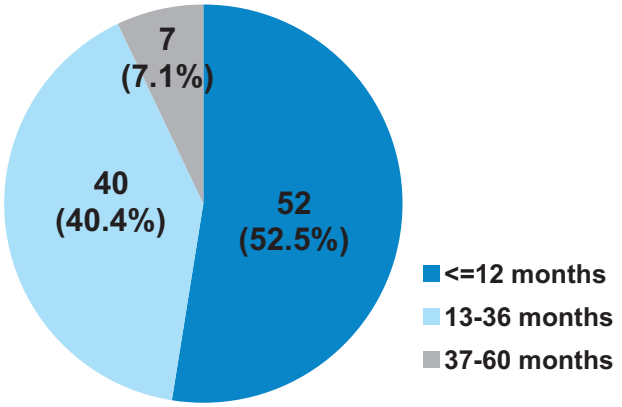

Figure 1: Distribution of Age in Months (n=99)

Gender-wise distribution of patients, 58 (58.6%) were male and 41 (41.4%) females (Figure 2).

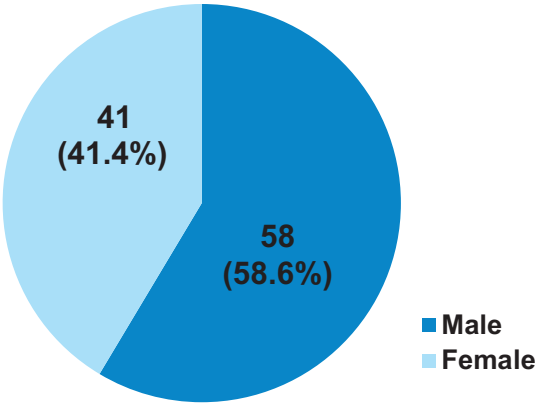

Figure 2: Distribution of Gender

Concerning area of residence was rural in 58 (58.6%) children while the remaining 41 (41.4%) belonged to urban areas (Figure 3).

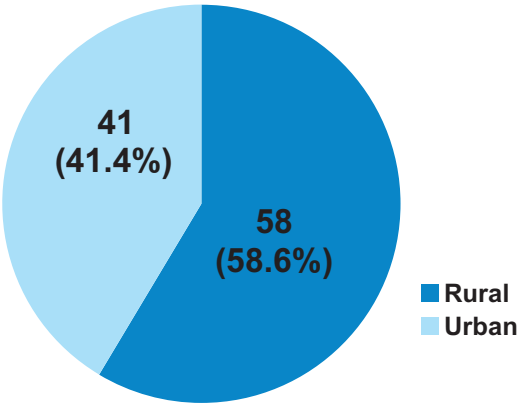

Figure 3: Distribution of Area of Residence (n=99)

The frequency of maternal education status was 32 (32.3%) for illiterate mothers and 67 (67.7%) for literate mothers. Monthly family income was between 25,000 and 40,000 PKR among 53 (53.5%) children, less than 25,000 PKR in 36 (36.4%), whereas the remaining 10 (10.1%) children had monthly family income above 40,000 PKR. Distribution of body weight at the time of discharge showed that most of the children, 59 (59.6%), had body weight between 3000 and 5000 grams. The mean body weight at the time of discharge was calculated to be 4100 ± 620 grams. By the end of 2 months, weight gain was noted among 91 (91.9%) children, while the remaining 8 (8.1%) did not have weight gain (Table 01).

Table 1: Frequency Distribution of Various Variables

Variable	Characteristics	Frequency (%)
Maternal Education	Illiterate	32 (32.3%)
	Literate	67 (67.7%)
Monthly Family Income	< Rs. 25,000	36 (36.4%)
	Rs. 25,000 – 40,000	53 (53.5%)
	> 40,000	10 (10.1%)
Body Weight at the Time of Discharge	<3 kg	27 (27.3%)
	3-5 kg	59 (59.6%)
	>5 kg	13 (13.3%)
Weight Gain After 2 Months	Yes	91 (91.9%)
	No	08 (08.1%)

Frequency Distribution of Weight Gain after 2 months shows that weight gain was good in 51 (51.5%) children, moderate in 34 (34.3%) and poor in 14 (14.2%) (Figure 4).

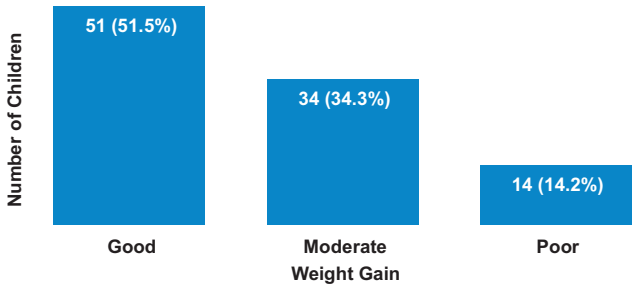

Figure 2: Frequency Distribution of Weight Gain after 2 months (n=99)

The statistically insignificant differences in gender (p=0.8147), area of residence (p=0.3256), and body weight at discharge (p=0.0970), along with weight gain among children with severe acute malnutrition who were monitored for two months after being discharged from the hospital. It shows a statistically significant observed between age (p=0.0085) with weight gain in severe acute malnutrition children after discharge from the hospital followed for 02 months. Of patients who gained weight, 54.9% were ≤ 12 days old, 40.7% were 13–36 days old, and 4.4% were 37–60 days old. The study found an insignificant relationship between residence and weight gain after two months (p=0.32560). The majority of participants (42.9%) gained weight from urban areas, while only 25% did not gain weight. The majority (57.1%) gained weight from rural areas, while 75% did not gain weight. A significant correlation between maternal education and weight gain in severely acute malnourished children after hospital

DOI: https://doi.org/10.54393/pjhs.v6i1.2559

discharge, with literate mothers experiencing a higher weight gain (71.4%) compared to illiterate (28.6%) children. In the distribution of monthly family income and weight gain after two months families earning less than Rs. 25,000 exhibited a weight rise of 34.1%, while those earning between Rs. 25,000 and Rs. 40,000 showed a weight gain of 56.0%, indicating a significant correlation (p=0.0416). The study revealed that 27.5% of weight gain participants had a body weight below 3 kg at discharge, with the majority (61.5%) gaining between 3-5 kg. 37.5% did not gain weight, and 11% gained above 5 kg. The p-value did not show a significant association between body weight and weight gain. (p=0.0970)(Table 2).

Table 2: Distribution of different variables concerning Weight Gain at 2 Months (n=99)

Variable	Characteristics	Weight Gain		p-Value
		Yes (n=91)	No (n=8)	
Gender	Male	53 (58.2%)	5 (62.5%)	0.8147
	Female	38 (41.8%)	3 (37.5%)	
Age	<12 Months	50 (54.9%)	2 (25.0%)	0.0085
	13-36 Months	37 (40.7%)	3 (37.5%)	
	37-60 Months	4 (4.4%)	3 (37.5%)	
Area of Residence	Rural	52 (57.1%)	6 (75.0%)	0.3256
	Urban	39 (42.9%)	2 (25.0%)	
Maternal Education	Illiterate	26 (28.6%)	6 (75.0%)	0.0071
	Literate	65 (71.4%)	2 (25.0%)	
Monthly Family Income	< Rs. 25,000	30 (34.1%)	6 (75.0%)	0.0416
	Rs. 25,000–40,000	52 (56.0%)	1 (12.5%)	
	> 40,000	9 (8.9%)	1 (12.5%)	
Body Weight at Time of Discharge	<3 kg	25 (27.5%)	2 (25.0%)	0.0970
	3-5 kg	56 (61.5%)	3 (37.5%)	
	>5 kg	10 (11.0%)	3 (37.5%)	

In demographic variable analysis, it was revealed that only the younger age group of children was significantly higher among SAM children, while in socioeconomic variables, weight gain had a significant relation with higher maternal education levels and higher family income. In the study, weight gain did not show an association with gender, area of residence, and body weight at the time of discharge.

DISCUSSION

Timely identification and appropriate treatment regarding various complications accompanying SAM, followed up with optimal feeding protocols, can result in a reduction of morbidity and mortality associated with it. In this study, we found that 58.6% of children with SAM were male. Nagar RP et al., evaluating 75 children under the age of 5 years with malnutrition, found that 74.6% were male [10]. Our observations differ from what was found by Dale NM et al., where the authors noted 58.0% of the cases with SAM under the age of 5 years to be female. [12]. A study from India by Sanghvi J et al., found 52.0% of the children under the age of 5 years with SAM to be female [13]. So, variation exists regarding the predominance of gender in children presenting with SAM in our region. In this study, the mean age was found to be 16.4 ± 8.2 months, while 52.5% of children were below 12 months of age. Our findings were consistent. with regional data where 52% of the children under the age of 5 years with SAM were aged below 1 year [10]. This study observed that weight gain after 2 months following hospital discharge was noted among 91.9% of children. It was also found that weight gain was good in 51 (51.5%) children, moderate in 34 (34.3%), and poor in 14 (14.2%). Mamidi et al., reported that 8% of children with SAM did not have gain by the end of the study period, 44% had poor catch-up growth described as weight gain below 5 grams per kilogram per day, 35% had moderate catch-up growth as described by 5 to 10 grams per kilogram per day, whereas 12% were found to have rapid catch-up growth as labeled weight gain of more than 10 grams per kilogram per day. 14.7% of the children gained weight poorly, 30.9% gained weight moderately, and the remaining 30.9% gained weight well [14]. The study found a significant association between weight gain after hospital discharge, particularly among younger age groups, literate mothers, and high-income families. Sanghvi J et al., from India showed similar results in terms of the relation of age with weight gain among children with SAM, where they reported that children having higher ages were not found to gain weight in comparison to children in younger age groups [13]. About 45% of all deaths among children under the age of five are related to undernutrition, which is concerning and should not be ignored. The majority of these deaths occur in low- and middle-income nations, particularly in Asia and Africa [15, 16]. Maternal educational status is regarded as a strong factor contributing to the prevalence of SAM. Maternal education is a crucial factor in enhancing the developmental status of children with severe acute malnutrition (SAM), who are at a higher risk for developmental delays in multiple areas [17]. Likewise, researchers from Bangladesh reported similar observations where it was noted that maternal education status as illiterate was linked with a 4-fold rise in the risk of SAM among the pediatric population [18]. Similar to our study, many researchers have found a significant relationship between poverty, poor socio-economic status, and the risk of SAM [19, 20]. The study conducted by Maharashtra emphasizes the various factors contributing to SAM, highlighting the necessity of interventions that focus on maternal education, healthcare accessibility, and vulnerable age groups [21]. The current study found an insignificant relationship between residence and weight gain after two months. In a Pakistani study, an estimated 5.9% of Pakistani children under five had both wasted and stunted growth, with a significant association with rural areas (6.8%), mother education (7.7%), and low-income families (10.7%) [22]. Pakistan's rural regions have higher

DOI: https://doi.org/10.54393/pjhs.v6i1.2559

child malnutrition rates, largely due to factors such as early marriage, large families, irregular pregnancy rates, low income, and inadequate or nonexclusive nursing, which contributes to malnutrition under age five. Lack of awareness about the importance of nutrition, poor educational status, poverty, and lack of attention to children by parents in our area could be a few reasons contributing to the presence of SAM among children. In this study, despite all possible education and advice about the required measures and treatment, children unable to gain satisfactory weight suggest that the literacy rate, especially among women, and economic aspects of the population of our area are important. As soon as children were discharged and sent home, many factors contributing to SAM must have been enabled in some cases. All this also hints towards measures and strategies to be planned. regarding comprehensive nutritional and health education to parents/caregivers/guardians of children with SAM when they attend healthcare facilities for help regarding the resolution of SAM so that they can further practice and implement measures and practices necessary at home to improve SAM among their children.

CONCLUSIONS

The research findings revealed that socio-demographic characteristics such as age, maternal education, and monthly family income showed a significant association with weight gain in severe acute malnutrition children after hospital discharge. The study emphasizes that socioeconomic factors reduce morbidity and mortality post-hospital discharge for a child's sustained recovery, ensuring therapy adherence, reducing complications, supporting nutritional needs, and aiding caregivers.

Authors Contribution

Conceptualization: M
Methodology: VKG
Formal analysis: NFS, DB, SA
Writing review and editing: SJ

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (P): 2790-9352, (E): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Knowledge and Attitude of Hypertensive Patients to Control Hypertension at Hayatabad Medical Complex, Peshawar

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ARTICLE INFO

Keywords:
Hypertension, Patient Knowledge, Attitudes, Medication Adherence

How to Cite:
Shah, S. H. A., & Basir, W. (2025). Knowledge and Attitude of Hypertensive Patients to Control Hypertension at Hayatabad Medical Complex, Peshawar: Knowledge and Attitude of Hypertensive Patients to Control Hypertension . Pakistan Journal of Health Sciences, 6(1),276 -282. https://doi.org /10.54393/pjhs.v6i1.2301

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Received date: 5th October, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

Hypertension is a major public health concern globally, including in Pakistan, contributing significantly to cardiovascular morbidity and mortality. Despite its prevalence, knowledge and attitudes toward hypertension management remain inadequately explored in Pakistan. **Objectives:** To assess the knowledge, attitudes, and practices of hypertensive patients toward hypertension control at Hayatabad Medical Complex (HMC), Peshawar. **Methods:** A descriptive cross-sectional study was conducted from July 2023 to July 2024, involving 584 hypertensive patients aged 40-75 years. Data were collected using a structured, physician-administered questionnaire, which assessed patients' knowledge of hypertension, attitudes toward lifestyle modifications, and medication adherence. Descriptive statistics summarized the demographic characteristics, while chi-square tests were used to explore associations between knowledge and adherence behaviours. **Results:** Of the participants, 34.8% demonstrated good knowledge of hypertension, and 69.8% recognized it as a cardiovascular risk. Medication adherence was high, with 72.5% of patients consistently following their prescribed regimen. Regular blood pressure monitoring was performed by 59.7% of participants, though 31.5% had not monitored their BP for over a month. A significant association was found between knowledge levels and adherence to medication ($p<0.05$). **Conclusions:** It was concluded that the study reveals substantial gaps in knowledge about hypertension among patients, despite good medication adherence rates. Targeted educational interventions are needed to improve understanding of hypertension and its management, especially in resource-limited settings.

INTRODUCTION

Hypertension, a leading global public health concern, has been linked to significant morbidity and mortality due to cardiovascular diseases. The global prevalence of hypertension has been increasing, particularly in low- and middle-income countries, where resources for diagnosis and management are often limited [1, 2]. In Pakistan, hypertension is a major risk factor contributing to complications such as myocardial infarction, stroke, and renal disease [3, 4]. A study conducted at various hospitals across the country indicated that knowledge and attitude towards hypertension control among patients remain suboptimal [5, 6]. Controlling hypertension effectively depends heavily on patients' knowledge, attitude, and practices (KAP) towards the disease. Studies have revealed that when patients are aware of the consequences of untreated hypertension and actively participate in its management, their compliance with treatment increases, leading to better outcomes [7, 8]. On the other hand, numerous studies pinpointed the flaws in the levels of patient education as a vast part of the population may not be aware of the critical lifestyle modifications and medication courses they might need to make to control their case of hypertension [9, 10]. In Pakistan, the management of hypertension frequently encounters significant challenges since the relevant patient education is hindered by the lack of sufficient healthcare resources

DOI: https://doi.org/10.54393/pjhs.v6i1.2301

and cultural considerations [11]. Several studies in the region have investigated knowledge and awareness in hypertensive patients, showing that there is a lack of understanding among affected patients about how hypertension is associated with lifestyle factors, such as diet and physical activity. In urban settings, where the burden of hypertension is rising, the control of the disease is often suboptimal due to factors such as limited patient education, low adherence to treatment, and barriers to accessing quality healthcare services [12, 13]. The knowledge of hypertension management was reported in Ethiopia only to be as 51.7% and lifestyle modification adherence was found to be low among hypertensive patients [7, 14]. This is a familiar theme in studies that underscore the need for patient education around medication adherence and lifestyle changes to mitigate complications of hypertension [15]. Several different educational strategies have been tested across a variety of healthcare settings to enhance patients' knowledge and attitudes about the management of hypertension. A clinical trial in Iran found that targeted educational interventions significantly improved patients' knowledge, attitudes, and practices, leading to better blood pressure control [16]. Similarly, a study from Zimbabwe highlighted that awareness programs focusing on the risks of untreated hypertension could lead to better management outcomes, especially in rural communities [11]. Pakistan has seen similar trends, with studies indicating that hypertensive patients who receive structured health education, particularly those in urban settings, show higher compliance with medication and lifestyle changes [17, 18]. However, there remains a considerable gap between knowledge and practice, which points to the need for continuous, community-driven educational initiatives that focus not only on hypertension but also on the broader spectrum of cardiovascular disease prevention [19, 20].

This study aims to assess the knowledge and attitudes of hypertensive patients at HMC, Peshawar. The findings will inform targeted educational interventions to enhance patient understanding of hypertension management. By identifying the common misconceptions and barriers to compliance, this study seeks to contribute to improving hypertension outcomes in a low-resource setting.

METHODS

A descriptive cross-sectional study was conducted at Hayatabad Medical Complex (HMC), Peshawar, from June 2023 to July 2024, for hypertensive patients aged 40-75 years. The sampling technique used was convenience sampling, where patients attending the Outpatient Department were approached for participation in the study. Data were collected using a structured, physician-administered questionnaire, which assessed patients' knowledge of hypertension, attitudes toward lifestyle modifications, and medication adherence. The sample size for this study was calculated using an assumed 50% prevalence of hypertension knowledge among patients, with a margin of error of 4% and a confidence level of 95%. Based on these assumptions and similar research, such as the study by Mekonnen et al., [7], the total sample size was determined to be 584 participants. The study included male and female patients aged 40-75 years who had been diagnosed with hypertension for at least three months before the beginning of the study. This age range was selected because hypertension commonly develops after the age of 40, and its prevalence increases with age, particularly in individuals aged 40-75. The patients have no major cardiovascular comorbidities, such as definite or probable heart failure, history of myocardial infarction, definite or history of diagnosed coronary artery disease, stroke, or peripheral arterial disease. The exclusion criteria in this study were pregnancy and diagnosis of psychiatric disorders that could affect the assessment of reliable data and compliance with therapy. The data were collected using a structured, physician-administered questionnaire in the Outpatient Department setting. The questionnaire used in this study was developed specifically for this research based on established hypertension knowledge, attitude, and practice scales used in prior studies. To ensure reliability, the questionnaire was pre-tested on a sample of 30 hypertensive patients. The Cronbach's alpha for the final version of the questionnaire was 0.82, which indicates good internal consistency. An interview schedule designed to assess the levels of knowledge and attitudes was presented in English but was translated verbally to the local language by the physician to ensure understanding by participants. The questionnaire included items related to basic demographic information, knowledge of hypertension, lifestyle modifications, medication adherence, and follow-up practices. It assessed attitudes toward hypertension management, including the importance of regular blood pressure monitoring, compliance with prescribed medication, and lifestyle modifications. The study specifically examined patients' understanding of hypertension, its stages, target blood pressure levels, associated risks, and the role of lifestyle factors such as physical activity, smoking, diet, salt intake, and body weight in controlling blood pressure. Data were entered into SPSS (Version 25.0) for statistical analysis. Descriptive statistics, including frequencies and percentages, summarized the demographic characteristics, knowledge levels, and attitudes of participants. A Chi-Square test was applied to assess associations between knowledge and attitude variables (such as knowledge of hypertension, awareness of lifestyle changes, and perception of hypertension as a

DOI: https://doi.org/10.54393/pjhs.v6i1.2301

cardiovascular risk factor) and demographic characteristics (such as age, gender, and duration of hypertension). Additionally, the Chi-Square test was also used to explore the relationships between knowledge of hypertension and adherence to antihypertensive medication and between the perception of hypertension as a cardiovascular risk factor and frequency of blood pressure monitoring. The study protocol was reviewed and approved by the Ethical and Research Committee of HMC, Peshawar (Reference No: 2207). All patients were informed of the study's objectives, assured that their participation was voluntary, and provided written informed consent before completing the questionnaire. Confidentiality of patient information was maintained, and all data were anonymized during analysis. This study did not involve any animal subjects.

RESULTS

A total of 584 hypertensive patients participated in this study, with 51.9% being female and 48.1% male. The average age of participants was 57.6 years (SD ± 10.61), with the majority falling within the age group of 50-59, followed by 40-49 and 60-69. These demographic details are shown in Table 1.

Table 1: Demographics and Knowledge Distribution (n=584)

Variables	Category	Frequency (%)
Gender	Male	281 (48%)
	Female	303 (52%)
Age Group	40-49 Years	150 (26%)
	50-59 Years	188 (32%)
	60-69 Years	160 (27%)
	70-75 Years	86 (15%)

In terms of knowledge about hypertension, 34.76% of patients (203 out of 584) reported understanding their condition, while the remaining 65.24% (381 out of 584) were either unsure or did not know about hypertension. Among those who were informed about optimal blood pressure (BP) levels, 64.90% (379 out of 584) knew, while 35.10% (205 out of 584) were not aware. Additionally, 35.44% (207 out of 584) of participants were informed about associated cardiovascular risks, while 64.56% (377 out of 584) were not. These findings are summarized in Table 2.

Table 2: Knowledge and Awareness of Hypertension Among Participants (n=584)

Variables	Category	Frequency (%)
Knowledge of Hypertension	Yes	203 (34.76%)
	No/Unsure	381 (65.24%)
Optimal BP Informed	Yes	379 (64.90%)
	No/Unsure	205 (35.10%)
Informed About Risks	Yes	207 (35.44%)
	No/Unsure	377 (64.56%)

The majority of participants, 69%, recognized hypertension as a significant risk factor for cardiovascular disease (CVD), while 17.1% were uncertain about this risk. Regarding the management of hypertension, 29% of patients believed that it could be managed without antihypertensive medications, while the majority acknowledged the importance of these drugs. These findings are summarized in Table 3.

Table 3: Patient Attitudes Toward Hypertension Management (n=584)

Variables	Yes Frequency (%)	No Frequency (%)	Uncertain Frequency (%)
Hypertension is a Risk for CVD	408 (69.9%)	76 (13.0%)	100 (17.1%)
Can Manage BP without Drugs	172 (29.4%)	204 (34.9%)	208 (35.7%)
Importance of Antihypertensives	424 (72.5%)	160 (27.5%)	0 (0%)

Regarding lifestyle modifications, 58.3% (340 patients) of patients were aware of the importance of making changes to their lifestyle, although only 49.1% (287 patients) had successfully quit smoking. The necessity for multiple drugs to control hypertension was recognized by 58.4% (341 patients) of patients. These findings are summarized in Table 4.

Table 4: Lifestyle Modifications Among Participants (n=584)

Lifestyle Modification	Frequency (%)
Regular Physical Activity	340 (58%)
Successfully Quit Smoking	287 (49.1%)
Recognizes Need for Multiple Drugs	341 (58.4%)
Smokes Cigarettes	152 (26%)
Follows Diet Control	356 (61%)
Reduces Salt Intake	316 (54%)
Monitors Body Weight	240 (41%)

Medication adherence was relatively high, with 72.6% (424 cases) of patients reporting consistent use of antihypertensive medications. However, 5.0% (29 cases) missed doses at least once a month, while 22.4% (131 cases) reported missing doses at other frequencies. This information is illustrated in Figure 1.

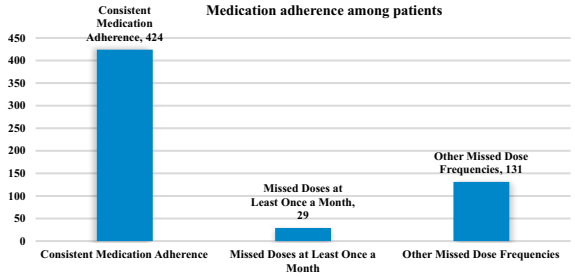

Figure 1: Medication Adherence Among Patients

Around 59.7% (348 patients) of participants regularly monitored their blood pressure. Among them, 21% (122 patients) monitored their blood pressure within the last

DOI: https://doi.org/10.54393/pjhs.v6i1.2301

month, 20% (116 patients) did so within the last week, and 19% (110 patients) monitored their blood pressure between 1 month and 1 year. However, 40.3% (236 patients) did not monitor their blood pressure, as shown in Figure 2.

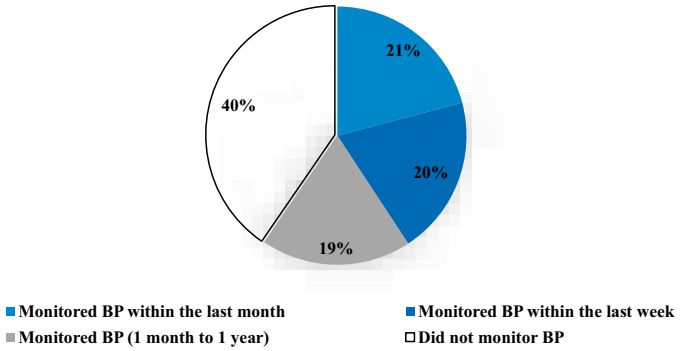

Figure 1: Frequency of Blood Pressure Monitoring

The study revealed that 58% of participants engaged in regular physical activity, such as walking, jogging, or other forms of exercise, while 42% did not incorporate any consistent physical activity into their routine. Regarding smoking habits, 26% of participants were current smokers, 15% were former smokers, and 59% had never smoked. In terms of diet control, 61% of participants reported following a specific diet, such as a low-salt or low-fat diet, to help manage their hypertension, whereas 39% did not adopt any particular dietary modifications for blood pressure control. Concerning salt intake, 54% of participants actively reduced their salt consumption to manage their blood pressure, while the remaining 46% did not consciously limit their salt intake. Finally, 41% of participants monitored their body weight as part of their hypertension management, while 59% did not follow any specific weight control strategies. These findings are summarized in Table 5.

Table 5: Lifestyle Modifications Among Participants (n=584)

Lifestyle Modification	Yes Frequency (%)	No Frequency (%)
Regular Physical Activity	340 (58.3%)	244 (41.7%)
Smokes Cigarettes	152 (26%)	432 (74%)
Follows Diet Control	356 (61%)	228 (39%)
Reduces Salt Intake	316 (54%)	268 (46%)
Monitors Body Weight	240 (41%)	344 (59%)

The analysis revealed that among the 392 patients who did not recognize hypertension as a cardiovascular risk factor, 131 patients (33.4%) regularly monitored their blood pressure, while the remaining 261 patients (66.6%) did not monitor their blood pressure. In contrast, of the 192 patients who recognized hypertension as a cardiovascular risk factor, 64 patients (33.3%) regularly monitored their blood pressure, and 128 patients (66.7%) did not. These findings indicate that recognition of hypertension as a cardiovascular risk factor was not strongly associated with an increased likelihood of monitoring blood pressure. The majority of patients in both groups, regardless of risk factor recognition, did not engage in regular blood pressure monitoring, as shown in Table 6.

Table 6: Relationship Between Risk Factor Recognition and Blood Pressure Monitoring (n=584)

Risk Factor Recognition	Monitoring (Count %)	Non-Monitoring (Count %)	Total (Count)
Not Recognized	131 (33.4%)	261 (66.6%)	392
Recognized	64 (33.33%)	128 (66.7%)	192
Significance value: <0.01			

Patients' knowledge of hypertension showed a more balanced association with medication adherence. Among the 203 patients categorized as having better knowledge of hypertension, 104 patients (51.2%) adhered to their prescribed antihypertensive medications, while 99 patients (48.8%) did not adhere. Conversely, of the 381 patients with poor knowledge of hypertension, 191 patients (50.1%) adhered to their prescribed medications, and 190 patients (49.9%) did not. These results indicate that patients with better knowledge of hypertension were slightly more likely to adhere to their medication regimen compared to those with poor knowledge; however, the difference in adherence rates was minimal, with adherence observed in approximately half of the patients in both groups, as shown in Table 7.

Table 7: Relationship Between Knowledge Group and Medication Adherence (n=584)

Knowledge Group	Adherence (Count %)	Non-Adherence (Count %)	Total (Count)
Better Knowledge	104 (51.2%)	99 (48.8%)	203
Poor Knowledge	191 (50.1%)	190 (49.9%)	381
Significance value: <0.01			

DISCUSSION

This study represents a significant contribution to the understanding of hypertensive patients' knowledge and attitudes toward hypertension management at HMC in Peshawar, Pakistan. While there have been studies conducted in Pakistan on hypertension knowledge and attitudes, such as those by Naseem *et al.*, in Lahore and Sumaira *et al.*, in Rawalpindi, comprehensive assessments of both knowledge and attitudes of hypertensive patients in public healthcare settings have been relatively limited [21, 22]. These studies have focused on specific aspects of hypertension management, such as awareness of risk factors, treatment adherence, and lifestyle modifications. However, this study is one of the to comprehensively assess both knowledge and attitudes toward hypertension and its management among hypertensive patients in a public healthcare setting in Peshawar, which adds valuable insight into the challenges faced by patients in urban Pakistan. In various countries, especially in lower- and middle-income regions like Ethiopia and Zimbabwe,

DOI: https://doi.org/10.54393/pjhs.v6i1.2301

researchers have faced similar challenges with patient knowledge and the management of hypertension. For example, a study by Mekonnen *et al*. found that 51.7% of the participants in Ethiopia understood how to manage their hypertension. This is higher than what we observed in our study, where only 34.8% of the participants showed a comparable level of knowledge. Chimberengwa and Naidoo conducted a study in Zimbabwe, where they found that only 35.2% of participants had a good understanding of hypertension management, which is more in line with our results [11]. These findings underscore the critical role knowledge plays in managing hypertension and reflect similar patterns seen in other resource-limited settings around the world. There's been limited research in Pakistan on how hypertensive patients manage their condition and their level of knowledge about it. Unlike countries like Ethiopia and Zimbabwe, where this issue has been studied more thoroughly, Pakistan lacks a significant body of work in this area. This gap makes it harder to understand how people here deal with hypertension and highlights where education is most needed. While studies such as Khan *et al.*, have explored hypertension care in private healthcare, there's almost no research focusing on public hospitals like HMC [18]. Although research on hypertension management in Pakistan is limited, some studies have been conducted. Nadeem *et al.*, found that patient knowledge about hypertension and its management had a direct effect on blood pressure control in a semi-private hospital in Karachi [6]. The medication adherence rate of 72.5% observed in our study is in line with Nadeem's findings, where patients' awareness played a significant role in their adherence to antihypertensive medications. Hypertension as a public health issue is well-reported in Pakistan's medical literature, but gaps in patient education and attitude remain underexplored. Mahmood *et al.*, found that in primary and secondary care settings, only 40% of patients adhered to their antihypertensive medications, which is much lower than the 72.5% adherence rate observed in our study [20]. This difference could be due to the urban setting of Peshawar, where patients have better access to healthcare. However, it's important to investigate these regional differences more closely and explore how improving patient education could help raise adherence rates across different parts of Pakistan. Our study's results match what we're seeing worldwide: patients' knowledge and attitudes are really important for managing high blood pressure. We discovered that only about 35% of our participants understood their hypertension well, highlighting a significant gap that could make controlling blood pressure more difficult. Other research, like the 2020 study by Ramadaniati and colleagues, has shown that education programs led by pharmacists or nurses can greatly improve both patients' understanding and their adherence to medications [9]. We were encouraged to find that about 60% of our participants regularly monitor their blood pressure. However, there's still plenty of room to improve since many aren't checking it often enough to prevent potential complications. We need to boost educational efforts to highlight just how important regular BP checks are for managing hypertension effectively. Additionally, while the study used a cross-sectional design to assess knowledge and attitudes, a longitudinal approach would provide more insight into how patient education impacts long-term hypertension management. Future studies should consider exploring rural populations and implementing intervention programs that focus on improving patient knowledge and medication adherence over time. Given the substantial gaps in knowledge revealed in this study, structured community-based educational programs are recommended to enhance awareness and promote self-management of hypertension, especially in under-resourced areas of Pakistan.

CONCLUSIONS

It was concluded that this study highlights the significant gaps in knowledge about hypertension among patients at Hayatabad Medical Complex, Peshawar, despite high rates of medication adherence and awareness of hypertension as a cardiovascular risk. The findings underscore the need for targeted educational interventions to improve patient understanding of hypertension management and the importance of regular blood pressure monitoring. Enhancing patient education can lead to better self-management and overall health outcomes, particularly in resource-limited settings like Pakistan.

Authors Contribution

Conceptualization: SHAS, WB
Methodology: SHAS, WB
Formal analysis: SHAS, WB
Writing review and editing: SHAS, WB

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v6i1.2301

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DOI: https://doi.org/10.54393/pjhs.v6i1.2634

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Comparison of Continuous Versus Simple Interrupted Polypropylene Suture Closure of Midline Emergency Laparotomy Wound in Terms of Wound Outcome in Adult Patients Presenting with Acute Abdomen

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ARTICLE INFO

Keywords:
Simple Interrupted Suture, Continuous Closure Technique, Polypropylene, Midline Laparotomy

How to Cite:
Nasir, M., Siddique, M., Zaeem, A., Raza, A., Rizwan, M., & Abbas, M. (2025). Comparison of Continuous Versus Simple Interrupted Polypropylene Suture Closure of Midline Emergency Laparotomy Wound in Terms of Wound Outcome in Adult Patients Presenting with Acute Abdomen: Continuous Vs Interrupted Polypropylene Suture Closure of Laparotomy Wound . Pakistan Journal of Health Sciences, 6(1), 283-288. https://doi.org/10.54393/pjhs.v6i1.2634

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Received date: 27th November, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

The best method and material for sutures to use while closing wounds are still unknown. This study aimed the results of this trial to determine which method works best and should be recommended as hospital policy. **Objectives:** To compare outcomes of simple interrupted versus continuous closure techniques using no.1 polypropylene sutures for emergency midline laparotomy wounds regarding frequency of wound dehiscence. **Methods:** This quasi-experimental study was conducted after obtaining approval from the College of Physicians and Surgeons Pakistan over six months from June 2024 to November 2024. 104 emergency midline laparotomy patients were recruited from the Surgical Department of Sir Ganga Ram Hospital, Lahore. Patients were divided into 2 groups A, continuous suture closure and Group B, simple interrupted suture closure. Postoperatively patients were observed for wound dehiscence. Data were analyzed using SPPS version 26.0. The occurrence of dehiscence was compared among groups using the chi-square test. **Results:** Wound dehiscence was found to be higher in Group A as compared to Group B. Group A: 21.1% vs. Group B: 11.5%, and p-value=0.185. Gender and Body mass index had no significant association with wound dehiscence in study groups. However, among the younger age group patients' frequency of wound dehiscence was significantly higher while among the elderly age group, no significant difference was obtained. **Conclusions:** It was concluded that results of this study showed no significant difference for wound dehiscence for simple interrupted suture compared with versus continuous closure techniques using polypropylene suture for patients who underwent emergency midline laparotomy.

INTRODUCTION

Midline laparotomy is a simple procedure that provides quick access to all abdominal quadrants [1]. Linea alba, the weak midline aponeurotic zone opens during laparotomy, and it becomes even more fragile when its fibres are cut vertically. The mechanical forces acting on these fibres during closure increase the tension [2]. Following fascial closure, complications such as wound dehiscence, incisional hernia, suture sinus formation, and wound infection can occur [3]. Laparotomy wounds can be closed using, absorbable versus non-absorbable sutures, single-layer versus mass closure, and continuous versus interrupted closure. The continuous closure technique offers benefits such as faster healing times and more uniform tension distribution across the suture line [4]. Interrupted sutures also offer multiple advantages, including reduced risk of wound edema, proper alignment

DOI: https://doi.org/10.54393/pjhs.v6i1.2634

of wound edges during suturing, and greater tensile strength. This technique ensures healing even if one of the sutures breaks. However, it requires more time to complete due to the additional knots and demands more suture material [1, 5]. Previous studies have highlighted notable differences between continuous and interrupted polypropylene closures of midline laparotomy wounds, particularly in the occurrence of wound infection and stitch granuloma [6]. Although these studies suggest that continuous closure might have a lower frequency of complications compared to interrupted closure, the reported outcomes are inconsistent and vary considerably across studies [7, 8]. The literature on abdominal wound dehiscence, and significant surgical complications following midline laparotomy, also shows a wide range of frequencies, reflecting a lack of standardization and reliable data in this area [9]. This variation in findings indicates that further research is necessary to establish clearer guidelines and better understand the factors influencing these outcomes. Studies conducted locally and regionally indicate that the incidence of abdominal wound dehiscence varies significantly in both elective surgeries and emergency laparotomies [10]. Globally, research has shown varying wound dehiscence rates for continuous and interrupted closure techniques. Notably, a local study highlighted the statistically significant difference in the frequency of ruptured abdomens, showing a higher dehiscence rate with continuous polypropylene suture compared to interrupted polypropylene closure in midline emergency laparotomies [11]. Given the limited local data and the inconsistency in findings, particularly concerning rural versus urban healthcare settings, this study aims to critically compare the outcomes of simple interrupted versus continuous closure techniques using No. 1 polypropylene suture for emergency midline laparotomy wounds, focusing on the frequency of wound dehiscence. By addressing the gaps in local literature and considering the broader applicability to different healthcare environments, this research seeks to provide evidence-based recommendations for surgical practice.

This study aims to compare outcomes of simple interrupted versus continuous closure techniques using no.1 polypropylene sutures for emergency midline laparotomy wounds regarding frequency of wound dehiscence.

METHODS

This quasi-experimental study was conducted from June 2024 to November 2024 after getting approval from the College of Physicians and Surgeons Pakistan (CPSP) (REU: 53140) and ref no: CPSP/REU/SGR-2019-059-11304. 104 patients undergoing midline laparotomy were recruited from the Surgical Department of Fatima Jinnah Medical University (FJMU)/Sir Ganga Ram Hospital (SGRH), Lahore. Patients of both genders and >18 years of age presenting in an emergency with acute abdominal conditions, including bowel obstruction, infection, or trauma requiring vertical midline laparotomy incision were included. Patients with previous midline laparotomy wound or scar/ abdominal malignancy, ascites, comorbid i.e. end-stage renal disease (ESRD) (glomerular filtration rate (GFR) <15ml/min/m2 or on renal replacement therapy), chronic liver disease (CLD) (as determined on Ultrasonography (USG) abdomen cirrhotic liver), Ischemic heart disease (IHD) (ST-T changes in electrocardiogram (ECG)), presenting with burst abdomen or incisional hernia at the time of presentation, and immunocompromised patients were excluded. A sample size of 104 patients (52 in each group) was estimated using 80% power of the test, a level of significance of 5% and wound dehiscence incidence of 20.5% in continuous and 4.5% in interrupted sutures [12]. Patients were enrolled using a non-probability consecutive sampling technique, used this method because it was practical for the emergency setting, allowing for the inclusion of all eligible patients within a specific time frame to ensure a comprehensive analysis. Written informed consent was obtained from all patients/guardians. In this study, content analysis was employed to systematically evaluate the data collected through the predesigned research proforma. All patients were evaluated with history, physical examination and relevant laboratory and imaging investigations. X-ray chest and abdomen (supine). USG and computed tomography (CT) of the abdomen and pelvis were obtained selectively as indicated by the diagnosis and condition of the patient. Additional investigations, like ECG, were obtained as required by the anesthesiologist during preoperative evaluation. Predesigned research proforma was used to enter the initial data, all patients were operated on under general anesthesia. All patients had fluid and electrolyte replacement before surgery. Antibiotic prophylaxis included IV Cefuroxime 750 mg. Further doses and additional antibiotics (Amikacin and Metronidazole) were administered in appropriate doses as dictated by patient diagnosis and operative findings. Patients were divided into two equal groups (Group A=continuous suture closure and Group B=simple interrupted suture closure) in a 1:1 ratio by using random allocation software to obtain a trial sequence which was hidden in pre-sealed numbered opaque envelopes. Each envelope had a closure method assigned to a single patient. Emergency laparotomy was performed employing a vertical midline incision skirting the umbilicus. Intraoperative findings were recorded. Patients in both groups had thorough peritoneal lavage with warm normal saline and abdominal drains were placed

DOI: https://doi.org/10.54393/pjhs.v6i1.2634

appropriate to operative findings and procedure. Polypropylene no. 1 suture was used for the closure of laparotomy wounds in all patients. In Group A, the continuous suturing technique was used. A strand of suture was started at the upper end of the incision. Six knots were tied initially, and the suture ran onward to the middle of the incision after placing the knots underneath the fascia. The second strand of suture was started at the lower end of the incision taking 6 initial knots and burying under the fascia and was carried towards the middle of the incision. Both sutures were tied with 6 knots in the middle of the incision and knots were buried under the fascia. In long incisions, three or more segments of continuous sutures were used to maintain the wound and suture length ratio of 1:4.3 In Group B, simple interrupted stitches technique was used employing consecutive sutures taking 6 squared knots in a single suture tie. All closures were performed by surgical residents under the supervision of the senior registrar. Skin closure depended upon operative findings and skin was left open in contaminated and dirty wounds. In surgical wards postoperatively, the wound was examined and the incidence of dehiscence if present was noted within 10 days. Partial: disruption limited to one part of fascial closure resulting in visible loose sutures and gaping wound edges, with or without visible bowel loops, which may or may not require surgical closure; Complete: Total disruption of fascial closure along its full length with eviscerated of bowel loops through the wound, which require a new closure. Data were analyzed by SPSS version 26.0. Quantitative variables were presented as mean and SD and qualitative variables as frequency and percentage. Both groups were compared for dehiscence incidence by using the chi-square test, p-value ≤0.05 was considered as significant. Data were stratified for effect modifiers, both groups were compared for wound dehiscence using the chi-square test for each stratum, a p-value≤0.05 was considered significant.

RESULTS

The mean age of patients in Group A and Group B calculated was 44.96 ± 12.28 years and 42.80 ± 13.65 years, respectively. The age of patients in both treatment groups ranges between 21-70 years. In Group-A 51.9% of patients were male and 48.1% were female and in Group B 55.8% were male vs 44.2% female. In Group A, body mass index (BMI) was found to be normal in 34.6% of patients, 28.8% were overweight and 36.5% were obese while in Group B, 28.8% of patients BMI was normal, 51.9% were overweight and 19.2% were found to be obese. In Group A, 15% of participants were identified as diabetic, while 13% had hypertension. In Group B, 12% were diabetic, and 10% had hypertension (Table 1).

Table 1: Patient Demographics

Variables n (%)		Group A (n=52)	Group B (n=52)
Gender	Male	27 (51.9%)	29 (55.8%)
	Female	25 (48.1%)	23 (44.2%)
BMI	Normal	18 (34.6%)	15 (28.8%)
	Overweight	15 (28.8%)	27 (51.9%)
	Obese	19 (36.5%)	10 (19.2%)
Age	(Mean ± SD) years	44.96 ± 12.28	42.80 ± 13.65
DM	Yes	8 (15%)	6 (12%)
	No	44 (85%)	46 (88%)
HTN	Yes	7 (13%)	5 (10%)
	No	45 (87%)	47 (90%)

The frequency of wound dehiscence was higher in Group A (21.2%) compared to Group B (11.5%). However, this difference was not statistically significant (p=0.185) (Table 2).

Table 2: Frequency of Wound Dehiscence in Study Groups

Variables	Group A	Group B	Total
Yes	11 (21.2%)	6 (11.5%)	17
No	41 (78.8%)	46 (88.5%)	87
Total	52	52	104
Chi-Square test	1.758		
p-value	0.185		

In the younger age group (20–40 years), wound dehiscence was significantly higher in Group A (12.5%) compared to Group B (4.3%, p=0.005). However, no significant differences were observed in the middle-aged (41–60 years) or elderly (>60 years) age groups. Wound dehiscence rates were similar between male (p=0.382) and female (p=0.331), showing no significant gender-related differences. Furthermore, no significant difference was seen in wound dehiscence among patients about their BMI in this study. i.e. Normal- BMI (Group-A: 11.1% vs Group-B: 26.7%, p-value=0.249), Overweight (Group-A: 26.7% vs. Group-B: 7.4%, p-value=0.087) & Obese (Group-A:26.3% vs. Group-B: 0%, p-value=0.075) (Table 3).

Table 3: Data Stratification

Variables		Group A		Group B		p-Value
BMI						
Normal	Yes	2	11.1%	4	26.7%	0.249
	No	16	88.9%	11	73.3%	
Overweight	Yes	4	26.7%	2	7.4%	0.087
	No	11	73.3%	25	92.6%	
Obese	Yes	5	26.3%	0	0.0%	0.075
	No	14	73.7%	10	100.0%	
Gender						
Male	Yes	5	18.5%	3	10.3%	0.382
	No	22	81.5%	26	89.7%	
Female	Yes	6	24.0%	3	13.0%	0.331
	No	19	76.0%	20	87.0%	

DOI: https://doi.org/10.54393/pjhs.v6i1.2634

Age						
20-40	Yes	2	12.5%	1	4.3%	0.005
	No	14	87.5%	22	95.7%	
41-60	Yes	5	16.7%	4	17.4%	0.944
	No	25	83.3%	19	82.6%	
>60	Yes	4	66.7%	1	16.7%	0.944
	No	2	33.3%	5	83.3%	

DISCUSSION

Over the years, a range of techniques for abdominal wound closure has been developed, but wound dehiscence remains a significant and challenging complication. The ideal technique and choice of suture material for abdominal wall closure continue to be subjects of ongoing debate and research [13]. Closure methods encompass the choice of continuous versus interrupted sutures, the size of fascial bites, inter-stitch distance, and the span and magnitude of sutures used [14]. Continuous sutures offer the advantage of quicker performance with fewer knots, thus streamlining the closure process. However, a potential drawback is that a single suture line holds the fascia together, which could lead to slackening of the entire suture if a cut-through occurs at any point. In contrast, the interrupted suture method, while more time-consuming, is believed to pose a lower risk of wound dehiscence, though it may result in a higher incidence of stitch sinuses [15]. In our study, we compared the outcomes of simple interrupted versus continuous closure using no. 1 polypropylene for emergency midline laparotomy wounds regarding wound dehiscence. The results showed no significant difference in wound dehiscence between the two groups. However, patients in the continuous suture closure group exhibited a higher rate of wound dehiscence (21.2%) compared to those in the interrupted suture group (11.5%), though the p-value (0.185) indicated no statistically significant difference. This finding is consistent with a previous study that reported a higher rate of wound dehiscence with continuous suturing (25.91%) compared to interrupted suturing (5%) in emergency laparotomy patients [16]. However, it is worth noting that our findings contrast with other studies that suggest interrupted suturing has a lower risk of dehiscence. One such study reported significantly lower dehiscence rates with interrupted sutures, emphasizing the need for critical examination of the conflicting results in this area [17]. In contrast to studies showing low occurrences of dehiscence with interrupted X-suturing, Indian studies reported higher wound dehiscence rates (16.7% for continuous and 23.3% for interrupted techniques) [18]. These discrepancies highlight the importance of considering patient demographics, surgical settings, and technique variations when evaluating the outcomes of different closure methods. Some researchers argue that interrupted sutures provide more tensile strength, reducing the risk of dehiscence, whereas others suggest that dehiscence may occur with interrupted sutures only if the wound edges overlap improperly [19, 14]. Moreover, one study found that the relative risk of wound dehiscence was lower in patients whose incisions were closed with interrupted sutures, further supporting the idea that interrupted suturing may provide better outcomes in some cases [20]. Beyond the closure technique itself, the choice of suture material and the involvement of skin layers also play critical roles in determining the outcome. Interrupted sutures typically involve the entire skin layer, ensuring a secure closure. In contrast, continuous subcutaneous sutures, placed just below the external skin layer, offer potential advantages such as improved aesthetic outcomes compared to continuous transdermal sutures [21]. The ideal wound closure method should ensure sufficient tensile strength, proper tissue alignment, and security even in the presence of infection. Studies suggest that continuous closure is preferred for its speed and cost-effectiveness, though rates of dehiscence, complications, and incisional hernias are comparable with interrupted sutures. Continuous sutures may distribute tension evenly, but the rare risk of a single knot or strand breaking can compromise the entire suture line [22]. Interrupted sutures have shown advantages in reducing wound dehiscence, but the time and cost involved, along with potential complications such as stitch sinuses and patient irritation, limit their widespread use. The choice between continuous and interrupted sutures should be guided by patient factors, surgical expertise, and the specifics of the procedure. Conflicting results across studies underscore the complexity of this issue, highlighting the need for further research to refine best practices in abdominal wound closure [22, 23].

CONCLUSIONS

It was concluded that results of this study showed no significant difference in wound dehiscence for simple interrupted suture compared with continuous closure techniques using polypropylene sutures for patients who underwent emergency midline laparotomy. Still with simple interrupted suture frequency of wound dehiscence was lower in patients when compared with continuous closure techniques.

Authors Contribution

Conceptualization: MN
Methodology: MN, MS, AZ, MA
Formal analysis: AR
Writing review and editing: AR, MR, MA

All authors have read and agreed to the published version of the manuscript

DOI: https://doi.org/10.54393/pjhs.v6i1.2634

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2647

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Frequency of Anemia in Type 1 Diabetic Adolescent Patients in Tertiary Care Hospital of Karachi, Pakistan

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ARTICLE INFO

Keywords:
Type 1 Diabetes, Anemia, Complete Blood Count, Serum Ferritin

How to Cite:
Uddin, S., Hameed, T., Ali, S. B. ., Saeed, M., Anjum, A., & Mubarak, M. (2025). Frequency of Anemia in Type 1 Diabetic Adolescent Patients in Tertiary Care Hospital of Karachi, Pakistan: Frequency of Anemia in Type 1 Diabetic Adolescent Patients . Pakistan Journal of Health Sciences, 6(1), 289-294. https://doi.org/10.54393/pjhs.v6i1.2647

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Received date: 5th December, 2024
Acceptance date: 24th January, 2025
Published date 31st January, 2025

ABSTRACT

Anemia in type 1 diabetes (T1D) can impair glucose management by reducing red blood cells, reducing oxygen delivery and affecting insulin sensitivity. Low hemoglobin levels may cause falsely higher HbA1c readings, misleading healthcare providers about glycemic control. **Objective:** To determine the frequency of anemia in type 1 diabetic adolescent patients. **Methods:** A cross-section study was conducted at Baqai Medical University, Karachi, from April 2023 to November 2023. The sample size was 169 diagnosed type 1 diabetes patients. After getting informed consent, HbA1c and Complete Blood Count (CBC) were measured. In the CBC of individuals with hypochromic microcytic anemia, the particular subjects underwent further investigation of serum iron, ferritin and total iron binding capacity (TIBC) levels. All data analyses were performed on SPSS version 23.0. **Results:** The study analyzed adolescent T1Dpatients, focusing on their age and anthropometric parameters. Out of 169 type 1 diabetes patients, 81 were diagnosed with anemia while 88 weren't. There is a statistically significant difference in anthropometric parameters among anemic and non-anemic type T1D patients. The hematological parameters between T1Dsubjects with anemic and non-anemic were significantly lower in those with anemia, with p-values of 0.000**. Out of 81 anemic patients, 47 had iron deficiency anemia with lower levels of iron and ferritin and higher levels of TIBC. **Conclusions:** It was concluded that the study highlights a substantial prevalence of anemia among adolescents with T1D. Hematological analysis showed lower blood parameters and higher TIBC in anemic patients. HbA1c is higher in anemic T1D patients than in non-anemic ones.

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by insufficient insulin synthesis or an inadequate response to the insulin receptor. Hyperglycemia is a serious adverse effect of uncontrolled diabetes that damages numerous systems, including blood vessels, retina and neurons [1]. According to International Diabetes Federation (IDF) in 2021, it was estimated that 537 million people living with diabetes, globally make up 10.5% of the world population. The number is predicted to increase to 643 million by 2030 and 783.2 million by 2045 [2]. The prevalence of diabetes was common in both sex man and women. According to the World Health Organization (WHO), DM is the sixth leading cause of death. IDF reported that 26.7% of people in Pakistan were diagnosed with diabetes mellitus in 2022, for almost 33.3 million people living with DM [3]. Diabetes is classified into many classes such as type 1 diabetes (T1D), type 2 diabetes (T2D), gestational diabetes mellitus (GDM) and neonatal diabetes. T2D is a major class of diabetes. It is estimated about 80 to 90 % diabetic population have T2D. GDM is a kind of diabetes that is not pre-existing and diagnosed during 2nd and 3rd trimester of pregnancy [4]. Neonatal

DOI: https://doi.org/10.54393/pjhs.v6i1.2647

diabetes starts before six months. A primary monogenic etiology can be found in about 80% to 85% of cases [5]. Maturity onset of Diabetes in Young commonly exhibits early progress of hyperglycemia typically earlier than 25 years; however, diagnosis can occur at older ages [6]. T1D was previously known as "insulin-dependent diabetes" or "juvenile-onset diabetes". The immune system damages pancreatic beta cells that produce insulin. 5% to 10% of people with diabetes have T1D, worldwide [7]. Death of T-mediated cells contributes significantly to the pathophysiology of T1D, even though the exact cause of the disease is unknown. Anemia is defined Hemoglobin (Hb) less than 12 g/dL in females and below 13 g/dL in males. Normal ranges of Hb are 12-16 g/dL (local cut-offs) [8]. Compared to the healthy population, subjects with T1D had a higher prevalence of anemia [9]. Anemia in T1D adolescent patients can result in numerous challenges, due to the interaction between these two conditions. The β-cell of the pancreas produces insulin that requires iron to function properly. It can weaken insulin secretion and sensitivity, making it stiff to regulate plasma sugar. This may lead to more episodes of hyperglycemia and hypoglycemia, decreasing the efficiency of T1D management [10]. Anemia can reduce physical growth and development in adolescents. Iron intake is vital for puberty-related growth secretions and achieving health, especially in adolescent girls. Insufficient iron levels in a body can cause growth delays and decrease cognitive function. Iron deficiency Anemia (IDA) can absorb other essential macro and micronutrients, including vitamins and minerals, vital for maintaining overall health and controlling T1D. The health of adolescents with T1D patients may worsen due to a disturbance in the dietary cycle. IDA class of anemia is more common in Pakistan particularly in adolescent subjects with T1D across various ethnic groups. Anemia occurs due to fewer intakes of iron-rich foods including meat, leafy green vegetables and fortified cereals [11]. The amount of these meals has a higher concentration of particular nutrition which may prevent anemia due to socioeconomic circumstances may be restricted by some ethnic groups. Limited access to healthcare can result in undiagnosed or untreated anemia, particularly in rural or remote areas, due to limited awareness about the importance of iron-rich diets, iron supplementation and the consequences of anemia can contribute to its prevalence among the majority of the population in Pakistan particularly in adolescents T1D patients [12]. Therefore, the present study was conducted to anticipate the frequency of anemia in T1D patients visiting Outpatient Departments at the Tertiary care hospital in Karachi, Pakistan. This will help in the identification of anemia in individuals with T1D and subsequently assist diabetologists in managing glycemic control. Anemia can falsely elevate HbA1c levels which may mislead the proper treatment of T1D and its complications. Anemia is a global health concern, particularly in developing countries like Pakistan. T1D is prevalent in children and young adults. This research aims to examine anemia frequency in Pakistani type 1 diabetic patient; inaccurately elevated HbA1c measurements due to low hemoglobin levels might potentially deceive medical professionals on glycemic management. Early identification of anemia in Type 1 diabetic patients is crucial for effective management and improved patient outcomes. Addressing this issue is essential due to the growing prevalence of Type 1 diabetes and anemia worldwide.

This study aims to determine the prevalence of anemia, particularly iron deficiency anemia, in adolescents with Type 1 Diabetes patients and to investigate the association between anemia and HbA1c levels in type 1 diabetic patients.

METHODS

This cross-sectional study was conducted at the Department of Biochemistry, Baqai Medical University. The diagnosed T1D patients were recruited from Baqai Institute of Diabetology and Endocrinology, Karachi, from April 2023 to November 2023 after approval from the Institutional Review and Ethics Board and Advance Research Study Board with reference (BMU-EC/05-22). The sample size was 169 diagnosed type 1 diabetic adolescent patients, calculated through open Epi with a 95% confidence interval and a 5% margin of error. The power of the study was used at 80%. Blood sample collection was done by trained phlebotomist. The data were collected by using convenience nonprobability sampling. The inclusion criteria were adolescents (both male and female) diagnosed with T1D with the age range of 10 to 19 years [13]. The exclusion criteria were subjects with type 2 diabetes; T1D patients with thalassemia, sickle cell anemia, and end-stage renal and liver disorders were excluded from the study. After getting informed consent from the patients, parents, or guardians, age and anthropometric measurements, including weight, height, body mass index, and waist and hip circumference, were measured via standard protocols [14]. The ethnicity and socio-economic class of every participant were asked by pre-papered questionnaires designed. Initially, the Complete Blood Count (CBC) and HbA1c were done for every subject included in the study who visited the OPD. The CBC was performed using the Sysmex XT-1800i (Sysmex, Kobe, Japan)[15]. HbA1c was measured by the high-performance liquid chromatography method. Approved by standardized Diabetes Control and Complication assay [16]. Anemia was categorized by Hb levels less than 13 g/dL in men and 12 g/dL

DOI: https://doi.org/10.54393/pjhs.v6i1.2647

in women. The mean corpuscular volume (MCV) below 76 fL or above 96 fL and mean corpuscular hemoglobin (MCH) below 26 pg. was considered microcytic hypochromic anemia. T1D patients diagnosed with hypochromic microcytic anemia underwent further investigation of serum iron, ferritin, and TIBC levels. Serum iron level was performed through a spectrophotometer. Serum ferritin level is done by an enzyme-linked immunosorbent assay (ELISA) laboratory method, and the total iron-binding capacity (TIBC) test was performed by a calculation method. All data analyses were performed on SPSS version 23.0. Appropriate statistical tests such as chi-square and Fisher exact test were applied for data analysis. The result was analyzed and a conclusion was drawn.

RESULTS

Results show the basic anthropometric and hematological characteristics of T1D adolescent patients included in the study and it is seen that the mean age of the participants was 15.34 ± 2.69 years. The gender distribution in the study was 93, (55.0) male and 76, (45.0) female included. The mean weight, height, BMI, waist and hip circumference, HbA1c, Hb, MCV and MCH were 45.54 ± 13.49 Kg, 98 ± 14.60 cm, 19.74 ± 8.1, 74.94 ± 10.78 cm, 79.8 ± 13.13 cm, 9.65 ± 2.40%, 12.33 ± 2.56 g/dL, 79.7 ± 10.21 fL and 29.85 ± 5.69 pg respectively, (Table 1).

Table 1: Anthropometric and Hematological Characteristics of the Adolescent T1D Patients

Variables (n=169)	Mean ± SD
Age (Years)	15.34 ± 2.69
Male	93 (55.0%)
Female	76 (45.0%)
Weight (kg)	45.54 ± 13.49 kg
Height (cm)	152.98 ± 14.60 cm
BMI	19.74 ± 8.1
HbA1c (%)	9.65 ± 2.40%
Waist Circumference (cm)	74.94 ± 10.78 cm
Hip Circumference (cm)	79.8 ± 13.13 cm
Hb (g/dL)	12.33 ± 2.56 g/Dl
MCV (fL)	79.7 ± 10.21 fL
MCH (pg)	29.85 ± 5.69 pg.

A Study was shown among 169 adolescents subject to T1D, 81, (47.7%) individuals were diagnosed with anemia and 88, (52.4) were non-anemic (Figure 1).

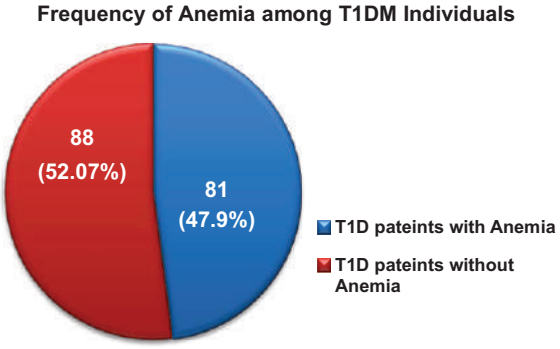

Figure 1: Frequency of Anemia among T1D Patients

Table shows the comparison of anthropometric and hematological characteristics of adolescent subject with T1D with Anemia and without Anemia and it is seen that the mean age of individuals with anemia is significantly lower than without anemic counterparts (p=0.026). Gender distribution shows no significant difference between the two groups. However, several anthropometric measurements exhibit significant variations with anemic presenting significantly lower mean weight, height, hip circumference, and waist circumference (p=0.031*), (p=0.040*), (p=0.030*) (p=0.001**) respectively compared to non-anemic T1D subjects. The mean Hb level was significantly lower in individuals with T1D with anemia (11.03 ± 1.5 g/dL) compared to them without anemia counterparts (13.64 ± 1.06 g/dL) p=0.000**, the MCV values in anemic T1D subjects (75.19 ± 11.83 fL) are significantly reduced compared to non-anemic (84.21 ± 8.6 fL), suggesting a microcytic nature of anemia. MCH is significantly lower in anemic (27.72 ± 4.96 pg.) compared to non-anemic (31.98 ± 6.43 pg.) p=0.000**. HbA1c levels are significantly lower in anemic (9.1 ± 2.11%) compared to without anemic (10.2 ± 2.7%) (Table 2).

Table 2: Comparison of Anthropometric and Hematological Characteristics of Adolescents Individuals with T1D with Anemia and without Anemia

Variables (n=169)	Anemic T1D subjects (n=81)	Without anemia (88)	p-Value
Age (Years)	14.88 ± 2.8	15.81 ± 2.59	0.026*
Male	46 (56.8%)	47 (53.4%)	0.659
Female	35 (43.2%)	41 (46.6%)	
Weight (Kg)	43.29 ± 13.95kg	47.8 ± 13.03kg	0.031*
Height (cm)	150.65 ± 13.83cm	155.32 ± 15.38cm	0.040*
BMI	18.59 ± 4.22	20.9 ± 11.98	0.090
Hip Circumference (cm)	77.65 ± 13.93cm	81.95 ± 12.33cm	0.030*
Waist Circumference (cm)	72.17 ± 11.55cm	77.72 ± 10.02cm	0.001**
Hb (g/dL)	10.89 ± 1.51g/dL	10.86 ± 1.94g/dL	0.953
MCV (fL)	68.73 ± 9.49fL	84.12 ± 8.5fL	0.000**
MCH (pg)	24.81 ± 3.22pg.	31.75 ± 4.03pg.	0.000**
HbA1c (%)	9.18 ± 2.39	8.94 ± 1.67	0.612

An Independent t-test was applied. p-value<0.05 was considered significant

DOI: https://doi.org/10.54393/pjhs.v6i1.2647

Analysis shows the comparison of biochemical parameters between adolescents with T1D with IDA and other anemia yielded significant variations. T1D subjects with IDA exhibited a markedly lower mean serum Iron level of 48.87 ± 22.86 µg/dL compared to those diagnosed with other anemias have a substantially higher mean of 96.51 ± 13.69 µg/dL, this difference was statistically significant (p=0.000**). The TIBC was significantly higher in the IDA group (583.34 ± 140.51 µg/dL) compared to the other anemia (466.59 ± 132.32 µg/dL) with a p-value of 0.000** (Table 3).

Table 3: Comparison of Iron Profile between Adolescents Individuals with T1D with IDA and without IDA

Variables	T1D Patients with Other Anemia (N=34)	T1D Patients with Iron Deficiency Anemic Subject (n=47)	p-Value
	Mean ±SD		
Serum Iron	96.51±13.69	48.87±22.86	0.000**
Serum Ferritin	50.03±29.19	54.54±131.92	0.845
Serum TIBC	466.59±132.32	583.34±140.51	0.000**

An Independent t-test was applied for comparison. p-value<0.05 was considered significant

DISCUSSION

Anemia is a widespread issue in public health. Although it affects people of all ages, pregnant women and children of school age are the most affected subjects [8]. An iron deficiency is known to be the most frequent cause of anemia, accounting for around 30% to 50% of cases of anemia globally. The IDA is also the most common cause of anemia in Pakistan. Low hemoglobin levels may cause falsely higher HbA1c readings, misleading healthcare providers about glycemic control. The present study investigated the prevalence of anemia with T1D patients, among, 169 patients, 81 were diagnosed with anemia. In contrast, 88 patients, did not exhibit signs of anemia. These results underline the relatively common co-occurrence of anemia in adolescents with T1D patients. The prevalence of anemia in over half of the study population with T1D suggests potential implications for healthcare professionals, urging a closer examination of the relationship between T1D and anemia. One of the previous research showed similar result trends by Safinaz *et al.*, [17]. The prevalence of anemia was 14% in T1D children diagnosed with anemia. These studies supported the findings and reported a higher prevalence of anemia in T1D subjects. According to the present study the mean age of subjects with anemia was found to be lower than (14.88 ± 2.8), (15.81 ± 2.59) non-anemic subjects, which was shown in another study by. Nosheen *et al.*, [18]. Out of 90 children with T1D, 60 had anemia and their mean age was less than non amenic subjects. According to present study in gender distribution, no significant difference was observed b/w anemic & non-anemic, suggests that anemia prevalence does not exhibit a gender bias within the studied population. Another study was conducted by H. Kırmzbekmez *et al.*, [19], in which the gender of the subjects with T1D did not matter in the comorbidity of anemia. According to present the anthropometric and hematological measurements in anemic subjects had lower mean values in weight, height, BMI, hip, waist circumference, Hb, MCV, MCH and HbA1c respectively compared to their non-anemic subjects, which also showed in another study Safinaz *et al.*, [17], in which anthropometric & hematological parameters were lower in anemic individuals with T1D as compared to a non-anemic population. Furthermore, the study explores glycemic control through HbA1c levels, revealing a significant difference between anemic and non-anemic adolescents with T1D. Anemic subjects with T1D have higher HbA1c levels (9.1±2.11%) compared to non-anemic (8.94±1.67). Previous studies Akkermans *et al.*, have found similar findings and stated that anemic subjects have higher HbA1c levels as compared to non-anemic. The study concluded that among T1D patients, anemia is associated with higher concentrations of HbA1c [20]. Researchers looked at the iron levels of T1D patients and IDA. They found that T1D patients with IDA had significantly lower iron levels (48.87 ± 22.86 µg/dL) than other anemia subjects (96.51 ± 13.69 µg/dL) (p=0.000**). The comparison of serum total iron-binding capacity (TIBC) further supports the distinction between the IDA and non-IDA groups. Subjects with T1D and IDA demonstrate a significantly higher mean TIBC of 583.34 ± 140.51 µg/dL, in contrast to the other anemic group with a mean of 466.59 ± 132.32 µg/dL (p-value=0.000**). A high TIBC level means that the body is trying to take in more iron, which means that iron transport proteins can bind more iron because there is less iron in the blood.

CONCLUSIONS

It was concluded that the study highlights the higher prevalence of anemia in type 1 diabetes patients. This study shows that iron deficiency anemia is the most common cause of anemia among type 1 diabetic patients. There was variation in age, anthropometric, and hematological parameters in anemic and non-anemic type 1 diabetic patients. There were seen low iron and ferritin levels and higher TIBC levels in iron deficiency anemia than in other anemic patients. There is also a higher level of HbA1c seen among anemia and non-anemic patients with type 1 diabetes.

DOI: https://doi.org/10.54393/pjhs.v6i1.2647

Authors Contribution

Conceptualization: SU
Methodology: SU, TH, SBA, MS, AA, MM
Formal analysis: SU, TH, SBA, AA, MM
Writing review and editing: SU, TH, MM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2647

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DOI: https://doi.org/10.54393/pjhs.v6i1.2448

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Association of Klotho Gene Polymorphisms with Type 2 Diabetes Mellitus

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ARTICLE INFO

Keywords:
Diabetes, Genotype, Lipid, Glucose Level

How to Cite:
Mudassar, S., Sarfraz, A., Shahid, A., Ahmad, E., Joher, I., & Anam, . (2025). Association of Klotho Gene Polymorphisms with Type 2 Diabetes Mellitus: KL Gene Polymorphisms and T2DM. Pakistan Journal of Health Sciences, 6(1), 295–301. https://doi.org/10.54393/pjhs.v6i1.2448

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Received date: 12th November, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

Genetic variants in the Klotho gene could influence the way β-cells function and effectively glucose functions, and this might influence the development of Type 2 Diabetes Mellitus. **Objectives:** To investigate the association between Klotho gene polymorphisms rs677332 and to determine the risk of developing type II diabetes in a case-control study. **Methods:** This case-control study was conducted from Feb 2024 to July 2024 at the Department of Pathology, Rashid Latif Medical College, Lahore. The total number of participants was n=586, sample n=293 case diabetics and 293 controls. DNA was extracted from blood samples and genotyped using Polymerase Chain Reaction followed by restriction digestion and validated through Sanger sequencing. To evaluate the genetic and clinical data, statistical tests were performed with SPSS version 25.0 and PLINK (v1.07). Logistic regression analysis, adjusted for age, sex, and region, was used to determine associations between Klotho polymorphisms and Type 2 Diabetes Mellitus. Fasting blood glucose levels were used as a reference variable in multiple nominal regression. **Results:** The SNPs rs677332 polymorphism and type 2 diabetes were significantly correlated, underscoring the importance of age, BMI, and heredity in diabetes risk. Logistic regression confirmed that individuals in the AA genotype were linked to a 73% rise in the likelihood of diabetes (OR=1.73, p=0.004). **Conclusions:** The rs677332 polymorphism of the Klotho gene may serve as a potential protective factor against Type 2 Diabetes Mellitus. The outcomes report the significance of Klotho gene variants for metabolic health and indicate the possible advantages of genetic screening for early treatment.

INTRODUCTION

Two-thirds of Asians and Westerners suffer from Type 2 Diabetes Mellitus (T2DM), a common illness. The development of type 2 diabetes in later life is known to be influenced by lifestyle factors like obesity and inactivity. However, there have been numerous scientific studies done to date to identify the hereditary factors that contribute to the risk of T2DM. It has been determined that some genetic mutations cause type 2 diabetes (T2DM), and some of these mutations regulate the body's glucose levels [1]. A protein that is highly involved in metabolism, insulin control, and aging is encoded by the Klotho (KL) gene. KL genetic polymorphisms may impact glucose metabolism, insulin resistance, and beta-cell function, which could be linked to type 2 diabetic mellitus [2]. Beta-glucuronidase, which can be found in the membrane of the blood vessel as a single-transmembrane glycoprotein, is made up by KL. Its anti-aging properties have been demonstrated in the klotho loss-of-function (kl-/kl-) mice, whose ageing symptoms, such as osteoporosis and arteriosclerosis, were comparable to those observed in elderly humans. Furthermore, the lifespans of the co-isogenic wild type mice were shorter than that of the genetically altered mice that overexpressed Klotho [3]. Recent advancements in genome-wide association studies (GWASs) have identified hundreds of genetic variants associated with diabetes, most of which could be in critical genes vital in modulating

DOI: https://doi.org/10.54393/pjhs.v6i1.2448

insulin secretion and sensitivity. Furthermore, a recent analysis has successfully grouped diabetes-related variants into five clusters, i.e., beta cell, proinsulin, obesity, lipodystrophy, and liver/lipid, representing five diabetes-causing pathways which are corresponding to insulin production, insulin processing, adiposity, fat redistribution, and lipid metabolism, respectively. Using the genetic risk score (GRS) generated by diabetes-related and pathway-specific variants, we could comprehensively explore the potential modifying effect of genetic predisposition to T2D or diabetes-causing pathway on the association between serum pyrethroids and T2D risk [4]. Chronic metabolic disease known as type 2 diabetes mellitus (T2DM) mainly affects the body's glucose metabolism. Insulin is a hormone that is necessary for controlling blood sugar levels, and in type 2 diabetes, the pancreas may not generate enough of it. Insulin helps cells absorb glucose so they can use it as fuel [5, 6]. The pancreatic beta cells' ability to secrete insulin decreases as the illness worsens. Insulin resistance occurs in the body, which means that cells do not react to the hormone as well. This leads to insulin resistance, and elevated blood glucose levels as the cells get less able to uptake glucose [7]. Fall in insulin secretion and action leads to the retention of glucose in the blood stream (hyper-glycaemia). Long-term managing of hyper-glycaemia with may lead to several complications in the long run including failure of the kidney, nerve damage, heart disease and problems with the eyes [8]. Type 2 diabetes mellitus (T2DM) is a pandemic metabolic disease characterized by increased blood sugar and caused by resistance to insulin in peripheral tissues and damage to pancreatic beta cells. Kruppel-like Factor 14 (KLF-14) is proposed to be a regulator of metabolic diseases, such as diabetes mellitus (DM) and obesity. Adiponectin (ADIPOQ) is an adipo-cytokine produced by the adipocytes and other tissues and was reported to be involved in T2DM [9]. Klotho (KL) gene appears to have important function in regulation of glucose homeostasis through modulation of pancreatic beta-cell function and glucose utilization. The KL gene variants may affect the KL levels or activity and, in turn, contribute to elevated oxidative stress and inflammation as well as dysregulation of signaling through the insulin/IGF-1 and Wnt pathways. These pathways are important for the growth, survival and function of the beta cells and insulin secretion. When KL function is impaired through polymorphisms, then beta cells are rendered vulnerable to dysfunctions which make the insulin producing rate to decline and the body cells' sensitivity to insulin reduce. This impairment of insulin secretion and insulin sensitivity leads to dysglycaemia and further to the development of T2D. Hence, genetic variation within the KL gene is strongly associated with insulin secretion dysfunction, disturbed glucose homeostasis, and T2D development [10]. Polymorphism in KL gene can alter pancreatic β-cell structure and function, which can lead to reduced insulin release capability when facing high blood glucose levels. The well-known hallmark of type 2 diabetes is reduced βcell function, which leads to chronic hyperglycemia. KL gene can modulate the glucose-stimulated manufacture of insulin. Mutations in this gene could affect β-cell response to glucose, leading to compromised insulin secretion, which accompanies the ability to maintain normal plasma glucose levels. Because KL participates in multiple metabolic pathways, including those associated with glucose homeostasis and insulin signaling, KL is a strong candidate gene for T2DM susceptibility. The KL gene contains SNPs (e.g. rs677332) that have been associated with T2DM and insulin resistance.

The study aimed to investigate the association between KL gene polymorphisms rs677332 and the risk of developing type II diabetes in a case control study.

METHODS

This case-control study was conducted for the duration of six months from Feb 2024 to July 2024 at the Department of Pathology, Rashid Latif Medical College, Lahore. The age of the patient was 50 to 65 years. Inclusion criteria were patients having confirmed diagnosis with diabetes II, FBG> 126 mg/DI, HbA1c > 6.5%, written authorization was acquired for genetic analysis along with data usage from patients. Exclusion criteria were excessive blood glucose level, metabolic disorder, and metformin medication use. Purposive sampling was employed to select participants meeting specific inclusion criteria related to ensuring relevant data for genetic analysis. The formula sample size comparing two proportions (control and case group) with binary outcomes (presence or absence of T2DM) yields the following useful formula: n= Zα/2·(p1(1–p1) + p2(1–p2)) / (p1-p2)2. Proportion of allele frequency in case group p1=0.60, proportion of allele frequency in control group p2=0.40, (p1–p2=0.20), and α=0.05 [11]. The total sample size of participants was n= 586 and divided into n= 293 case and 293 controls group. In this experiment, coagulant tubes and an anticoagulant vacutainer containing EDTA were used to collect 5ml of venous blood for biochemical and molecular analysis. PCR was used for DNA extraction and genotyping to identify specific KL polymorphisms. DNA was extracted from 244 EDTA blood samples using the Qiagen DNA extraction kit (Qiagen, USA) following the manufacturer's protocol. The extracted DNA was diluted in TE buffer and stored at -20°C until further use. For genotyping, the DNA samples were prepared by amplifying the KL rs677332 polymorphism using polymerase chain reaction (PCR). The reaction mix included PCR master mix, specific primers, purified water, and genomic DNA. The

DOI: https://doi.org/10.54393/pjhs.v6i1.2448

amplified PCR products were then digested using the HPY1888III restriction enzyme and analyzed on a 2% agarose gel to confirm genotyping results. Primers were designed using Primer3 or NCBI Primer-BLAST tools. Here is a suggested primer pair for amplifying the KL rs677332 region. Forward Primer: 5'- TGC TGG AAG AGA AGT GGA AGC -3'. Reverse Primer: 5'- AGA GTC CTC CGA GGC TCA TT -3'. To evaluate metabolic status, fasting blood glucose (FBG), insulin, and HbA1c were tested in addition to genetic data. For evaluating metabolic health in a study on KL gene polymorphisms, biochemical assays are essential. After an 8-hour fasting, fasting blood glucose (FBG) was measured; were indicative of diabetes. An average blood glucose level over the previous two to three months was provided by hemoglobin A1c (HbA1c), with values above 6.5% indicating diabetes. Clinical and genetic data imported from Excel were statistically analyzed by using SPSS version 25.0. For comparison of diabetic patients and controls, t-test, Hardy-Weinberg Equilibrium (HWE), and multiple logistic regression were used. Using fasting blood glucose (FBG) as a reference, multiple nominal regression analysis was also carried out and significant level of $p<0.05$. The study was approved by the Institutional Review Board of Rashid Latif Medical College, Lahore under the reference number IRB00010673. Informed consent was obtained from all study participants prior to enrollment in the study.

RESULTS

A comparison of the clinical and demographic traits of the control group with the diabetes cases is shown in table 1. With a mean age of 56.4 years compared to 52.5 years ($p<0.001$), the results show that diabetics were much older than controls. This implies a risk of diabetes that varies with age. Furthermore, the diabetes group's body mass index (BMI) is significantly higher (28.5 kg/m2) than that of the control group (25.1 kg/m2), and the p-value (<0.001) further supports this finding. Additionally, the diabetes cohort's fasting blood glucose (FBG) levels are much higher (151.5 mg/dL) than the controls' (90.0 mg/dL), and this difference is statistically significant ($p<0.001$). Furthermore, supporting the presence of diabetes is the fact that the glycated hemoglobin (HbA1c) levels in cases of the disease (7.9%) are significantly higher than in controls (5.7%). The gender ratio is approximately equal between controls and diabetic patients, as revealed by the Chi-Square Test's finding of no significant difference in sex distribution ($p=0.18$) between the two groups in table 1.

Table 1: Association Between Controls and Diabetic Cases for rs677332 Polymorphism

Variables	Groups	Mean ± SD	Test Statistic	p-Value
Age (Years)	Controls (n=293)	52.5 ± 8.9	t=3.20	<0.001
	Diabetic (n=293)	56.4 ± 9.5		
BMI (kg/m^2)	Controls (n=293)	25.1 ± 3.6	t=5.90	<0.001
	Diabetic (n=293)	28.5 ± 4.0		
FBG (mg/dL)	Controls (n=293)	90.0 ± 11.5	t=11.30	<0.001
	Diabetic (n=293)	151.5 ± 31.8		
HbA1c (%)	Controls (n=293)	5.7 ± 0.5	t=14.20	<0.001
	Diabetic (n=293)	7.9 ± 1.4		
Sex (M/F)	Controls (n=293)	165 / 125	χ^2=1.75	0.18
	Diabetic (n=293)	161 / 135		

Table 2 shows the genotype frequencies of the rs677332 polymorphism in both diabetic patients and control subjects. There is a clear correlation between the AA genotype and a higher risk of developing diabetes, as seen by the considerably higher AA genotype frequencies in the diabetic group (44.9%) compared to 30.0% in the control group ($p = 0.003$). In contrast, the prevalence of the AG genotype is considerably lower in cases of diabetes (37.2%) compared to controls (50.0%), suggesting that this genotype may offer some protection against the development of diabetes. However, the p-value for this comparison is not stated directly. There was no statistically significant difference in the frequencies of the GG genotype between the two groups (20.0% in controls and 17.9% in diabetics), indicating that higher risk of diabetes was not linked to this genotype in table 2.

Table 2: Genotype Frequencies of rs677332 Polymorphisms in Diabetic Cases and Control Subjects

Polymorphism	Genotype	Control Subjects (n=293)	Diabetic Cases (n=293)	p-Value	Interpretation
rs677332	AA	87 (30.0%)	133 (44.9%)	<0.003	Significant Association; Higher in Diabetic Cases.
	AG	145 (50.0%)	110 (37.2%)	<0.005	Significant Association; Lower in Diabetic Cases.
	GG	58 (20.0%)	53 (17.9%)	0.088	No Significant Difference.

To reveal the relationship between genotypes of rs677332 and Type 2 Diabetes Mellitus (T2DM). With an odds ratio (OR) of 2.10 (95% CI: 1.45 - 3.06) and a p-value of 0.003, the data demonstrate that those with the AA genotype had a markedly elevated risk of T2DM. This implies that the risk of developing diabetes is more than twice as high for those who carry the AA genotype as for people who do not. With an OR of 0.63 (95% CI: 0.45 - 0.88) and a p-value of 0.012, on the other hand, the AG genotype appears to lessen the risk of T2DM, suggesting that those who carry it may be at a lesser risk for illness. On the other hand, the GG genotype does not significantly correlate with T2DM (OR = 0.88, p = 0.78), meaning that it has no effect on the risk of getting diabetes in table 3.

DOI: https://doi.org/10.54393/pjhs.v6i1.2448

Table 3: Association of rs677332 Genotypes with Diabetes Type 2

Geno-type	Control Subjects (n=293)	Diabetic Cases (n=293)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-Value	Interpretation
AA	87 (30.0%)	133 (44.9%)	2.10	1.45-3.06	0.003	AA Genotype Associated with Increased Risk of T2DM.
AG	145 (50.0%)	110 (37.2%)	0.63	0.45-0.88	0.012	AG Genotype may Confer Resistance to T2DM.
GG	58 (20.0%)	53 (17.9%)	0.88	0.58-1.33	0.78	No Significant Association: GG Genotype is Not Protective.

Results presents the findings of a multivariate logistic regression study aimed at determining risk variables for diabetes. The results highlight the significance of age as a risk factor, showing that every year of age beyond 50 raises the likelihood of diabetes by 5% (OR=1.05, p=0.016). Moreover, there may be gender variations in the risk of diabetes, as being female is linked to a 52% increased chance of getting the disease (OR=1.52, p=0.004). BMI also demonstrates a strong correlation, emphasizing the significance of obesity in the incidence of diabetes. For every unit increase, there is an 8% increase in the likelihood of diabetes (OR=1.08, p=0.006). The AA genotype rs677332 is linked to a 73% rise in the likelihood of diabetes (OR=1.73, p=0.004), confirming its important role in the risk of developing diabetes. Lastly, with an odds ratio of 2.12 (p<0.001), a family history of diabetes is a powerful predictor, meaning that those who have one are more than twice as likely to get the illness as in table 4.

Table 4: Multiple Logistic Regression Analysis for Factors Associated with Diabetes

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-Value
Age	1.05	1.01-1.09	0.016
Sex (Female)	1.52	1.13-2.04	0.004
BMI	1.08	1.02-1.14	0.006
rs677332 Genotype AA	1.73	1.14-2.62	0.004
Family History of Diabetes	2.12	1.55-2.90	<0.001

SNP rs659117 in the KL gene has a Regulome DB score of 2, indicating moderate regulatory potential. It acts as an eQTL in tissues like the liver and pancreas, influencing gene expression. The SNP affects transcription factor binding (e.g., FOXO1, STAT3) and is in a DNase-hypersensitive region, suggesting its role in gene activation and insulin regulation, and further impact the pathogenesis of T2DM, see table 5.

Table 5: SNP rs659117 in the KL Gene has a Regulome DB Score

Feature	Value/Details	Interpretation
Regulome DB Score	2	A score of 2 suggests that the SNP has moderate regulatory potential, with potential impacts on gene regulation.
eQTL	Yes (Liver, Pancreas)	SNP rs659117 influences gene expression in liver and pancreas tissues, which are relevant to glucose metabolism.
TFBS (Transcription Factor Binding Sites)	Yes, Binding to FOXO1 and STAT3	The SNP affects regions bound by FOXO1 and STAT3, which are transcription factors involved in meta-bolic regulation and insulin signaling.
DNase Hypersensitivity	Yes, Located in Active Enhancer Region	The SNP is in an open chromatin region, likely to be involved in transcriptional regulation.
Protein Binding	Yes, Histone H3K4me3 Binding	The SNP influences a region bound by histone modification proteins, which is critical for gene activation.
Motif Impact	Yes, Alters Motif for STAT3 Binding	The SNP changes the STAT3 binding motif, suggesting it could modulate the transcription factor's role in regulating insulin sensitivity.

First band indicate AA genotype, second band indicate AG and third band indicate GG genotype. The band size 150kb, see figure 1.

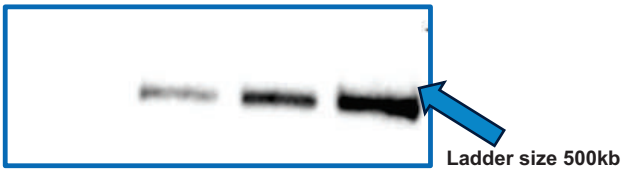

Figure 1: Gel Image of Genotype

DISCUSSION

Diabetes has become a common disorder in our century. An unregulated diet, inactivity, and a sedentary lifestyle have all contributed to the elevated incidence of type 2 diabetes, a chronic metabolic disease, in the 20th century. Moreover, every inherited family is influenced by genetics [12, 13]. Comparing the demographic, clinical, and genetic traits of diabetic patients and control participants allowed researchers to examine the potential link between the rs677332 polymorphism and diabetes. The findings revealed major variations in age, BMI, fasting blood glucose (FBG), and glycated hemoglobin (HbA1c) levels among the two groups as well as notable relationships with specific genotypes of the rs677332 polymorphism. In the present study, the mean age of the diabetes group was 56.4 years, which was substantially older than the mean age of the control group (52.5 years). This result is in line with multiple studies that have shown aging to be a significant risk factor diabetic patient, emphasizing the significance of age-

DOI: https://doi.org/10.54393/pjhs.v6i1.2448

related pathophysiological alterations that may predispose people to the disease [14]. Further supporting the literature that links obesity to a higher risk of diabetes type 2 by associating excess adipose tissue with insulin resistance is the considerably higher BMI (28.5 kg/m2) in the diabetic group [15]. The FBG and HbA1c level analysis provides additional evidence for the participant classification; diabetics had significantly higher levels (FBG: 151.5 mg/dL; HbA1c: 7.9%) than controls (FBG: 90.0 mg/dL; HbA1c: 5.7%). These findings support earlier studies, showing that diabetic patients typically have higher blood glucose levels, underscoring the importance of glycemic control in the management of diabetes [16]. In the current study finding that, the rs677332 polymorphism genotype frequencies showed a p-value of 0.003 and that the AA genotype was substantially more common in diabetic patients (44.9%) compared to controls (30.0%). This result is consistent with earlier research showing that some genetic variations can affect diabetes susceptibility and reveals a strong correlation between the AA genotype and T2DM [17]. In contrast, the AG genotype was found in diabetic cases in 37.2% of cases compared to controls in 50.0% of cases, suggesting a possible protective effect against diabetes and supporting earlier findings that certain genotypes may confer resistance to metabolic diseases. This reinforces the concept that different alleles/variants within the same gene may have different effects as well as the evidence that the GG genotype is not significantly associated with diabetes [18]. Current results were consistent with those from a multiple logical regression study that identified independently unfavorable prognostic factors for T2DM are age, sex, BMI, the rs677332 AA genotype and history of diabetes in the family. The risk of diabetes increased by 5% per year of age over the age of 40, and being female was associated with 52% higher risk of diabetes. These findings align with previous studies that highlight the differential impact of sex and age on diabetes outcomes and prevalence [19]. Furthermore, a unit increase in BMI raised the risks of diabetes by 8% which corroborates the finding with previous studies that cholesterol was obesity and insulin resistant [20]. There were 73% increased odds of diabetes associated with the rs677332 AA genotype, which argues for contributions of specific genes to type 2 diabetes risk through genetic predisposition. Consistent with this finding, family history emerged as a predictor of diabetes indicating the importance of interaction between genetic and environmental effects in the etiology of this condition. These observations correlate with some previous epidemiological findings that type 2 diabetes fall into the category of heritable diseases [21, 22]. The KL (Klotho) gene, while primarily associated with type 2 diabetes mellitus (T2DM), plays a broader role in various metabolic pathways. KL gene variants influence calcium-phosphorus regulation through fibroblast growth factor (FGF) signaling, which is crucial for mineral homeostasis and linked to conditions like chronic kidney disease (CKD) and osteoporosis. Additionally, KL polymorphisms are associated with aging and longevity by reducing oxidative stress and inhibiting cellular senescence, contributing to protection against cardiovascular diseases such as vascular calcification and atherosclerosis. These findings highlight the systemic relevance of KL variants, positioning them as potential biomarkers or therapeutic targets for metabolic and age-related diseases beyond T2DM [23]. We have expanded the discussion to emphasize the clinical and genetic implications of present findings, particularly the significant association of the AA genotype with an increased risk of Type 2 Diabetes Mellitus (T2DM). Additionally, we highlighted the potential protective role of the AG genotype, which appears to reduce the risk of T2DM. The AA genotype may increase the risk of Type 2 Diabetes Mellitus (T2DM) due to its potential effect on the expression or function of genes involved in glucose metabolism, insulin resistance, or β-cell function. Specific genetic variants in key genes, like those influencing insulin secretion or action, can lead to an impaired ability to regulate blood sugar levels. In the case of the AA genotype, it may be associated with higher expression of risk-related alleles or less favorable interactions with other metabolic pathways, making individuals more susceptible to insulin resistance, beta-cell dysfunction, and, ultimately, T2DM. [24]. We also discussed how these genetic insights could contribute to personalized medicine and risk prediction for T2DM, supporting the development of tailored preventive and therapeutic strategies.

CONCLUSIONS

Analysis of the rs677332 polymorphism, on the other hand, shows age, BMI and genetic factors. The latter is also a significant contributor to the risk of type 2 diabetes. This study complements previous research and lends support to the need for genetic screening and tailored prevention efforts in high-risk groups. KL gene polymorphisms play a significant role in various metabolic and age-related conditions. Future studies should explore their therapeutic potential and utility in early genetic screening, which could help identify individuals at risk and guide targeted interventions.

DOI: https://doi.org/10.54393/pjhs.v6i1.2448

Authors Contribution

Conceptualization: SM
Methodology: AS[1], AS[2]
Formal analysis: AS[1], A
Writing, review and editing: SM,EA, IJ, AS[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.1975

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Assessment of Deranged Lipid Profiles and Correlated Dependent Factors in Patients with Ischemic Stroke at a Tertiary Care Setup in Islamabad

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ARTICLE INFO

Keywords:
Cerebrovascular, Dyslipidemia, Ischemic stroke, Lipid Profiles, Assessment

How to Cite:
Ghafoor, A., Rehman, A., Sarfaraz, M., Badshah, S., Jan, D. A., & Hayat, N. (2025). Assessment of Deranged Lipid Profiles and Correlated Dependent Factors in Patients with Ischemic Stroke at a Tertiary Care Setup in Islamabad: Assessment of Deranged Lipid Profiles and Dependent Factors in Patients . Pakistan Journal of Health Sciences, 6(1), 302-307. https://doi.org/10.54393/pjhs.v6i1.1975

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Received date: 19th October, 2024
Acceptance date: 18th January, 2025
Published date: 31st January, 2025

ABSTRACT

The deranged lipid profile of patients is greatly associated with multiple complications hence leading towards the co morbidities and eventually been a reason of high mortalities. **Objectives:** To determine the cases of deranged lipid profiles among patients with confirmed diagnosis of ischemic stroke, dependent variables & co morbidities. **Methods:** A Descriptive, cross-sectional study was conducted at the Department of Medicine Fauji Foundation Hospital Rawalpindi from 20th March 2024 to 19th September 2024 a sample size of 110 was calculated using a WHO sample size calculator with a confirmed diagnosis of ischemic stroke from the age range of 30 years to 80 years of age were recruited in the study. A total of 5ml of the venous sample was obtained after 8 hours of fasting, and centrifuged at 40 Celsius for 15 minutes to analyze the serum lipid profile for obtaining true levels of high-density lipoproteins HDL, and low-density lipoprotein LDL using the auto analyzer machine. The collected data were assessed by data stratification using SPSS and post-stratification Chi-square test was applied and the P value of <0.05 was considered significant. **Results:** The total cholesterol was deranged in 57.27%, LDL cholesterol was deranged in 60.0%, deranged triglyceride levels in 67.27% and deranged HDL cholesterol in 32.73% of patients. **Conclusions:** The current study concluded that the frequency of dyslipidemia is significantly high among patients with ischemic stroke. The functions of HDL are dependent on certain factors such as genetics, lifestyle changes, and environmental factors.

INTRODUCTION

Stroke is a cerebrovascular disease, and remains one of the major causes of disabilities and death worldwide. It is more prevalent among the elderly population, and commonly diagnosed among individuals with lower socioeconomic status [1]. World Health Organization (WHO), in 2002 reported that approximately 5.51 million people died due to stroke, among those 20% of deaths were reported from the South Asia region [2]. The cases of strokes reported in Pakistan are no less than 350, 000 each year and the incidents have grown over the last few decades [3]. Stroke is a condition that not only worsens the cognitive impairments and pre-existing dementias but is responsible for disabilities among the elderly populations with co-morbidities, which is predicted possibly due to the absence of lack of clear diagnosis and timely management of the condition [4]. Unfortunately, the lower-income countries lack sufficient literature, and adequate database registry systems, and the clear cases, and strokes among the population are not timely managed and treated with optimal care [5]. In a conclusion made from research published in 2022, data showed the high prevalence of risk factors i.e., hypertension, and diabetes among stroke

DOI: https://doi.org/10.54393/pjhs.v6i1.1975

patients along with a higher rate of complications requiring longer hospitalization periods [6]. Dyslipidemia is undoubtedly a major risk factor in vascular diseases and a prime contributor in worsening pre-existing conditions and the same way for coronary artery diseases, the dreadful burden of this disease has led us to the condition of categorizing dyslipidemia as a major factor behind disabilities and mortalities among vascular disease patients. While some other associated contributors also participate in the occurrence of stroke [7-8]. The extrapolative role of lipid profile has been studied by various researchers and continues to be the topic of discussion similar to myocardial infarction, hypertension, and other independent factors. Many previous researches have investigated serum cholesterol levels as a dependent factor in stroke, but few studies have indicated that hypercholesterolemia is a major risk factor for intra-cerebral hemorrhage (ICH) [9]. WHO defines stroke as an old term and a "neurological deficit" of the cerebrovascular system and it may persist for more than 24 hours and may cause a death or permanent disability among patients. This definition was proposed for the permanent neural tissue damage and reversible symptoms diagnosed among individuals [10]. The symptoms may subside upon timely management and availability of treatment, and resolve over the period. The time duration of 24 hours was chosen to distinguish the stroke from "transient ischemic attacks" [11]. Various research has shown that a stroke association exists between the lipid profile and the risk of developing cardiovascular and neural diseases. The high cholesterol levels specifically low-density lipoproteins (LDL) and High-density lipoproteins (HDL) are associated with ischemic strokes [12]. Lowering the Serum lipid profiles by adopting preventive strategies reduces the risks of developing serious diseases and in strokes, patients prevent the recurrence of strokes from coronary heart diseases [13]. A stroke is clinically diagnosed as the loss of neurological functioning that may persist up to certain days due to the loss of blood supply in the brain however hemorrhagic strokes result from the rapturing of certain blood vessels and irregular vascular structure, from classification, the 87% of strokes are ischemic and remain 13% are of hemorrhagic type [14]. The development of hemorrhagic strokes that might develop in the ischemic area. The cases of ischemic strokes rise with considerable disabilities every year, approximately 795,0000 people suffer strokes in the United States, however, the strokes vary among different individuals based on gender, ethnicity, race, and other lifestyle factors [15]. It was assessed from previous scientific literature that an inverse relation exists It was found from the previous literature that there exists an inverse relation between lipid profile and death from stroke [16]. Stroke subtypes also vary greatly in different parts of the world. For example, the proportion of hemorrhagic strokes may be even higher in certain populations. The different clinical investigations showed a remarkable number of individuals suffering each year from strokes and other associated complications, the number of studies mentioned the factors and predictors however, the frequency of such cases is high among the developing countries like Pakistan, where only a limited number of studies are conducted. The assessment of lipid profiles among stroke patients may help predict the national burden and overall status of the healthcare system with the evident data.

This study aimed to determine the frequency of deranged lipid profile in patients with ischemic stroke at a tertiary care Hospital in Islamabad.

METHODS

A descriptive, cross-sectional study was conducted at the Department of Medicine, Fauji Foundation Hospital, Rawalpindi. 20th March 2024 to 19th September 2024. After getting ethical approval from the hospital research committee & Research Evaluation Unit of College of Physicians & Surgeons, Pakistan (CPSP/REU/MED-2021-122-17817). A total of 110 patients were enrolled after calculating the sample by using the WHO sample size calculator based on rate of prevalence at 95% of the confidence interval and the margin of error kept at 8% the expected percentage for HDL was assumed 24% [17]. Patients from the age range of 30-80 years of both genders were diagnosed with ischemic stroke and admitted at the Department of Medicines, Fauji Foundation Hospital Rawalpindi fulfilling the criteria of consecutive sampling and agreed to the informed consent were included in the study. However, the patients. Assessed based on history patients with past head injuries, hematomas, and unaccepting to sign the informed consent were excluded from the study. The blood samples were collected from patients after 8 hours of fasting centrifuged at 40 Celsius for 15 minutes and analyzed for estimated serum lipid profile including the total cholesterol, triglycerides HDL, and LDL, by automatic analyzer. Data were obtained in a structured format; all the dependent variables were assessed using SPSS version 23. Qualitative variables like gender, diabetes mellitus (yes/no), hypertension (yes/no), smoking (yes/no), place of living (rural/urban), lifestyle (simple/sedentary), monthly income (<25000/25000-50000/>50000) and deranged lipid profile i.e. total cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein (yes/no) presented as frequency and percentage. Effect modifiers like age, gender, duration of a stroke, BMI, diabetes mellitus (yes/no), hypertension (yes/no), smoking (yes/no), place of living (rural/urban), lifestyle (simple/sedentary) and monthly

DOI: https://doi.org/10.54393/pjhs.v6i1.1975

income (<25000/25000-50000/>50000) assess by data stratification. The post-stratification Chi-square test was applied and the P value of <0.05 was considered significant.

RESULTS

The result of the study showed a mean age of 54.53 ± 12.47 years. The percentages were calculated for the age ranges 56 (50.91%) between 30 to 55 years of age as shown below (Figure 1).

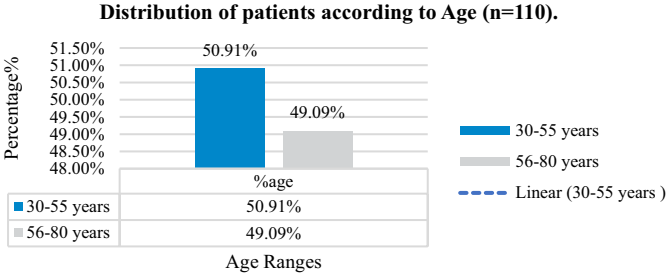

Figure 1: Age Ranges among study participants (Mean ± SD = 54.53 ± 12.47)

Out of 110 patients, 63 (57.27%) were male and 47 (42.73%) were female with male to female ratio of 1.3:1. The Mean duration of disease in our study was 5.84 ± 2.57 hours. Mean BMI was 27.47 ± 2.95 kg/m^2. The distribution of patients with the status of other confounding variables was shown in Table 1.

Table 1: Dependent Variables among Patients (n=110)

Confounding variables		Frequency (%)
Gender	Male	63 (57.27%)
	Female	47 (42.73%)
Duration (hours)	≤6	75 (68.18%)
	>6	35 (31.82%)
BMI (kg/m^2)	≤27.5	56 (50.91%)
	>27.5	54 (49.09%)
DM	Yes	52 (47.27%)
	No	58 (52.73%)
HTN	Yes	70 (63.64%)
	No	40 (36.36%)
Smoking	Yes	28 (25.45%)
	No	82 (74.55%)
Place of living	Rural	41 (37.27%)
	Urban	69 (62.73%)
Monthly income	<25000	14 (12.73%)
	25000-50000	52 (47.27%)
	>50000	44 (40.0%)
Lifestyle	Simple	43(39.09%)
	Sedentary	67(60.91%)

In this study, the frequency of deranged lipid profile in patients with ischemic stroke was as follows; total cholesterol was deranged in 57.27%, LDL cholesterol was deranged in 60.0%, deranged triglyceride levels in 67.27% and deranged HDL cholesterol in 32.73% of patients (Figure 2).

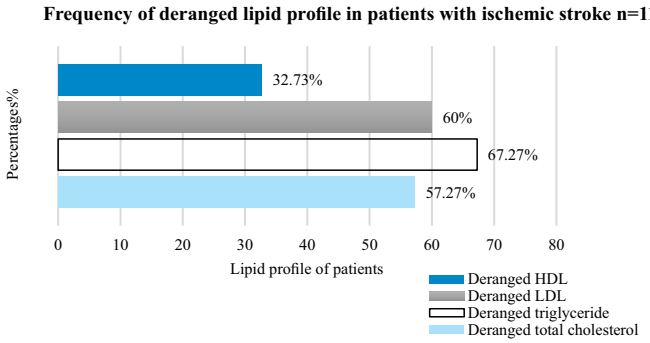

Figure 2: Lipid Profile Presented Among Ischemic Stroke Patients

Stratification of deranged lipid profile concerning age, gender, duration of stroke, BMI, diabetes mellitus, hypertension, and smoking, place of living, lifestyle, and monthly income was described (Table 2).

Table 2: Stratification Data of Deranged Total Cholesterol with Multiple Dependent Variables

Variables		Yes (n=63)	No (n=47)	P-value
Age (year)	30-55	36 (64.29%)	20 (35.71%)	0.130
	56-80	27 (50.0%)	27 (50.0%)	
Gender	Male	40 (63.49%)	23 (36.51%)	0.127
	Female	23 (48.94%)	24 (51.06%)	
Duration (hours)	≤6	39 (52.0%)	36 (48.0%)	0.102
	>6	24 (68.57%)	11 (31.43%)	
BMI (kg/m^2)	≤27.5	34 (60.71%)	22 (39.29%)	0.457
	>27.5	29 (53.70%)	25 (46.30%)	
Diabetes Mellitus	Yes	32 (61.54%)	20 (38.46%)	0.392
	No	31 (53.45%)	27 (46.55%)	
Hypertension	Yes	39 (55.71%)	31 (44.29%)	0.662
	No	24 (60.0%)	16 (40.0%)	
Smoking	Yes	15 (53.57%)	13 (46.43%)	0.647
	No	48 (58.54%)	34 (41.46%)	
Place of living	Rural	24 (58.54%)	17 (41.46%)	0.836
	Urban	39 (56.52%)	30 (43.48%)	
Monthly income	<25000	07 (50.0%)	07 (50.0%)	0.457
	25000-50000	33 (63.46%)	19 (36.54%)	
	>50000	23 (52.27%)	21 (47.73%)	
Lifestyle	Simple	21 (48.84%)	22 (51.16%)	0.152
	Sedentary	42 (62.69%)	25 (37.31%)	

Stratification of deranged lipid profile concerning age, gender, duration of stroke, BMI, diabetes mellitus, hypertension, and smoking, place of living, lifestyle, and monthly income is described in Table 3.

Table 3: Stratification of Deranged Triglyceride Concerning Multiple Variables

Dependent variables		Yes (n=74)	No (n=36)	P-value
Age (year)	30-55	37 (66.07%)	19 (33.93%)	0.785
	56-80	37 (68.52%)	17 (31.48%)	
Gender	Male	47 (74.60%)	16 (25.40%)	0.058
	Female	27 (57.45%)	20 (42.55%)	

DOI: https://doi.org/10.54393/pjhs.v6i1.1975

Duration (hours)	≤6	47 (62.67%)	28 (37.33%)	0.132
	>6	27 (77.14%)	08 (22.86%)	
BMI (kg/m^2)	≤27.5	40 (71.43%)	16 (28.57%)	0.344
	>27.5	34 (62.96%)	20 (37.04%)	
DM	Yes	38 (73.08%)	14 (26.92%)	0.219
	No	36 (62.07%)	22 (37.93%)	
HTN	Yes	43 (61.43%)	27 (38.57%)	0.046
	No	31 (77.50%)	09 (22.50%)	
Smoking	Yes	21 (75.0%)	07 (25.0%)	0.313
	No	53 (64.63%)	29 (35.37%)	
Place of living	Rural	27 (65.85%)	14 (34.15%)	0.807
	Urban	47 (68.12%)	22 (31.88%)	
Monthly income	<25000	08 (57.14%)	06 (42.86%)	0.017
	25000-50000	42 (80.77%)	10 (19.23%)	
	>50000	24 (54.55%)	20 (45.45%)	
Lifestyle	Simple	27 (62.79%)	16 (37.21%)	0.422
	Sedentary	47 (70.15%)	20 (29.85%)	

DISCUSSION

The current study assessed the possible risk factors associated with ischemic stroke patients, the possible dependent factors were analyzed such as smoking, hypertension, coronary heart diseases, and dyslipidemias. The role of coronary heart disease is convincing evidence among patients with ischemic stroke patients. The burden of diabetes and hypertension has been a controversial and important one. The dyslipidemia has always been a topic of discussion in cardiovascular diseases [18]. Current study determined the frequency of deranged-lipid profiles of ischemic stroke patients and among 110 patients with a confirmed diagnosis of ischemic stroke profile of 30- 80 years of age, the mean age was 54.53±12.47 years, the majority of patients were among the age group of 30-55 years which is similar to the pattern of age ranges observed in a study conducted by Li X *et al.*, on the same theme [19]. Han Y *et al.*, conducted a study in 2022 also confirmed the findings and associated risk factors studied, the mean age noticed in the study was 63.42 similarly found in our study [20]. The gender distribution was assessed among the patients which showed 52.27% were male however 42.73% were female, similarly found in the study conducted by Chen Y *et al.*, showing the majority of male patients with ischemic stroke diagnosis, several studies confirmed the high ratio of male compared to female [21]. Ammad *et al.*, conducted a study on ischemic stroke patients assessed the high cholesterol and deranged lipid profiles among the ischemic stroke high cholesterol was 57.27%, and LDL cholesterol was 32.7% which has a similar pattern of deranged lipid profiles in a previous study 60% of patients showed deranged triglycerides and high-density lipoprotein (HDL) profile with 32.73% of cases [22]. However, in contrast to another similar pattern study found 1,008 ischemic stroke patients with 60% of dyslipidemia cases, 39% of patients with hypertension, and 44% cases of smoking. A study conducted by Ammad et al. 2023, on ischemic stroke patients showed the data of patients with the registry confirmed the cases of smoking as a major depending factor and dyslipidemia 41% which agrees with the results of our study [22]. Lee SH *et al.*, indicated that the consecutive involvement of risk factors may aggravate the disease conditions and develop complications [23]. The association of dyslipidemia and stroke has been studied multiple times yet it has been declared as a complex one. Everest S *et al.*, 2020 studied the levels of high cholesterol and dyslipidemia conditions that may aggravate the evidence of cholesterol leading to strokes and relevant complications similar to our study [24]. Han Y *et al.*, showed in the study the elevated high-density lipoproteins and evidence of high triglyceride levels are still conflicting; however, the risks seem to be leading toward ischemic strokes stroke subtypes meanwhile these risk factors are inversely associated with the hemorrhagic strokes found in the observational studies [20]. A study by Everest *et al.*, confirmed that the risk of developing ischemic strokes rises as the HDL and LDL cholesterol levels rise among patients [24]. The study also showed an inverse relationship between hemorrhagic strokes and high cholesterol levels, however, the results of the study confirmed that cholesterol levels of patients exceedingly similarly by Taimuri *et al.*, more than 200mg/dl surely developed ischemic strokes later in life, the risks of developing ischemic strokes and other vascular complications doubles for the serum cholesterol levels of 289mg/dl [25].

CONCLUSIONS

The current study concluded the frequency of deranged lipid profiles among patients with ischemic stroke. The high frequency of dyslipidemia has been seen among ischemic stroke patients. The study based on findings also recommends the early detection of disease through various new advancement techniques and awareness programs on cerebrovascular events (CVE) which will impart a true impact on lowering the disease burden which is essential among countries like Pakistan where health care services are limited.

Authors Contribution

Conceptualization: AR
Methodology: AG, AR, DAJ
Formal analysis: SB, NH
Writing, review and editing: AG, MS

DOI: https://doi.org/10.54393/pjhs.v6i1.1975

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

The authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

Acknowledgement

The authors would like to acknowledge the Medical Affairs department of Getz Pharma for their technical support and assistance in the publication process.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2542

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

The Pattern of Hematological and Biochemical Parameters in Dengue Fever among Patients Presenting to HIT Hospital, Taxila Cantt

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ARTICLE INFO

Keywords:
Dengue Fever, Haematological, Biochemical Markers, Liver Transaminases

How to Cite:
Umar, S., Javed, A., Aslam, U., Abbas, S. H. B., Yasmin, R., Rauf, M., Javed, A., Sadiq, S., & Rauf, S. (2025). The Pattern of Hematological and Biochemical Parameters in Dengue Fever among Patients Presenting to HIT Hospital, Taxila Cantt: Hematological and Biochemical Parameters in Dengue Fever . Pakistan Journal of Health Sciences, 6(1), 308-313. https://doi.org/10.54393/pjhs.v6i1.2542

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Received date: 11th November, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

Dengue fever affects over 600 million people globally each year, with its burden increasing eightfold in the past 15 years. It is endemic in 129 nations. **Objective:** To identify the pattern of hematological and biochemical parameters in patients at HIT Hospital, Taxila, and examine their correlation. **Methods:** This retrospective cross-sectional study analyzed data from 118 patients with positive serology reported between August and November 2022. Parameters studied included hemoglobin, hematocrit, platelets, leucocyte count, and plasma Alanine transaminase (ALT) levels. **Results:** Among 118 patients, 77 were male, and 41 were female. Patients under 18 years comprised 8.5%, those aged 18–49 years constituted 61.0%, and those aged 50+ accounted for 30.5%. Severe dengue cases showed significantly reduced platelet counts across all age groups ($p < 0.05$). In mild dengue, 3 of 17 patients had normal ALT levels, while 11 showed abnormal levels. In moderate cases, 27 of 87 had normal ALT levels, while 60 exhibited elevated levels. Severe cases showed elevated ALT levels in 16 of 17 patients. **Conclusions:** Males and individuals aged 18-49 are more vulnerable to dengue and should take extra precautions. Elevated liver transaminases, leucopenia, and thrombocytopenia indicate a high likelihood of dengue infection, aiding diagnosis and treatment planning. Awareness campaigns must be expanded to larger populations, including literate individuals, to prevent the disease effectively.

INTRODUCTION

Dengue fever affected over 6.5 million people worldwide in 2023, and as of 30th April 2024 WHO has reported 3.4 million confirmed cases making it a serious health risk [1, 2]. It is a virus-borne illness that is transmitted by female *Aedes aggypti* mosquito bites [3]. Over the past 15 years, the burden of sickness has increased eightfold. Dengue is endemic in around 129 countries of the world, i.e., Africa, America, Southeast Asia, and the Mediterranean region. Around 70% of the disease burden is present in Asia [4]. In Pakistan, major outbreaks of dengue fever were reported in Lahore (Punjab) and Swat (KPK) in 2011 and 2013 respectively with a 20% mortality rate. The total number of cases reported during 2000-2019 was 201,269. The majority of dengue-infected cases were reported as Dengue fever (74.4%) followed by DHF (dengue hemorrhagic fever) (24.1%) and DSS (dengue shock syndrome) (1.5%). Overall the deaths during the survey were 1082, of which the maximum mortalities were reported from KPK (N=248) followed by Punjab (N=220) [5]. In year 2019 cases reported were with 75 deaths, while in 2022 79,009 confirmed cases of dengue were reported with 149 deaths [1]. There are four serotypes of the encapsulated RNA virus known as dengue: DEN1,

DOI: https://doi.org/10.54393/pjhs.v6i1.2542

DEN2, DEN3, and DEN4. Travelers contribute significantly to the spread of this virus. The World Health Organization (WHO) classifies the disease into two categories: dengue with or without warning signs, and severe dengue. Primary infection with any serotype provides immunity against the respective serotype, whereas secondary infection with the heterologous serotype leads to severe dengue [6]. The clinical manifestations of dengue infection typically include sudden onset of high fever, severe headache, retro-orbital pain, myalgia, arthralgia, and rash. While most of the cases of dengue fever resolve with supportive care, dengue hemorrhagic fever and dengue shock syndrome can lead to vascular leakage, hemorrhage, and shock, necessitating prompt medical intervention [7]. According to literature, there is an important role of hematological factors such as thrombocytopenia, raised hematocrit, leukocytosis, and decreased hemoglobin levels in the diagnosis and prognosis of dengue fever [8]. Many studies have revealed the involvement of the liver in this disease. The serum transaminases are raised during a viral illness. This is +due to multiple causes, including viral load, apoptosis, and immunological factors [9]. Urbanization, high humidity, inadequate sanitation, and a lack of vector control measures are the main causes of dengue's quick spread [10]. Supportive care, fluid replacement, and monitoring for complications like shock-causing plasma leakage are all part of managing a dengue infection. In extreme situations, prompt intravenous fluid and blood product administration may be required to stabilize the patient and avoid death [11]. Additionally, in order to stop dengue disease from spreading, vector control techniques are crucial. This entails removing Aedes mosquito breeding grounds and launching community-wide pesticide spraying initiatives [12, 13]. Taxila is an urbanized tehsil of around 6 million populations densely populated with humid temperature conditions favoring the dengue spread and its recurrent episodes. A large number of people have suffered from dengue infection and are susceptible to recurrent episodes. It is very important to study different patterns of Dengue fever among patients because few studies have been done on dengue in Taxila.

The objective of this study was to identify the pattern of dengue fever in relation to the hematological and biochemical parameters of patients who presented to Heavy Industries Taxila Cantt (HIT) Hospital, with the aim of examining the correlation between these parameters of dengue patients in the vicinity of Taxila.

METHODS

Institutional Review Board Approval was taken from the research committee of Heavy Industries Taxila institute of medical sciences (HITEC-IMS) under reference number HITEC-IRB-35-2023. After obtaining the necessary approvals, a retrospective cross-sectional study was conducted, including all 118 patients who presented to HIT Hospital, Taxila Cantt, between August 2022 and November 2022 and tested positive for dengue serology. Informed consent was obtained from each patient during their hospital stay, ensuring their agreement to use information related to their clinical features, laboratory parameters, treatment, and outcomes for future research purposes. Patients were divided into three groups: Group-I, representing mild dengue fever; Group-II, representing moderate dengue fever; and Group-III, representing severe dengue fever. Mild dengue fever: Patients who test positive for dengue have normal hematocrit and platelet counts. Moderate dengue fever: Dengue-positive patients with raised hematocrit or low platelet count. Severe dengue fever: Dengue-positive patients with warning signs along with plasma leakage, shock, fluid accumulation, severe bleeding, and respiratory distress [14]. All the patients with positive dengue serology, regardless of their age, gender, or other parameters were included. However, patients with thrombocytopenia resulting from other hematological diseases were excluded from study. Demographic characteristics and biochemical parameters were studied. Blood samples were collected through venipuncture from the antecubital vein using a sterile syringe or vacuum collection system. A tourniquet was applied to facilitate vein identification, and approximately 3–5 mL of blood was drawn per patient. The blood was then processed using an automated hematology analyzer for parameters like hemoglobin, hematocrit, platelet count, and leukocyte count, while ALT levels were measured using a biochemistry analyzer. Once collected, the samples were processed and stored according to standard laboratory procedures, ensuring accuracy in the analysis of hematological and biochemical parameters. Demographic data including gender, age distribution, marital status, education, and occupation of patients while, biochemical parameters including hemoglobin (Hb) level (10-14 gm/dl), hematocrit (40-50%), platelets (150,000-400,000/ µl), leucocyte count (45,00 to 11000// µl), and plasma Alanine transaminase (ALT) levels (4-36// µl) were checked from collected blood samples of the patient. The sample size of 118 patients, while sufficient for preliminary analysis, may not be large enough to capture the full variability in hematological and biochemical parameters among dengue patients but detailed and accurate data collection from 118 patients enabled robust analysis of hematological and biochemical patterns in dengue. The sample size was calculated using the Open-Epi software, based on a population size of 56,590 individuals who could have dengue. The calculation considered an expected proportion (p) of 0.5, which represents the maximum

DOI: https://doi.org/10.54393/pjhs.v6i1.2542

variability in the population, ensuring the sample would capture a broad range of responses. The study aimed for a 95% confidence level (Z value = 1.96) and a 5% margin of error (E = 0.05), which is standard for health-related research. These parameters ensured that the sample size was sufficient for accurate and reliable analysis of the data on dengue severity and related biochemical parameters. The data were collected and analyzed using SPSS version 23.0. Confidence interval was targeted at 95 % with 5 % margin of error. The effect size for this study was determined based on expected differences in key hematological and biochemical parameters, such as platelet count and hematocrit, between dengue severity groups. From existing literature, moderate to large effect sizes (e.g., Cohen's *d*=0.5–0.8) were anticipated, reflecting clinically meaningful variations. This guided the analysis and interpretation of the observed findings. The quantitative data were analyzed in the form of mean, median, and standard deviation. The chi-square test of significance was applied and the p-value <0.05 was considered significant. The chi-square test was used in this study to analyze associations between categorical variables, as it is well-suited for assessing the independence or relationship between two categorical datasets. This non-parametric test is appropriate given the nature of the variables and the study's objective to identify significant patterns in patient outcomes.

RESULTS

Among the 118 dengue cases reported at HIT Hospital, Taxila, with confirmed diagnoses from August 2022 to November 2022, there were 14 patients classified as group I (mild dengue), 87 patients in group II (moderate dengue), and 17 patients in group III (severe dengue). There were 77 male patients (65.3%) and 41 female patients (34.7%). Individuals under 18 years comprised 10 (8.5%); those aged 18 to 49 years constituted 72 (61.0%); and individuals aged 50 years and above accounted for 36 (30.5%). The proportion of married patients was greater (60.8%) compared to unmarried patients (32.0%) (Table 1).

Table 1: Analysis of Demographic Variables of Patients

Demographic Variables	Groups/Subgroups	Frequency (%)
Age Group	<18 Years	10 (8.5%)
	18-49 Years	72 (61.0%)
	> 50 Years	36 (30.5%)
Gender	Male	77 (65.3%)
	Female	41 (34.7%)
Marital Status	Married	80 (68%)
	Unmarried	38 (32%)
Occupation	Student	37 (31.4%)
	Housewife	21 (17.8%)
	Employee/Job	20 (16.9%)
	Skill Person	35 (29.7%)
	Retired	5 (4.2%)
Education	Illiterate	1 (0.8%)
	Middle School	8 (6.8%)
	Primary	30 (25.4%)
	High School	61 (51.7%)
	Graduation	18 (15.3%)

Patients with severe dengue demonstrate a substantial reduction in platelet counts across all age demographics, with a p-value of less than 0.05. In persons under 18 years of age, platelet values range from 297.50 ± 33.23 in mild dengue, 118.62 ± 18.60 in moderate dengue, to 154.4 ± 7.97 in severe dengue. In the 18 to 49 age group, which constitutes the majority of individuals in the study, platelet counts are as follows: 173.83 ± 21.48 in mild dengue, 94.27 ± 22.77 in moderate dengue, and 36.50 ± 13.76 in severe dengue. In patients over 50 years old, platelet counts are as follows: 163.00±5.79 for mild dengue, 93.36±21.95 for moderate dengue, and 34.60±17.55 for severe dengue making platelet count clear and consistent marker if dengue severity. We additionally assessed other biochemical markers, including hemoglobin, hematocrit, and leukocyte count; they exhibited no significant alterations, except for total leukocyte count in individuals over 50 years, which demonstrated a p-value of less than 0.05 (Tables 2).

Table 2: Comparison of Hemoglobin, Hematocrit, Platelets, leukocyte, ALT with Dengue Severity among Age groups

Variables	Age Groups	Dengue Severity			p-value
		Mild Mean ± SD	Moderate Mean ± SD	Severe Mean ± SD	
ALT	<18	21.00 ± 12.72	31.62 ± 9.42	29.50 ± 10.35	0.212
	18-49	72.83 ± 52.09	49.17 ± 31.09	76.08 ± 45.20	0.033
	> 50	63.50 ± 18.39	64.28 ± 33.99	80.60 ± 13.55	0.533
Hb	<18	10.90 ± 1.41	13.16 ± 0.85	0	0.016
	18-49	13.26 ± 1.75	13.50 ± 1.75	13.36 ± 1.44	0.930
	> 50	14.08 ± 1.13	13.16 ± 1.62	14.20 ± 1.15	0.217
Hematocrit	<18	0.33 ± 0.00	0.38 ± 0.03	0	0.084
	18-49	0.38 ± 0.03	0.38 ± 0.03	0.39 ± 0.02	0.782
	> 50	0.40 ± 0.01	0.39 ± 0.02	0.41± 0.01	0.220
Platelets	<18	297.50 ± 33.23	118.62 ± 18.60	154.4 ± 7.97	0.000
	18-49	173.83 ± 21.48	94.27 ± 22.77	36.50 ± 13.76	0.000
	> 50	163.00 ± 5.79	93.36 ± 21.95	34.60 ± 17.55	0.000
Leukocyte Count	<18	6.40 ± 2.82	5.46 ± 2.73	0	0.677
	18-49	4.38 ± 0.96	3.86 ± 1.72	3.00 ± 1.05	0.157
	> 50	4.73 ± 1.05	3.68 ± 1.09	2.86 ± 0.89	0.022

Table 3 presented a comparison of hemoglobin (Hb), hematocrit, platelets, leukocytes, and alanine aminotransferase (ALT) levels with dengue severity among male and female participants. The data highlighted variations in these hematological and biochemical parameters across different severity levels of dengue infection, providing insights into gender-specific differences in disease progression and response.

DOI: https://doi.org/10.54393/pjhs.v6i1.2542

Table 3: Comparison of Hb, Hematocrit, Platelets, Leukocyte, ALT with Dengue Severity among Male and Female Participants

Variables	Age Groups	Dengue Severity			p-value
		Mild Mean ± SD	Moderate Mean ± SD	Severe Mean ± SD	
ALT	Male	52.70 ± 22.57	47.33 ± 25.26	84.36 ± 43.89	0.001
	Female	83.25 ± 63.88	60.16 ± 40.30	64.66 ± 22.40	0.570
Hb	Male	13.65 ± 1.68	14.26 ± 1.02	14.30 ± 1.20	0.287
	Female	12.35 ± 1.69	11.77 ± 1.31	12.33 ± 0.45	0.475
Hematocrit	Male	0.38 ± 0.03	0.40 ± 0.02	0.40 ± 0.03	0.130
	Female	0.36 ± 0.03	0.36 ± 0.03	0.38 ± 0.01	0.426
Platelets	Male	190.60 ± 57.77	96.21 ± 24.92	33.27 ± 16.07	0.000
	Female	177.50 ± 25.59	96.32 ± 19.78	40.83 ± 4.17	0.000
Leukocyte Count	Male	5.15 ± 1.42	4.10 ± 1.99	2.87 ± 0.65	0.018
	Female	3.97 ± 0.86	3.69 ± 1.12	3.13 ± 1.47	0.467

Three out of seventeen individuals with mild dengue exhibited normal serum ALT levels, whereas eleven demonstrated abnormal levels. Among patients with moderate dengue, 27 of 87 exhibited normal serum ALT levels, whereas 60 patients presented with elevated serum ALT levels. In cases of severe dengue, 16 of 17 patients exhibited elevated serum ALT levels. In the 18 to 49 age demographic, the p-value is less than 0.05, indicating a strong link with dengue severity. In other subgroups, p-value is not significant because the sample size is insufficient (Table 4).

Table 4: Association of ALT with Dengue Severity

Variables		Dengue Severity			Total Frequency (%)	p-value*
		Mild Frequency (%)	Moderate Frequency (%)	Severe Frequency (%)		
Serum ALT	Normal (4-36)	3 (21.4%)	27 (31.0%)	1 (5.9%)	31 (26.3%)	0.001
	Not Normal	11 (78.6%)	60 (69.0%)	16 (94.1%)	87 (73.7%)	
Total		14	87	17	118	

*chi-square test

In a comparison of male and female patients with dengue severity, 71.4% of males exhibited moderate dengue, whereas 28.6% of females did. 64.4% of males experienced moderate dengue, whereas 35.6% of females did. 64.7% of males, in contrast to 35.3% of females, experienced severe dengue. Both sexes exhibit reduced platelet counts, with a p-value below 0.05 (Table 5).

Table 5: Association of Gender with Dengue Severity

Variables		Dengue Severity			Total Frequency (%)	p-value
		Mild Frequency (%)	Moderate Frequency (%)	Severe Frequency (%)		
Gender	Male	10 (71.4%)	56 (64.4%)	11 (64.7%)	77 (65.3%)	0.875
	Female	4 (28.6%)	31 (35.6%)	6 (35.3%)	41 (34.7%)	
Total		14	87	17	118	

DISCUSSION

Dengue still wreaks havoc for developing countries like Pakistan, ranging from febrile illness to multiorgan failure, and can cause death. In this study, the male population exhibited a higher prevalence than the female population, suggesting a predominance in the earlier population, potentially due to behavioral factors, biological and immunological factors, health care seeking behavior and socio-economic factors. Jayarajah U *et al.*, in 2018 studied demographic distribution and clinical and hematological findings in dengue patients from indoor patients. The study included 1167 patients (males and females). The study reported 775 cases of moderate dengue and 392 cases of severe dengue [15]. The population between 18 to 49 years of age showed a higher incidence of dengue, indicating a greater desire to earn a livelihood by venturing out and exposing themselves. Study by Prattay KM *et al.*, in 2022 showed similar results as 73.3% of patients were between 18 to 40 years of age [16]. This age group has more awareness of mosquito-borne disorders and approaches to health facilities. The majority of the population was literate, indicating the ineffectiveness of national awareness programs. Therefore, there is a need for increased government focus on educating people about mosquito-borne diseases and implementing more control programs. Jayaweckreme KP *et al.*, in 2021 notified the same concern in their study [17]. Most individuals showed signs and symptoms of moderate dengue, depicting its temperate and restrained presentation. Choong ZL *et al.*, in 2020 also observed same pattern on severity of disease [18]. In terms of biochemical parameters, both males and females showed a predominant loss of platelets compared to White Blood Counts (WBCs) and Red Blood Counts (RBCs). The severity of the disease increases with the decline in platelet levels. This study was concurrent with Zeeshan M *et al.*, in 2022 who demonstrated the pattern of dengue disease in 174 patients of Islamabad and Vicinity. They observed that in dengue disease 85% of patients had a platelet count of less than 100,000, and 46.8% had a reduced hematocrit. Total Leukocytes Count (TLC) was decreased in 50% of patients [19]. The virus caused damage to the liver, as evidenced by the alteration of liver enzymes from normal levels. ALT rise has an association with the severity of dengue; as it progresses, more damage is exhibited by the raised level of ALT, and this pattern was more trending in the male population as compared to females. Saghir H *et al.*, in 2022 in Islamabad conducted a study on 149 patients to assess hepatic by monitoring Alanine Transaminase (ALT) and Aspartate Transaminase (AST). They concluded that Dengue Disease (DD) is more

DOI: https://doi.org/10.54393/pjhs.v6i1.2542

common in males and have different pattern among patients below 30 years of age. 79 Patients with (DF) had normal ALT and 2 patients had elevated. Among 68 patients with Dengue haemorrhagic fever DHF, 41 had elevated ALT levels, and 23 patients had normal ALT levels. They found a significant correlation between platelet count and elevated ALT [20]. A study was done by Salam MA *et al.*, in 2023, to check the prevalence in the district of Rawalpindi. Blood samples were analyzed for dengue Immunoglobulin G, Immunoglobulin M, and NS1 (Nonstructural protein antigen of virus) who presented with the signs and symptoms of dengue fever. 78 people were from Rawalpindi, 47 belonged to Taxila, and 35 from Kahuta [21].

CONCLUSIONS

It is concluded that dengue is more prevalent among males as compared to females, affecting the age group (18-49) mainly. Moderate dengue is more common than mild and severe forms. The majority of the patients showed reduced platelet levels, which was related to the severity. Around two-thirds of patients showed abnormal liver function tests, and the severity of dengue is concurrent with the rise of ALT. These biochemical parameters are not only helpful in assessing the disease but severity of the disease can also be uncovered.

Authors Contribution

Conceptualization: SU, AJ, UA, SHBA, RY, MR, AJ, SS, SR
Methodology: SU, AJ, UA, SHBA, RY, MR, AJ, SS, SR
Formal analysis: SU, AJ, UA, SHBA, RY, MR, AJ, SS, SR
Writing, review and editing: SU, AJ, UA, SHBA, RY, MR, AJ, SS, SR
All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2547

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Perceptions and Factors Associated with Self-Medication for Oral Health Problems in Dental Patients of LUMHS, Jamshoro

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ARTICLE INFO

Keywords:

Self-medication, Perceptions, Oral Health Problems, Professional Advice

How to Cite:

Shah, F., Rajpar, S. P., Talpur, N., Kandhro, R., Shah, S., Shah, M., & Chandio, B. (2025). Perceptions and Factors Associated with Self-Medication for Oral Health Problems in Dental Patients of LUMHS, Jamshoro: Self-Medication for Oral Health Problems in Dental Patients. Pakistan Journal of Health Sciences, 6(1), 314-318. https://doi.org/10.54393/pjhs.v6i1.2547

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Received date: 1st December, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

The practice of self-medication is widespread in both industrialized and developing nations. It is characterized by the use of medications to treat self-diagnosed conditions and the prescription of medications without appropriate professional advice. However, the illogical use of antibiotics contributes to antibiotic resistance and has several negative repercussions. **Objectives:** To assess the perceptions and factors associated with self-medication for oral health problems among dental patients of Liaquat University of Medical and Health Sciences, Jamshoro. **Methods:** 335 respondents were included in this cross-sectional study conducted at the Oral Diagnosis Departments of Liaquat University of Medical and Health Sciences, Jamshoro. The study was completed in a time duration of two months by employing a non-probability consecutive sampling technique. The data were subjected to descriptive analysis. SPSS Version 26.0 was employed to analyze the data. **Results:** 73% of total subjects were taking self-medication as the reason for minor illness (36.3%). Most of the patients were affected by having age of 18-30 years (45.4%) and female had more predilection (54.9%). Toothache was the most common cause of self-treatment (49.4%), pain relievers were the most common drugs taken as self-medication (24.5%), and Friends and relatives were the main sources of advice (59.2%). **Conclusions:** It was concluded that self-medication for dental illnesses was quite popular among patients. Although the majority of patients got symptomatic relief through self-medication all the respondents agreed that this was not the right practice and that proper consultation is important. Literacy level had a bad impact on people's choices of self-treatment.

INTRODUCTION

Self-medication is very common and used worldwide [1]. It is described as selecting and taking medicines, and medicated products including herbal and traditional products by a person to treat self-evaluated health problems or continuous use of medicine previously advised by a doctor, for a chronic illness or a recurrent disease [2, 3]. Under some circumstances self-medication can be a beneficial tool for managing minor illnesses in mountainous and tribal areas where health facilities are not accessible due to geographical discrepancies and WHO has stated guidance for some over-the-counter medicines which are available without doctor's advice [4-6]. Self-medication also has possible hazards like failure to diagnose the problem correctly, failure or delay in getting proper medical advice, inappropriate selection of therapy, failure in detecting the possible drug interactions, contraindications not being able to inform current self-medication to the prescribing doctor (which increases the chance of double medication or serious interactions), improper dosage and duration of medication, the danger of dependence and abuse. The factors that affect self-medication are gender, socioeconomic factors, behavior toward personal well-being, and awareness about medication [7-9]. Some other causes of self-medication

DOI: https://doi.org/10.54393/pjhs.v6i1.2547

stated by another study were prolonged hours of waiting in health care centers and minor ailments. Frequent causes of self-medication are headache, cough, fever, and pain. Oral health problems such as dental pain, gum bleeding, discomfort, and bad breath along with some other problems are common causes of self-medication. As self-medication is a common problem in developing countries and antibiotic resistance is also becoming common nowadays, people take their symptoms lightly and self-medicate which has become a matter of concern [10-12]. Therefore, the rationale of this study is that the self-medication practice is becoming common in dental patients and only a few studies have also been done to evaluate the perceptions and factors associated with self-medication in dental patients but still, there is a need to assess self-medication among patients coming with dental problems, the socioeconomic factors and literacy rate associated with this problem, dental phobia, the type of medicine taken as self-medication and type of dental problem which led them to take medicine on their own.

This study aims to assess the perceptions and factors associated with self-medication in dental patients by a self-administered questionnaire, with close-ended questions.

METHODS

The cross-sectional study was conducted among dental patients at the Oral Diagnosis/Oral Medicine Out-Patient Department of Liaquat University of Medical and Health Sciences Jamshoro by a non-probability consecutive sampling technique contained by two months of the period i.e. (July to September 2021) after getting ethical approval from the university (NO. LUMHS/REC/-118). Informed consent was taken by patients / Guardians. Inclusion criteria consisted of gender, age between 18-50 years, patients showed a willingness to participate in the study by signing the written consent, and differently able patients and pregnant women were excluded from the study. The sample size was calculated by using the standardized formula for cross-sectional studies using an error margin of 5% at a confidence interval of 95% and a prevalence of self-medication67.8% [2]. The sample size calculated was 335. Patients fulfilling the inclusion criteria were asked to answer the questions from a questionnaire on Self-medication the first part of the questionnaire asked whether a respondent practices self-medication or not and the respondents who did not opt for self-medication were advised to discontinue the remaining portion of the survey and the subjects who admitted that they do adopt self-medication practices gave the answers of remaining questions. The questionnaire was designed by going through a few studies [6-8]. The initial part of the questionnaire had questions regarding personal information like age, gender, qualification, marital status, and occupation and the other questions were about the behaviors, patient's perceptions regarding this practice, reasons, and type of drugs being consumed as self-medication due to common oral health problems. The data were analyzed by SPSS version 26.0. Descriptive Statistical analysis was used for frequencies. The chi-square test was used to find out the association between self-medication and educational qualification.

RESULTS

The participants in this study were between 18 and 50 years old. A total of 335 subjects were included in the study. The majority of them belonged to the age group 18-30 years (45.4%), 27.8% were from the age group of 31-40 years, and 26.9% were from the age group 41-50 years. Gender distribution shows female were in preponderance 54.9% were female and 45.1% were male. Educational status of patients shows that 1.8% were educated up to Class 8 (Middle school), 22.7% were qualified with a bachelor's degree, 11% studied up to intermediate level, 7.8% were masters qualified, 13.7% were qualified to matriculation level, 13.1% had primary education, and 29.9% were unschooled (Table 1).

Table 1: Socio-Demographic Characteristics of the Participants

Variables	Frequency (%)
Age	
18-30	152 (45.4%)
31-40	93 (27.8%)
41-50	90 (26.8%)
Gender	
Male	151 (45.1%)
Female	184 (54.9%)
Education	
Eight grade	6 (1.8%)
Primary	44 (13.1%)
Matriculation	46 (13.7%)
Intermediate	37 (11.0%)
Graduate	76 (22.7%)
Masters	26 (7.8%)
Unschooled	100 (29.9%)

The percentage of self-medication in our study was 73% who responded positively when they were asked about opting for self-medication and the remaining 27% were not involved in self-medication practices. Total of 245 patients who said yes to self-medication, 31.4% patients opted for self-medication because of gum bleeding, 4.1% self-medicated for oral ulcers, 49.4% self-medicated for toothache, 12.7% went for self-medication practices. For toothache and gum bleeding, 2.4% of patients were self-medicating for toothache and oral ulcers. Among 245 patients who self-medicated for oral health problems

DOI: https://doi.org/10.54393/pjhs.v6i1.2547

13.9% used herbal products as treatment, 0.4% used herbal products and salt water rinse as treatment, 22.9% patients used other aids of treatment, 0.8% patients answered that they use salt water rinse and other things as self-medication measure, 17.6% used painkillers along with antibiotics for self-medication, 0.4% used pain killers, antibiotics and herbal products for self-medication, 0.8% used painkillers and herbal products, 24.5% used painkillers, 10.6% used pain killers along with other things, 4.9% patients used painkillers along with salt water rinse, 0.4% used painkillers, antibiotics and salt water rinse and 2.9% only used salt water rinse for self-medication. 245 patients who were doing self-medication the treatment duration was a few days in 13.1% of patients, only a single dose was taken by 46.9% of patients, and 40% of respondents used medicine till the symptom was relieved as shown in (Table 2).59.2%were self-medicating on friends and relatives advise, 9% were doing self-medication on friends, relatives and pharmacist advise, 1.6% were self-medicating from mass media sources, 11.8% self-medicated on basis of personal knowledge and 18.4% were getting advice from a pharmacist. Amongst 245 patients 26.1% said that they were self-medicating because of lack of time, 0.2% said that lack of time and shortage of money was the reason behind self-medication, 24.1% said that their reason for self-medication was a long distance from home to a health care facility, 36.3% thought that it was a minor illness,12.7% people gave the reason for the shortage of money. 245 subjects who did self-medication, 93.9% subjects said that their symptom was relieved by self-medication and 6.1% patients said that their symptom was not relieved by self-medication (Table 2).

Table 2: Self-Medication Practices, Types and Durations

Variable	Frequency (%)
Self-Medication	
Yes	245 (73%)
No	90 (27%)
Oral Health Problem	
Gum Bleeding	77 (31.4%)
Oral Ulcers	10 (4.1%)
Toothache	121 (49.4%)
Swelling	31 (12.7%)
Bad Breath	6 (2.4%)
Type of Medication	
Herbal Products	34 (13.9%)
Herbal Products/Salt Water Rinse	1 (4.0%)
Others	56 (22.9%)
Other/Herbal Products	2 (8.0%)
Painkiller/Antibiotic	43 (17.6%)
Painkiller/Herbal Product/Antibiotic	1 (4.0%)
Painkillers/Herbal Products	2 (8.0%)
Painkillers	60 (24.5%)
Painkiller/Others	26 (10.6%)
Painkiller/Salt Water Rinse	12 (4.9%)
Painkiller/Antibiotic/Salt Water Rinse	1 (4.0%)
Salt Water Rinse	7 (2.9%)
Treatment Duration	
Few Days	32 (13.1%)
Single Dose Only	115 (46.9%)
Till Symptoms Relieved	98 (40.0%)
Adviser	
Friends and Relatives	145 (59.2%)
Friends/Relatives/Pharmacist	22 (9.0%)
Mass Media	4 (1.6%)
Personal Knowledge	29 (11.8%)
Pharmacist	45 (18.4%)
Reasons for Practicing Self-Medication	
Lack of Time	67 (26.1%)
Lack of Time/Shortage of Money	2 (8.0%)
Long Distance From Home to Health Care Facility	59 (24.1%)
Minor Illness	89 (36.3%)
Shortage of Money	31 (12.7%)
Symptoms Relieved	
Yes	230 (93.9%)
No	15 (6.1%)

A chi-square test was applied to check the association between educational status and self-medication practices and we found that the p-value is less than 0.05, which means that there is a significant relationship between self-medication and education (p-value-0.000)(Table 3).

Table 3: Self-Medication versus Educational status

Variables		df	Asymptotic Significance (2-Sided)
Pearson Chi-Square	74.251[a]	6	0.000
Likelihood Ratio	71.742	6	0.000
N of Valid Cases	335	--	--

a.2 cells (14.3%) have an expected count of less than 5. The minimum expected count is 1.63.

DISCUSSION

In this study, the most common age group of study participants was 18-30 years and more participants were female, this is in contrast with another study conducted in Dehradun, Uttara hand by Kumar *et al.*, in which the most common age group was 30-39 years and most patients were male [13]. Another study by AlQahtani *et al.*, conducted a study in the United Arab Emirates (UAE) which found the prevalence of self-medication at 70.7% for dental illnesses, which is close to the results of this study which found the percentage of self-medication at 73% [14]. In this study, 46.9% of participants took a single dose of medicine for symptom relief and the majority of subjects (53.1%) took medicines for a few days. Our study noted that taking medicine on their own without prescriptions was seen in a

DOI: https://doi.org/10.54393/pjhs.v6i1.2547

higher proportion among female than male which is in contrast with another study being done at Davangere city, Karnataka, which noticed that men were more inclined towards this practice than women [15]. There was a research done in Davangere city in which the perception of self-treatment for oral health problems among participants was mainly minor illness, which is in agreement with this study which also noticed subjects were mainly inclined towards self-treatment for oral health problems most commonly because they think that it is a minor illness. Another study conducted in Riyadh Saudi Arabia noticed a higher female-participant ratio of self-treatment than male. Among oral health problems, toothache was the main reason for self-treatment (49.4%) similar to our study [16]. A study held in a teaching Hospital in Lahore Pakistan by Baig *et al.,* found 58.8% use of oral painkillers and painkillers with antibiotics (13.4%) among participants for dental problems [17], which is in contrast with this study that found 13.9% of respondents using herbal products, 24.5%respondents used pain killers, 22.9% used other modes of oral health problem solutions and 10.6% subjects consumed pain relievers along with others. The percentage of antibiotics used with painkillers is close to this present study which is 17.6%. The main advisors were friends and relatives for the self-treatment in our study, pharmacists were a second common source of self-treatment and personal knowledge was the third common factor of self-medication in our study. There was research done by Kalyani et al., whose findings were close to our results, found that the people residing in city areas were mainly seeking self-medication advice from family and friends, then their knowledge and then getting advice from pharmacists [18]. In the present study, self-treatment was seen more in participants who had no formal education, also seen in considerable percentage in those respondents who had primary education, middle education, and studied up to graduate level. The respondents who were qualified up to masters were least involved in self-treatment practices and we found an association existed between self-medication and education level. The results of our study are close to another study that found self-treatment was more in respondents who had secondary and tertiary education [19, 20]. This can be because educated people have knowledge of medicines and their uses and they try to treat their ailments by themselves instead of going to the concerned doctor, whereas individuals like those in our study who are qualified up to master are more concerned about the proper diagnosis and treatment rather than self-medicating and the people who do not have a formal education tend to self-treat themselves because of lack of awareness regarding drug side effects, interactions and socioeconomic reasons [21, 22]. Self-treatment is a common practice in developing countries, which can lead to several problems like antibiotic resistance, drug interactions, late diagnosis and management of serious diseases, worsening of the existing condition of disease, and many other problems.

CONCLUSIONS

There was a huge number of participants practicing self-medication for oral health problems in this study, the majority of them were females. Toothache remained the most common reason for self-medication, the main factors were considering oral health problems as minor illness, lack of time, and long distance from home to a health care facility, the most common medicine taken was painkillers, friends, pharmacists, and relatives were the main sources of self-treatment. In this study, a significant association between self-medication and education was found.

Authors Contribution

Conceptualization: FS
Methodology: FS, SPR, NT, SS
Formal analysis: RK
Writing review and editing: RK, SS, MS, BC

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2446

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Evaluating the Rising Incidence of Multidrug-Resistant and Extensively Drug-Resistant *Salmonella typhi* and *Salmonella paratyphi* in Sialkot City

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ARTICLE INFO

Keywords:
Salmonella typhi, Multi-Drug Resistance, Extensive Drug Resistance, Antimicrobial Resistance

How to Cite:
Zaman, U., Nasir, S., Asim, S., Azmat, J., Khan, R. M. A., & Soomro, A. K. (2025). Evaluating the Rising Incidence of Multidrug-Resistant and Extensively Drug-Resistant Salmonella typhi and Salmonella paratyphi in Sialkot City : Drug-Resistant Salmonella typhi in Sialkot. Pakistan Journal of Health Sciences, 6(1), 319-324. https://doi.org/10.54393/pjhs.v6i1.2446

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Received date: 18th October, 2024
Acceptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

In the Developing countries, Typhoid is one of the major health concerns. Most importantly the disease management is getting complicated due to multi and extensive drug resistance incidence. **Objective:** To investigate the incidence of causative agent's salmonella typhi and para-typhi in the affected patients of Sialkot who were either multi drug resistant or extensive drug resistant. **Methods:** This descriptive cross-sectional study was conducted at the department of microbiology, Khawaja Muhammad Safdar medical college, Sialkot from January, 2024 to July, 2024. A total of 2000 patients with febrile illness were examined for the study, 500 samples of neonates were excluded and blood samples of remaining 1500 patients were collected. The blood samples were cultured on MacConkey agar and blood agar. Among the 1500 patients, only 73 were found to be infected with either *Salmonella typhi* or *Salmonella paratyphi* according to CLSI criteria. Antibiotic sensitivity was investigated and resistant to trimethoprim-sulfamethoxazole (septran), chloramphenicol, and ampicillin were labeled as multi drug resistant while resistant to ciprofloxacin and third generation cephalosporins in addition to aforementioned antibiotics were labeled as extensively drug resistant. **Results:** From a total of 1500 samples, n=73 *salmonella* positive samples were included in this research. Incidence of extensively drug resistant *Salmonella* was 23 (32%) and multidrug drug resistant *Salmonella* was 7 (10%). **Conclusion:** This study highlighted significant resistance rates, emphasizing the need for sensible antibiotic prescriptions and judicious antimicrobial use to combat rising multidrug and extensive resistance.

INTRODUCTION

The causative agent of typhoid fever is *Salmonella enterica* serovar Typhi, which is a Gram-negative microbe, and it considerably contributes to the overall burden of the disease worldwide. In 2017, over 14 million individuals were affected by typhoid and paratyphoid fever, with more than 130,000 deaths reported. About 70 percent of these deaths occurred in South Asia [1]. In the 1940s, chloramphenicol was introduced as the first-line antibiotic for treating typhoid fever [2-4]. However, the emergence of resistance to chloramphenicol led to the introduction of other antibacterial drugs. This contains the inclusion of co-trimoxazole, in the 1970s. By the 1980s, research indicated that *Salmonella typhi* strains had developed resistance to all available antibiotics of that time [5]. Consequently, ampicillin and trimethoprim-sulfamethoxazole became the preferred choices for typhoid treatment. On the other hand resistance to these antibiotics also emerged globally within a few years. Clinicians then shifted to fluoroquinolones (e.g., ciprofloxacin) for the treatment of typhoid fever and enteric [6]. The growing prevalence of

DOI: https://doi.org/10.54393/pjhs.v6i1.2446

Multidrug-Resistance (MDR) as well as Extensively Drug-Resistance (XDR) in *Salmonella typhi* has severely compromised the efficacy of many treatment options. MDR strains are defined as resistant to at least one antibiotic in three or more different classes.These includes chloramphenicol, sulfonamides (trimethoprim-sulfamethoxazole) and ampicillin. Strains of XDR exhibit resistance to a broader spectrum of antibiotics which also includes third-generation cephalosporins, sulfonamides, ampicillins and ciprofloxacin [7, 8]. Alarmingly, resistance to fluoroquinolones has also increased globally, with South Asia as the epicenter. While cephalosporins and azithromycin remain options for treatment based on clinical efficacy, cases of cephalosporin-resistant Salmonella typhi have been reported worldwide. This showed the tendency of exacerbating the typhoid burden in regions like South Asia where XDR and MDR strains are predominant [9]. In Pakistan, the escalating rates of typhoid fever, driven by XDR and MDR *Salmonella typhi* has raised concerns about antibiotic treatment failure [10]. Between 2016 and 2017, in Hyderabad alone, over 800 cases of XDR typhoid were reported, leading to the declaration of the district as typhoid endemic [11, 12]. The first case of XDR *Salmonella typhi* in Karachi was documented in 2016, and over 17,000 cases have been reported in Sindh since then [13]. Although previous studies have primarily focused on Sindh, recent cases have emerged across Pakistan [14, 15] and internationally, often linked to travel [16]. Additionally, during the COVID-19 pandemic, an increase in typhoid cases resembling COVID-19 in clinical presentation was observed; in June 2020 alone, over 20,000 cases were diagnosed in Pakistan [17]. Despite the rising prevalence of MDR and XDR *Salmonella typhi*, there is limited data from cities like Sialkot, highlighting a critical gap in the regional understanding of antimicrobial resistance patterns.

This study aimed to determine the incidence of MDR and XDR *Salmonella typhi* and *Paratyphi* in Sialkot and investigate the antimicrobial sensitivity patterns of commonly prescribed antibiotics (chloramphenicol, ciprofloxacin, cefixime, azithromycin, and ceftriaxone) against typhoidal *Salmonella.*

METHODS

After receiving an approval from the Ethical Review Committee (approval number 133/REC/KMSMC), this descriptive cross-sectional study was conducted in the Microbiology Department of Government Khawaja Safdar Medical College and Allied Hospitals, Sialkot, from January, 2024, to July, 2024. The sample size of 73 cases was determined using the RAOSOFT sample size calculator with 5% margin of error and a 95% confidence level. An assumed prevalence rate of 10% based on local data to ensure statistical power. Written informed consent was obtained from all participants or their guardians in the case of children. A non-probability purposive sampling method was adopted to select the participants, ensuring the inclusion of cases clinically suspected of typhoid fever based on patient history and symptoms. Patients of all age groups, both male and female, with a history of fever and clinical suspicion of typhoid fever, were included. Out of the 2,000 suspected typhoid cases, neonates (500 cases) were excluded due to the inability to obtain large blood samples (8-10 mL) safely. The remaining 1,500 patients were selected for blood sample collection under aseptic conditions. Blood samples were injected into Bactec™ Plus Anaerobic and Aerobic culture bottles containing 20 mL of broth and incubated overnight at 37 ± 1°C, following standard microbiological measures. Blood cultures were administered using the BACT/ALERT 3D system (Biomerieux, France). Isolates were identified as *Salmonella typhi* and *Salmonella paratyphi* using the API 20E identification system (Biomerieux, France) and serological confirmation was done with polyvalent antisera (Bio-Rad). To evaluate the Antimicrobial susceptibility, the Kirby-Bauer disc diffusion protocol was employed. The inoculum density was adjusted to match the turbidity level of 0.5 McF standard (nearly 1.5×10.0^8 organisms/mL) and uniformly spread on the surface of Mueller-Hinton agar plates. Antibiotic susceptibility was tested using the following antibiotics, grouped and presented in table 1. Plates were incubated overnight at 36°C, and Zone of Inhibition (ZOI) for each plate was measured in millimeters. Outcomes were shown as "Resistant," "Intermediate," or "Susceptible" depending upon the Clinical and Laboratory Standards Institute (CLSI) guidelines [18]. The varying number of samples for each antibiotic test was due to availability constraints, clinical indications, and the focus of analysis on specific antibiotics most relevant to MDR/XDR cases. The descriptive cross-sectional design accounted for confounders by stratifying data based on age, gender, and comorbidities. This was essential for ensuring representative findings across the population. Data were examined using SPSS version 22.0. Descriptive statistics were adopted to compute the frequencies and percentages for qualitative variables.

RESULTS

Among 2000 recruited patients 500 (25%) of neonates were not included in the research. From remaining 1500 (75%) samples, 1200 showed no growth, from remaining 300, 73 (24%) yielded growth of *Salmonella typhi* and paratyphi. A total of 73 Salmonella positive samples were statistically analyzed. From positive, 62% female and 38 % were male. Mean age was 29 years ranging from 1 to 80 years. From total *Salmonella* species, 64 (88%) Salmonella typhi and 9 (12%) *Salmonella paratyphi.*Extensively drug

DOI: https://doi.org/10.54393/pjhs.v6i1.2446

resistance *Salmonella* species were 32% and multidrug drug resistance *Salmonella* species were 10%.

Table 1: Grouping of Antibiotics with Their Disc Concentrations Used in the Study

Antibiotic Groups	Antibiotics	Disc Concentration
Penicillins	Ampicillin	10.0 µg
Phenicols	Chloramphenicol	30.0 µg
Sulfonamides	Co-trimoxazole	1.250/23.750 µg
Quinolones	Ciprofloxacin	5.0 µg
Cephalosporins	Ceftriaxone, Cefixime	30.0 µg each
Macrolides	Azithromycin	15.0 µg
Carbapenems	Imipenem, Meropenem	10.0 µg each

The table 2 showed incidence of *Salmonella* from *salmonella typhi* there are 4 MDR and 9 XDR between age 1-20 years, 2 MDR and 9 XDR cases of age 21-40 years, only 4 XDR cases of age 41-60 years and no MDR or XDR cases between age 61-80 years. Similarly, there is only 1. MDR case of age 1-40 years and 1 case of XDR between ages 61-80 years of *Salmonella paratyphi.*

Table 2: Incidence of *Salmonella* spp. from Enrolled Samples (n=73)

Age Range	*Salmonella typhi*			*Salmonella paratyphi*			Total 73 (100%)
	MDR n =6	XDR n =22	Other n =36	MDR n =1	XDR n =1	Other n =7	
1-20	4	9	16	-	-	-	29
21-40	2	9	14	1	-	5	31
41-60	-	4	6	-	-	1	11
61-80	-	-	-	-	1	1	2

Inhibition zones were measured in millimeters (mm) and tabulated (Table 3). Each result represents the mean value (±SD) obtained from three independent replicates of susceptibility tests. Resistance categories were classified according to CLSI 2024 guidelines. MDR refers to resistance to at least three classes of antibiotics, including amoxicillin, co-trimoxazole, and chloramphenicol. XDR strains were resistant to all first-line agents (amoxicillin, co-trimoxazole, and chloramphenicol) and second-line fluoroquinolones but remained sensitive to azithromycin and carbapenems.

Table 3: Zone of Inhibition Measurements for MDR and XDR Strains

Antibiotics	Breakpoint (mm)	Mean Zone of Inhibition (Mean ± SD)	Category (R = Resistant, S = Sensitive)
Amoxicillin	≤13	10.5 ± 0.6	R
Ceftriaxone	≥23	30.2 ± 1.4	S
Ciprofloxacin	≤15	12.4 ± 0.7	R
Azithromycin	≥14	27.1 ± 1.2	S
Imipenem	≥16	28.8 ± 0.8	S

The results of the study presented in table 4 show that, most *Salmonella typhi* isolated have significant resistance to first-line antibiotics, with 56.3% resistant to amoxicillin and 64.1% resistant to ciprofloxacin.Comparatively, resistance rates in S. *paratyphi* were generally lower, except for azithromycin and ciprofloxacin, where resistance reached 77.8% and 66.7%, respectively. Multidrug Resistance (MDR) was higher in *Salmonella typhi* (44.4%) compared to *S. paratyphi* (12.5%). Extensively Drug-Resistant (XDR) strains were rare, with only 2.5% of *Salmonella typhi* isolates classified as XDR, and none in S. *paratyphi.*

Table 4: Antibiogram formation: A Pattern of Drug Resistant against *Salmonella typhi* and *Salmonella paratyphi* Isolates

Drugs	*Salmonella typhi*		*Salmonella paratyphi*	
	Cases Tested	Resistant Frequency (%)	Cases Tested	Resistant Frequency (%)
Amoxicillin	64	36 (56.3%)	9	3 (33.3%)
Azithromycin	50	30 (60.0%)	9	7 (77.8%)
Cefixime	35	3 (8.6%)	5	1 (20.0%)
Ceftriaxone	64	4 (6.3%)	9	1 (11.1%)
Chloramphenicol	63	28 (44.4%)	9	2 (22.2%)
Ciprofloxacin	64	41 (64.1%)	9	6 (66.7%)
Co-trimoxazole	61	38 (62.3%)	9	3 (33.3%)
Imipenem	50	2 (4.0%)	8	0 (0%)
Nalidixic acid	62	56 (90.3%)	9	8 (88.9%)
MDR tested (a)	45	20 (44.4%)	8	1 (12.5%)
XDR tested (b)	40	1 (2.5%)	6	0 (0%)

a Amoxicillin, chloramphenicol, and *co-trimoxazole* were tested together.
b Amoxicillin, ceftriaxone, ciprofloxacin, co-trimoxazole, and *chloramphenicol* were all *tested together.*

For the MDR strains, sensitivity to third-generation cephalosporins such as cefixime and ceftriaxone persisted to be high, with 92.0% and 92.5% of *Salmonella typhi* isolates, respectively, showed sensitivity. *Salmonella paratyphi* also showed 100% sensitivity to cefixime and ceftriaxone. Resistance to ciprofloxacin was substantial, with only 10.0% of *Salmonella typhi* MDR strains and none of the *Salmonella paratyphi* MDR strains being sensitive. Importantly, imipenem showed excellent efficacy, with 96.7% of *Salmonella typhi* MDR strains and all *Salmonella paratyphi* MDR strains being sensitive. All XDR *Salmonella typhi* strains were sensitive to azithromycin and imipenem table 5.

Table 5: Pattern of Drug Susceptibility MDR and XDR strains of *Salmonella* Isolates

Drugs	*Salmonella typhi*		*Salmonella paratyphi*	
	Cases Tested	Sensitive Frequency (%)	Cases Tested	Sensitive Frequency (%)
Multidrug-Resistant				
Azithromycin	30	10 (33.3)	2	1 (50.0%)
Cefixime	25	23 (92.0)	2	2 (100%)
Ceftriaxone	40	37 (92.5)	3	3 (100%)
Ciprofloxacin	40	4 (10.0)	3	0 (0%)
Imipenem	30	29 (96.7)	2	2 (100%)
Extensively Drug-resistant	-	-	-	-

DOI: https://doi.org/10.54393/pjhs.v6i1.2446

Azithromycin	2	2 (100)	-	-
Imipenem	2	2 (100)	-	-

DISCUSSION

The results of this study highlighted the alarming rise of Extensively Drug-Resistant (XDR) Salmonella typhi, which accounted for the majority of infections, alongside a smaller proportion of Multidrug-Resistant (MDR) Salmonella cases. Historically, the treatment of typhoid fever relied on first-line antibiotics such as chloramphenicol, ampicillin, and co-trimoxazole. However, the emergence of MDR strains resistant to these antimicrobials in the late 1980s led to the adoption of fluoroquinolones and third-generation cephalosporins as the primary treatments. This transition provided effective alternatives but also contributed to increasing resistance rates due to overuse and misuse of these drugs [19, 20]. These findings revealed that alarmingly high resistance to ciprofloxacin, with only 4% of organisms showing sensitivity. Resistance to third-generation cephalosporins was also significant, with 45% of isolates showing resistance to ceftriaxone. These results underscore the dwindling efficacy of critical antibiotics. This trend is consistent with previous studies in South Asia that reported increasing resistance due to widespread over-prescription of fluoroquinolones [21]. The implications of these findings are profound, as both ciprofloxacin and ceftriaxone are considered essential components of current typhoid treatment protocols. The emergence of resistance jeopardizes the effective management of enteric fever. Particularly in resource-limited settings where alternative therapies like azithromycin may not always be accessible. Azithromycin which is often reserved for cases of MDR and XDR typhoid, also showed high resistance rates in this study. These rates are higher particularly among Salmonella paratyphi isolates (77.8%). This resistance trend is concerning, given the limited availability of other oral therapeutic options and the potential for cross-resistance with related macrolides. These findings emphasize the urgent need to rationalize antibiotic use in typhoid management, and enhance diagnostic capabilities for tailored treatments. These also emphasize on the importance to invest in public health measures to mitigate further resistance escalation. The gender distribution in this study, with a higher prevalence of infection among females (62%), aligns with prior research. This suggests that women may be more susceptible to typhoid fever, particularly those with underlying biliary morbidities such as cholelithiasis [22]. Furthermore, these results reinforced the established epidemiological trend that Salmonella typhi is more prevalent than Salmonella paratyphi infections [23]. Typhoid fever remains a significant public health concern in Pakistan. The increasing antibiotic resistance is adding to the burden. The lack of basic hygiene, inadequate sanitation, and unregulated antimicrobial usage have been identified as major drivers of resistance in low- and middle-income countries [24, 25]. The COVID-19 pandemic may have exacerbated this situation by increasing the use of azithromycin and other antibiotics as off-label treatments, inadvertently fostering resistance among typhoidal and non-typhoidal Salmonella strains [26]. Similar factors, combined with urban overcrowding, unvaccinated populations, and inadequate water supplies, contribute to the ongoing emergence and spread of XDR strains, as observed in previous outbreaks in Lyari town of Karachi, Pakistan [27]. Limitations of this study should be acknowledged. The exclusion of neonates (25% of initially recruited participants) may have introduced selection bias, potentially limiting the generalizability of these findings to all age groups. Additionally, the reliance on non-random sampling may have led to overrepresentation of certain demographic groups or resistance profiles. Future research should aim to incorporate broader and more illustrative sampling frameworks to improve the robustness and applicability of results.

CONCLUSIONS

This research discovered a significant rate of resistance and antibiotic susceptibility changes among Salmonella isolated to fluoroquinolones and ceftriaxone necessitating the importance of adhering to the sensible antibiotic prescription and judicious usage of antimicrobials. A pattern of drug susceptibility unique to the samples was found for the first time from Sialkot city suggesting a need to continuously monitor drug susceptibility profiles for better treatment outcomes especially in underrepresented areas.

Authors Contribution

Conceptualization: UZ
Methodology: JA
Formal analysis: SN, SA
Writing, review and editing: JA, RMAK, AKS

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

DOI: https://doi.org/10.54393/pjhs.v6i1.2446

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DOI: https://doi.org/10.54393/pjhs.v6i1.2761

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Association of *Cyp11a* Gene with Polycystic Ovarian Syndrome Patients in Lahore, Pakistan

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ARTICLE INFO

Keywords:
Allele, Cyp11a1, Di-Hydro-Testosterone, Polycystic Ovary Syndrome

How to Cite:
Rao, A., Rao, A. U. J., Wahab, Z., Qudsia, H. K., & Javed, R. (2025). Association of Cyp11a Gene with Polycystic Ovarian Syndrome Patients in Lahore, Pakistan: Cyp11a Gene with Polycystic Ovarian Syndrome Patients . Pakistan Journal of Health Sciences, 6(1), 325-330. https://doi.org/10.54393/pjhs.v6i1.2761

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Received date: 13th November, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

Polycystic ovary syndrome is caused by gene polymorphisms that manufacture steroid hormones, androgens and cortisol. The overexpression or downregulation of *Cyp11a1* gene mutations of steroidogenesis worsens the hyper-androgenic phenomenon. However, there is a gap in the relationship between polycystic ovary syndrome, hyperandrogenism, and *Cyp11a* gene polymorphisms. **Objectives:** To investigate the association between *Cyp11a* gene in polycystic ovary syndrome, and to analyze the levels of di-hydro-testosterone in cases and controls. **Methods:** The study was conducted within six months at The University of Lahore. A sample of 75 participants (25 PCOS, 25 a-PCOS, and 25 controls was collected to test di-hydro-testosterone levels. Then 25 polycystic ovary syndrome patients and 25 control patient samples were used for PCR amplification for the *Cyp11a1* gene. **Results:** The mean age of polycystic ovary syndrome, a-PCOS (anovulatory), and Controls were 22.68, 22.5 and 22.13, respectively. The *Cyp11a1* (10:74348306 G>C) had an odds ratio of 1.199, indicating the presence of an allele in polycystic ovary syndrome and controls. Meanwhile, the odds ratio 1.179, indicated that the allele was 1.2 times more common in polycystic ovary syndrome than the controls. The polycystic ovary syndrome levels of di-hydro-testosterone were higher than the control and a-PCOS groups, with mean values of 278.18, 260.97, and 190.83, respectively. **Conclusions:** *Cyp11a* SNP rs6495096 was present in both polycystic ovary syndrome and controls, and a weak relationship exists between the *Cyp11a1* gene variation and polycystic ovary syndrome. The di-hydro-testosterone levels were high in both the polycystic ovary syndrome and a-PCOS groups compared to the control group.

INTRODUCTION

Polycystic ovarian syndrome is distinguished by anovulation, ovarian cysts, and endocrine variance [1]. In women between the ages of 17-45, Polycystic ovary syndrome (PCOS) prevalence is estimated to be between 5.5% and 12.6% worldwide [2]. The prevalence of PCOS is as high as 15.7-37% in Pakistan [3]. The most frequent androgen abnormality linked to PCOS is elevated free testosterone levels. Progesterone levels are moderate in an-ovulatory PCOS, and estradiol levels are moderate in the mid-follicular phase [4]. Research suggested that PCOS may emerge as a result of altered epigenetics brought on by the hormonal imbalance of the uterine environment, even if the genetic loci only account for 10% of its estimated 70% heritability [5]. The following biochemical pathways contain genes associated with PCOS: complement and coagulation cascade (VWF), steroidogenesis *(CYP11A1, CYP19A1, CYP17A1),* insulin secretion *(INSR, INS, IRS-1),* the signalling *(AMH, LHCGR, INS, ADIPOQ),* chronic inflammation *(TNF-α, IL-6),* and cancer *(MMP, INS, AR1)* pathways [6]. *CYP11* gene from the Cytochrome P450 family is among the critical genes involved in androgen secretion.The two primary components of this gene are *CYP11a1* and *CYP11b1.* These genes have 10 and 9 exons, respectively, and code for a member of the cytochrome P450 family [7]. Steroidogenesis gene abnormalities are the cause of androgen excess in PCOS. A crucial marker in the steroid synthesis pathway, *CYP11a1's* altered expression has been shown to interfere with steroid synthesis, increasing the likelihood of PCOS development [8]. Previous studies have not established a well-established relationship between

DOI: https://doi.org/10.54393/pjhs.v6i1.2761

PCOS, hyperandrogenism, and *Cyp11a* gene polymorphisms. Therefore, this study examined the relationship between Cyp11a gene polymorphism, levels of di-hydro-testosterone (DHT), and PCOS in a particular population.

This study aims to offer new perspectives on the genetic underpinnings of hyperandrogenism and PCOS, which could lead to the development of targeted therapies for PCOS.

METHODS

The descriptive cross-sectional study was conducted at the Institute of Molecular Biology (IMBB) and Biotechnology, The University of Lahore (UOL), Lahore from 1 March 2024 to 15 August 2024. The study period was six months after the approval of the synopsis. Ethical Approval (Ref-IMBB/BBBC/24/1341) was obtained from the Ethics Committee/ Institutional Review Committee of the IMBB at UOL. The sample size was 75 (25 PCOS, 25 atypical PCOS (a-PCOS), and 25 controls collected using Convenient sampling from the Department of Endocrinology and the Department of Gynaecology, Jinnah Hospital, Lahore. Informed consent was obtained from women aged 15-30 years before collecting data and blood samples. Questions related to Polycystic diseases were asked using the questionnaire from the PCOS, a-PCOS, and control groups. The polymerase chain reaction (PCR) for the genotype analysis of the *Cyp11a1* gene was performed on 25 PCOS Patients and 25 controls. The sample size was calculated through an online sample calculator. Blood samples were collected from veins punctured aseptically to collect each subject's blood sample 3CC in ETDA vials for PCR and ELISA. The blood sample was centrifuged at 3000 rpm for 10 minutes for serum isolation. The serum sample isolated was then frozen at 4°C for analysis, and all information, including the patient's name and reference number, was recorded on the form. The DNA was extracted using the DNA Extraction Kit "DONGSHENG BIOTECH Quick Tissue/Culture Cells Genomic DNA Extraction Kit N1141" following the manufacturer's instructions. Three primers were designed for *Cyp11a* using the "Oligo-Calc Website" (Table 1).

Table 1: Primers for *Cyp11a*

Primer Label	Sequence	TM	GC	Length
Hs_*CYP11a1*_FC	AGTTCCACAACTTGCTGACTG	59.5	48%	21
Hs_*CYP11a1*_RN	CAGCAACAGTGATCATAAATCTC	59.2	39%	23
Hs_*CYP11a1*_RM	CAGCAACAGTGATCATAAATCTG	59.2	39%	23

Quantification using PCR was conducted using The "SimpliAmp Thermal Cycler," which utilized the CYP11a1_TD PCR software. The Steps of PCR are described (Table 2).

Table 2: Steps of PCR

PCR Steps	Temperature (°C) / Time (second)	Cycles
Initial Denaturing	94°C/ 5 min	1/1
Cyclic Denaturing	94°C/ 45 Sec	6x
Annealing	56°C/ 90 sec	--
Cyclic Extension	72°C/ 45 sec	--
Final Extension	72°C/ 30 sec	25x
Storage	4°C	--

The DHT levels were measured using the "Human DHT ELISA Kit" provided by Bio-laboratories, available at (www.arigobio.com) following the manufacturer's instructions. Using the "PLINK toolset" the genotyping frequencies were calculated and Chi-square analysis was performed to confirm the association between variant 6495096 *G>C* and *CYP11a1*. Moreover, the p-value and OR were calculated. SPSS version 26.0 was used, qualitative data were presented as frequency/percentage, and quantitative data as mean ± S.D. p-value≤0.05 was taken as significant.

RESULTS

In the study, the mean ± SD of PCOS was 22.68, the mean ± SD 4.801, a-PCOS was 22.5 ± 4.585, and the control group was 22.13 ± 4.719. The health-related questions data of PCOS, a-PCOS, and Controls comprised aspects such as menstrual regularity, spotting, discomfort during menstruation, weight gain, infertility, acne issues, mood swings, and hair growth or facial hair. Participants were also asked if their ultrasound scans revealed any ovarian enlargement (Table 3).

Table 3: Descriptive Analysis of Health-Related Questions to All Patients

Questions	n	Frequency (%)					
		No	Yes	No	Yes	No	Yes
Q1.	25	0 (0%)	25 (100%)	0 (0%)	25 (100%)	0 (0%)	25 (100%)
Q2.	25	16 (64%)	9 (36%)	10 (40%)	15 (60%)	10 (40%)	15 (60%)
Q3.	25	12 (48%)	13 (52%)	13 (52%)	12 (48%)	13 (52%)	12 (48%)
Q4.	25	3 (12%)	22 (88%)	12 (48%)	13 (52%)	12 (48%)	13 (52%)
Q5.	25	12 (48%)	13 (52%)	13 (52%)	12 (48%)	12 (48%)	13 (52%)
Q6.	25	13 (52%)	12 (48%)	12 (48%)	13 (52%)	13 (52%)	12 (48%)
Q7.	25	15 (60%)	10 (40%)	12 (48%)	13 (52%)	11 (44%)	14 (56%)
Q8.	25	6 (24%)	19 (76%)	9 (36%)	16 (64%)	11 (44%)	14 (56%)
Q9.	25	12 (48%)	13 (52%)	13 (52%)	12 (48%)	10 (40%)	15 (60%)
Q10.	25	16 (64%)	9 (36%)	10 (40%)	15 (60%)	12 (48%)	13 (52%)
Q11.	25	13 (52%)	12 (48%)	14 (56%)	11 (44%)	13 (52%)	12 (48%)
Q12.	25	12 (48%)	13 (52%)	12 (48%)	13 (52%)	14 (56%)	11 (44)

Q1. Do you have a menstrual history? Q2. Do you have irregular menstruation? Q3. Do you have minute spotting in menstruation?

DOI: https://doi.org/10.54393/pjhs.v6i1.2761

Q4. Is your menstrual cycle regular? Q5. Do you have painful menstruation? Q6. Do you have pain between two successive menstrual cycles? Q7. Have you gained weight? Q8. Do you have difficulty in conceiving? Q9. Do you have an acne problem? Q10. Are you experiencing mood swings? Q11. Do you have hair growth or facial hair? Q12. Ovaries enlargement on ultrasound?

In PCR amplification of the *Cyp11a1* gene results, bands of heterozygous, homozygous wild, and homozygous mutant were detected on gel electrophoresis in both groups, with DNA ladder 100bp and product size 196 bp (Figure 1).

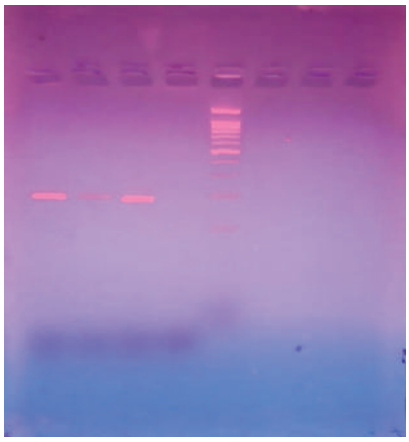

Figure 1a

Figure 1b

Figure 1c

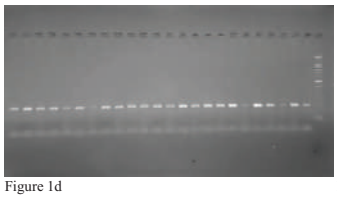

Figure 1d

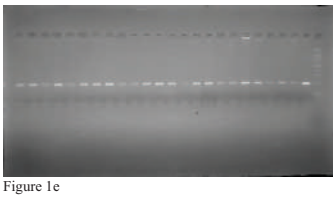

Figure 1e

Figure 1: PCR Amplification of the *Cyp11a1* Gene

There were 12 (48%) heterozygous, 5 (20%) homozygous wild, and 8 (32%) homozygous mutants present in Controls, while in PCOS, 16 (64%) heterozygous, 2 (8%) homozygous wild type, and 7 (28%) homozygous mutants were present. The data fits the Hardy-Weinberg Equilibrium (HWE) with a p-value of 0.3894. The Chi-square test, yielded a p-value of 0.6853, suggesting that allele frequencies between PCOS and Controls are not statistically significant. The odds ratio was 1.179, implying that the mutant allele is more frequent in PCOS than in the control group (Table 4).

Table 4: Chi-Square Analysis of Cyp11a1 gene SNP in PCOS

CHR	SNP	BP	A1	F_A	F_U	A2	CHISQ	p-value	OR
10	1	74348306	1	0.44	0.4	2	0.1642	0.6853	1.179

CHR: Chromosome; SNP: Single Nucleotide Polymorphism; BP: Base Pair. A1: alternative allele (mutant C); A2: reference allele; OR: Odds Ratio. F_A: Frequency of the alternative allele (mutant C) in affected individuals (PCOS). F_U: Frequency of the alternative allele in unaffected individuals (control group).

DHT levels were also measured in this study. DHT levels varied significantly between the groups (p=0.000). The PCOS group had considerably higher DHT levels than the Control group (p<0.001), and DHT levels were substantially greater in the a-PCOS group than in the Control group (p<0.01). The PCOS and a-PCOS groups did not differ significantly (p=0.45) (Table 5).

Table 5: DHT Analysis in PCOS, aPCOS and Control Group

DHT Analysis in Groups	n	Reference Range (pg/ml)	Minimum (pg/ml)	Maximum (pg/ml)	Mean ± SD (pg/ml)
PCOS	25	24 - 368	153.0	427.0	278.188 ± 84.1140
PCOS	25	24 - 368	96.00	393.00	260.9750 ± 89.98997
Control	25	24 - 368	29.00	359.00	190.8312 ± 95.74881

The link between *Cyp11a1* gene variations and DHT levels in the PCOS and control groups was assessed (Table 6).

Table 6: Correlation between Gene variants and DHT in PCOS and Control Group

Cyp11a1 Gene Variants			DHT Values of PCOS			DHT Values of Controls		
PCR-Results	n	Reference Range	Mean ± SD	Min	Max	Mean ± SD	Min	Max
Heterozygous	12	24-368	176.52 ± 100.80	49.75	352.0	244.25 ± 79.16	154.0	378.0
Homo-Mutant	8	24-368	282.43 ± 35.24	250.0	354.0	334.81 ± 46.18	267.0	398.0
Homo-Wild	5	24-368	234.00 ± 62.23	190.0	278.0	296.60 ± 56.24	211.0	354.0

DISCUSSION

It has been demonstrated that *CYP11A1*'s altered expression interferes with steroid production, a critical marker in the steroid synthesis pathway, and increases the risk of PCOS development [6]. While our study objectives were to determine whether *Cyp11a* gene variants, PCOS, and hyperandrogenism are related in a particular community, the current investigation showed a weak connection between the *CYP11a1* gene variation (10:74348306 G>C) and the Pakistani population with PCOS. Current study groups found the following age-related mean ± S.D.s: PCOS 22.68 ± 4.801, a-PCOS 22.5 ± 4.585, and the control group 22.13 ± 4.719. 57.5% acknowledged aberrant menstrual cycles, while 47.5% reported spotting. Menstrual cycle consistency was reported by 52.5% as irregular, 50% with no pain, whereas another 50% said they experienced depression. 47.5% reported pain between two consecutive

DOI: https://doi.org/10.54393/pjhs.v6i1.2761

menstrual cycles, 40% reported weight growth, 75% experienced difficulties during conceiving, and 52.5% reported acne. Furthermore, 35% reported mood swings. 50% reported facial hair, and 52.5% reported enlarged ovaries on ultrasound. A similar study on irregular menstrual cycles in patients with PCOS concluded that menstrual cycle issues affected 72.2% of the population overall, 24% of women, and 15.1% of overweight women were obese. Additionally, 56.4% had acne, and 36% had androgenetic alopecia [9]. Another study showed that about one in five to six women experience severe issues related to irregular menstruation cycles and infertility. Globally, stress, obesity, and fluctuations in hormone levels are the leading causes [10]. In another study, 88% of women experienced irregular menstruation, and 55.9% of participants experienced heavy menstrual flow. PCOS was estimated to have 25.5% and 5.2% prevalence rates, respectively [11]. The current investigation showed a weak connection between the CYP11a1 gene variation (10:74348306 G>C) and the Pakistani population with PCOS. All 50 samples, including 25 cases and 25 controls, were genotyped. Results indicated that of the total genotyped, 48% were heterozygous, 20% were homozygous wild type, and 32% were homozygous mutants. The Chi-square value that was computed is 0.1642. A p-value of 0.6853 indicates no statistically significant difference in allele frequencies between PCOS and Controls. However, the odds ratio in our study is 1.179. This suggests that the mutant allele is more common in the affected group than in the unaffected group. The mutant allele is approximately 1.2 times more common in the PCOS group than in the control group. These results were consistent with a past study that showed that a crucial marker in the steroid synthesis pathway, *CYP11a1's* altered expression, has been shown to interfere with steroid synthesis, increasing the likelihood of PCOS development [8]. A past study found that SNPs in the *CYP11a1* gene (rs1484215 and rs6495096) are associated with PCOS [12]. The rs6495096 polymorphism's C with G alleles was strongly related to PCOS susceptibility (p-0.001). The GG genotype of rs6495096 was also significantly connected with the length of infertility [12]. Another study showed a strong correlation between the *CYP11a1* gene and PCOS. According to dichotomous genotypic analyses, the (tttta) genotype may raise the risk of PCOS in a recessive model, and the (tttta)6 genotype may lower the risk of PCOS in a dominant model [13]. Another variable of the current study was DHT levels, measured in PCOS, a-PCOS, and Control. DHT is a potent androgen generated from testosterone, and elevated levels have been related to disorders like PCOS. In women with PCOS, the hyperandrogenic phenomenon may be exacerbated by overexpressed or downregulated CYP genes implicated in steroidogenesis, which alter androgen levels [14]. A study by Sukanti and colleagues included the testosterone-to-de-hydro-testosterone ratio. The PCOS group had a considerably greater testosterone-to-de-hydro-testosterone ratio than the control group, with p<0.001 [15]. In another study, the findings revealed a significant difference between the PCOS and control groups' levels of DHT p-value 0.009 and testosterone p-value 0.018 [16]. Similar results were found in another study. The study group's mean DHT value was 584.27 pg/mL, whereas the control group's was 257.15 pg/mL, with a p-value of less than 0.00001 and an area under the ROC curve of 0.895. According to the study findings, the DHT is the best biomarker available and can be used to diagnose hyperandrogenemia in PCOS women [17]. Excessive levels of *Cyp11a1* or any protein mutation may boost steroidogenesis, leading to hyperandrogenism and a role in the pathophysiology of PCOS [18, 19]. In the current study, PCOS group, people with the Heterozygous *Cyp11a1* gene variant (n=12) had DHT levels of 244.25. Those with the Homo-mutant *Cyp11a1* gene variation (n=8) had a higher mean DHT value of 334.81, whereas those with the Homo-wild *Cyp11a1* gene variation (n=5) had 296.60. In contrast, in the control group, people with the Heterozygous *Cyp11a1* gene variant (n=16) had a lower mean DHT level of 176.52. The homo-mutant group in the control (n=7) had a substantially higher mean DHT value of 282.43, whereas those with the Homo-wild *Cyp11a1* gene variant (n=2) had an average level of 234.00. These findings point to a potential role for *Cyp11a1* gene variants in regulating DHT levels in both PCOS and control persons, implying differences in DHT regulation between the two groups.

Our findings were consistent with a study, genotyping variations between the two groups and conducting a comparative study, the *CYP11A1* gene's promoter region was genotyped for penta-nucleotide (AAAAT) repeats. The mean levels of prolactin and testosterone differed considerably (p<0.05) between the PCOS and healthy groups. There were five unique *CYP11A1* (AAAAT) repetitions, which matched to repeat units 3, 6, 7, and 8. The study found a significant difference (p<0.05) in penta-nucleotides (AAAAT) between PCOS and healthy women, with five and three repetitions, respectively [20].

CONCLUSIONS

It was concluded that this study further studies the complex relationship between the *CYP11a1* gene and PCOS in a specific Pakistani community. The study implies that while the gene *Cyp11a1* may have a role in the start of PCOS,

DOI: https://doi.org/10.54393/pjhs.v6i1.2761

it is not the key driver. The study findings revealed significantly higher DHT levels in both the PCOS and a-PCOS groups compared to the control group. This result supports the previously established role of hyperandrogenism in the origin of PCOS, emphasizing the importance of hormonal imbalances in the disorder's genesis. The findings of this study add to the growing body of knowledge about the complex interplay between genetic factors, hormonal imbalances, and clinical indicators of PCOS. Nonetheless, the findings are limited due to the small sample size, only including the *CYP11a1* gene variant, and the focus on a specific Pakistani population. Further studies with more extensive and diverse populations are required to confirm the link between the *CYP11a1* gene variant and PCOS and investigate the potential effect of other genetic and environmental variables.

Authors Contribution

Conceptualization: AR
Methodology: AUJR, ZW, HKQ, RJ
Formal analysis: AR
Writing review and editing: AR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2430

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Serum Vitamin B12 as a Risk Factor and Prognostic Indicator in Acute Ischemic Stroke: A Case-Control Study at a Tertiary Care Hospital Mirpurkhas (Sindh)

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ARTICLE INFO

Keywords:
Vitamin B12 Deficiency, National Institutes of Health Stroke Scale, Acute Ischemic Stroke, Stroke Severity

How to Cite:
Ahsan, N., Shahbaz, L., Asim, S., Erum, H., Ansari, M. A., & Javaid, A. (2025). Serum Vitamin B12 as a Risk Factor and Prognostic Indicator in Acute Ischemic Stroke: A Case-Control Study at a Tertiary Care Hospital Mirpurkhas (Sindh): Serum Vitamin B12 as a Risk Factor and Prognostic Indicator in Acute Ischemic Stroke. Pakistan Journal of Health Sciences, 6(1).331-336. https://doi.org/10.54393/pjhs.v6i1.2430

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Received date: 1st November, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

Ischemic stroke is among the main causes of disability and death globally. Vitamin B12, through its role in homocysteine metabolism, may help prevent stroke, as its deficiency increases stroke risk. **Objective:** To compare the serum level of vitamin B12 in stroke patients and controls. **Methods:** The current case-control study was conducted in Mirpurkhas, Sindh, included 75 patients who suffered from stroke and 75 control subjects. Serum level of vitamin B12 and the levels of homocysteine were evaluated, along with the severity of stroke and functional outcomes were evaluated using the National Institutes of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS), respectively, at discharge and 28 days. Statistical analysis explored associations with the severity of the stroke and its outcomes. **Results:** Stroke patients showed significantly lower levels of vitamin B12 (188.4 ± 43.6 pg/mL) than controls (352.7 ± 54.1 pg/mL, p<0.001). Vitamin B12 insufficiency (<200 pg/mL) was more prevalent in stroke patients (65.3%) compared to controls (18.7%, p<0.001). NIHSS scores were higher in deficient patients (13.1 ± 4.2) than those with insufficient (9.6 ± 3.1) or sufficient levels (7.5 ± 2.5, p<0.001). Worse functional outcomes (mRS 3.9 ± 1.2) were noted in deficient patients compared to insufficient (2.8 ± 0.8, p=0.007) and sufficient levels (2.3 ± 0.6, p<0.001). Logistic regression identified vitamin B12 deficiency as an independent stroke risk factor (OR=5.9, 95% CI: 2.9–12.3, p<0.001). **Conclusions:** It was concluded Vitamin B12 deficiency was associated with increased stroke severity and poorer outcomes, suggesting its potential role in stroke management.

INTRODUCTION

Stroke ranks amongst the foremost reasons for death globally. Each year, approximately 15 million individuals worldwide experience a stroke, with 5 million succumbing to the condition and another 5 million facing long-term disability. This imposes significant burdens on both families and communities [1]. ischemic stroke (IS) contributes more to illness than mortality, it remains a critical challenge for healthcare systems. The risk factors for IS are largely preventable, with nearly 90% being controllable. These factors include cardiovascular diseases, diabetes mellitus, smoking, obesity, hyperlipidemia, sedentary lifestyles, excessive alcohol consumption, poor diet, psychological stress, and depression. Notably, one emerging and modifiable risk factor is the blood level of vitamin B-12. Despite this extensive list, other risk factors may still contribute to IS [2]. In Pakistan, ischemic strokes are prevalent [3]. A community-based study in Karachi's urban slums reported

DOI: https://doi.org/10.54393/pjhs.v6i1.2430

a stroke prevalence of 21.8%. Of these cases, 30% were hemorrhagic strokes, while 70% were ischemic strokes [4]. Vitamin B12, or Cobalamin, is a water-soluble vitamin vital for DNA synthesis and cellular metabolism. It plays a critical role in one-carbon metabolism, a network that integrates nutritional signalling with epigenetics, redox homeostasis and biosynthesis. This network also supports the preservation of epigenetic information. Dietary sources of vitamin B12 comprise animal-based diets such as eggs, fish, meat and dairy products. Although some gut bacteria like Escherichia coli produce vitamin B-12, the quantity is insufficient to meet the body's needs [5, 6]. Thus, vitamin deficiency. B12 or folate leads to high levels of blood homocysteine, which raises the risk of ischemic stroke since, through its several modes of action, homocysteine is interlinked with an increased danger of thrombosis [7]. According to studies, small vessel stroke is linked to elevated levels of plasma homocysteine (HCY). Supplementation of vitamin B12 and folate may lower homocysteine levels in the blood and the danger of stroke [8]. Data from 2007 to 2018 in the review of the National Health and Nutrition Examination Survey (NHANES) exposed that around 3.7% of persons aged 60 and above and 3.6% of those aged 19 and older suffer from vitamin B12 insufficiency, defined as blood levels of vitamin B12 less than 200 pg/mL or 148 pmol/L. However, vitamin B12 deficiency is more predominant, influencing almost 12.5% of all individuals over the age of 19 and 12.3% of those over the age of 60 (defined as serum levels of vitamin B12 less than 300 pg/mL (221 pmol/L) [9]. The link between vitamin B12 or folate levels in blood with stroke risk has been investigated in a minor number of prospective studies, however, the findings have been mixed.

This study aims to assess the association among serum vitamin B12 levels and ischemic stroke, compared to the patients with acute ischemic stroke to age- and sex-matched controls.

METHODS

This case-control observational study was conducted at Bhitai Medical and Dental College and Hospital, Mirpurkhas, Sindh, from June 2022 to May 2024. The study acknowledged ethical endorsement from the Ethics Review Committee of Bhitai Medical and Dental College and Hospital, Mirpur Khas (Ref No: BDMC/R&D/ERC/2022-12). This study employed comparing persons with a precise ailment (cases) to those without it (controls) to classify possible risk aspects. Cases in this study were defined as patients diagnosed with acute ischemic stroke, confirmed via clinical evaluation and neuroimaging, presenting to a tertiary care hospital in Mirpur Khas, Sindh. Age- and sex-matched individuals were Controls, without a history of stroke, recruited from the same hospital and local community to ensure similar demographic and environmental exposure. Participants were omitted if they had a preceding history of stroke, malignancy, severe hepatic or renal disease, or were on vitamin B12 supplementation. A total of 300 participants were recruited, including 150 cases identified with acute ischemic stroke and 150 age and gender-matched control participants. The sample size for the research was estimated based on a published study by Jiang et al., [10], which reported a significant difference in mean serum vitamin B12 levels between stroke patients and controls (stroke: 367.53 ± 127.30 pg/mL, controls: 495.18 ± 102.79 pg/mL). Using a significance level of 5%, power of 80%, and an effect size of 0.58, the required sample size was determined to be 300 participants (150 cases and 150 controls). The patients ≥40 years of age, diagnosed with acute ischemic stroke in the last 24 hours of the beginning of symptoms, and confirmed via neuroimaging (CT or MRI) were included in the case group. Age-matched controls were selected from individuals without any history of stroke or cerebrovascular disease, attending the hospital for routine checkups from the emergency department of the hospital. Participants with conditions such as hemorrhagic stroke, transient ischemic attacks (TIA), chronic kidney disease, liver disorders, malabsorption syndromes, or those receiving vitamin B12 supplementation were excluded. Moreover, individuals with severe comorbidities, pregnant women, and those unwilling to participate were also excluded. All participants were given informed written consent before being enrolled in the study. Data collection involved a structured questionnaire to capture demographic details, medical history, and lifestyle factors, such as smoking and alcohol use. The severity of the stroke was gauged using the NIHSS, and their functional aspects were evaluated at a 3-month follow-up via a modified Rankin Scale (mRS). Blood samples (5 mL) were drawn from all participants for the measurement of serum vitamin B12 and homocysteine levels using an enzyme-linked immunosorbent assay (ELISA). Participants were classified into three categories based on their vitamin B12 levels: lacking (<200 pg/mL), insufficient (200–400 pg/mL), and sufficient (>400 pg/mL). Other biochemical parameters, including blood glucose and lipid profiles, were also measured to adjust potential confounding factors. Data were examined using SPSS version 27.0. Quantitative data were represented as the mean ± standard deviation (SD). Qualitative data were expressed by frequency and proportion. To compare the proportions between two qualitative criteria, chi-square was employed. The mean values of the cases and controls were compared by analyzing with the help of an independent T-test. Logistic regression analysis was

DOI: https://doi.org/10.54393/pjhs.v6i1.2430

performed to assess the association of vitamin B12 deficiency with the risk of acute ischemic stroke. Less than 0.05 range for p-values was considered significant.

RESULTS

Results reflected the demographics and clinical aspects of the study participants. The mean value of the age of cases was 64.8 ± 9.8 years, while controls had a mean value of the age of control individuals was 63.4 ± 9.1 years. There was no statistically significant variance seen between the age of both groups (p=0.35) or gender distribution (p=0.64). However, diabetes mellitus, hypertension and smoking habits were significantly more prevalent in the cases as compared to the control individuals (p≤0.05 for all) (Table 1).

Table 1: Demographic Features and Clinical Profiles of Participants

Characteristic	Cases (n=150)	Controls (n=150)	p-value
Age (mean ± SD year)	64.8 ± 9.8	63.4 ± 9.1	0.35**
Gender (Male/Female)	92/58	89/61	0.64**
Hypertension (%)	104 (69.3%)	60 (40%)	<0.001*
Diabetes Mellitus (%)	86 (57.3%)	52 (34.7%)	<0.001*
Smoking (%)	60 (40%)	38 (25.3%)	0.03*
Mean Homocysteine (µmol/L)	16.33 ± 3.29	9.76 ± 4.55	<0.001*

*means that Independent sample t-test was used; ** represents that chi-square test was used

The mean serum vitamin B12 levels in the blood were found significantly decreased in the stroke group (188.4 ± 43.6 pg/mL) when compared to the control group (352.7 ± 54.1 pg/mL, p<0.001). Homocysteine levels in the blood were found meaningfully elevated in case patients with stroke (16.33 ± 3.29 µmol/L) compared to controls (9.76 ± 4.55 µmol/L, p<0.001). Additionally, a majority of stroke patients had vitamin B12 deficiency (65.3%) compared to controls (18.7%) (Table 2).

Table 2: Serum Vitamin B12 Levels and Stroke Severity

Vitamin B12 Category	Cases (n=150)	Controls (n=150)	p-value
Mean vitamin B12 (pg/mL)	188.4 ± 43.6	352.7 ± 54.1	<0.001*
Mean Homocysteine (µmol/L)	16.33 ± 3.29	9.76 ± 4.55	<0.001*
Deficient Vitamin B12 (<200 pg/mL)	98 (65.3%)	28 (18.7%)	<0.001**
Insufficient Vitamin B12 (200–400 pg/mL)	35 (23.3%)	60 (40%)	<0.002**
Sufficient Vitamin B12 (>400 pg/mL)	17 (11.3%)	62 (41.3%)	<0.001*

*means that the Independent sample t-test was used; **represents that the chi-square test was used.

Stroke severity, at the time of hospital admission, evaluated with the help of NIHSS, was significantly higher in patients with vitamin B12 deficiency (mean NIHSS: 13.1 ± 4.2) and elevated homocysteine levels (mean NIHSS: 12.9 ± 4.3). Functional outcomes at 3 months, as calculated using mRS, were worse in patients with both vitamin B12 deficiency (mean mRS: 3.9 ± 1.2) and high homocysteine levels (mean mRS: 3.7 ± 1.3) (Table 3).

Table 3: Stroke Severity and Outcomes Based on Vitamin B12 Levels in Cases

Category	NIHSS Scores	mRS Scores at 3 Months	p-value (NIHSS)	p-value (mRS)
Deficient Vitamin B12 (<200 pg/mL)	13.1 ± 4.2	3.9 ± 1.2	-	-
Insufficient Vitamin B12 (200–400 pg/mL)	9.6 ± 3.1	2.8 ± 0.8	0.001	0.007
Sufficient Vitamin B12 (>400 pg/mL)	7.5 ± 2.5	2.3 ± 0.6	<0.001	<0.001
Elevated Homocysteine (>15 µmol/L)	12.9 ± 4.3	3.7 ± 1.3	<0.001	<0.001
Normal Homocysteine (≤15 µmol/L)	8.4 ± 2.9	2.6 ± 0.7	0.002	0.004

Independent samples t-test was applied and Results are shown in Mean ± SD

Logistic regression examination revealed that vitamin B12 deficiency and elevated homocysteine levels in blood were independently linked with an increased acute ischemic stroke risk. vitamin B12 deficiency had an odds ratio (OR) of 5.9 (95% CI: 2.9–12.3, p<0.001), while elevated homocysteine levels had an OR of 4.5 (95% CI: 2.4–8.6, p<0.001), after the adjustment of confounding variables (Table 4).

Table 4: Association of Risk of Acute Ischemic Stroke with Vit. B12 insufficiency

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Vitamin B12 Deficiency (<200 pg/mL)	5.9	2.9–12.3	<0.001
Elevated Homocysteine (>15 µmol/L)	4.5	2.4–8.6	<0.001
Age (per year increase)	1.04	0.99–1.08	0.22
Male Gender	1.3	0.7–2.3	0.57
Hypertension	2.7	1.5–4.8	0.001
Diabetes Mellitus	1.9	1.1–3.5	0.03
Smoking	1.5	0.8–2.9	0.14

Logistic regression analysis.

DISCUSSION

Vitamin B12 which is a water-soluble vitamin, plays a critical role in neurological function, red blood cell formation and DNA synthesis. Its deficiency is increasingly being recognized as a modifiable risk factor for several cardiovascular and neurological disorders, including acute ischemic stroke [7]. One of the primary mechanisms linking vitamin B12 deficiency to stroke is its impact on homocysteine metabolism. Elevated homocysteine levels, a result of vitamin B12 deficiency, can cause endothelial dysfunction, oxidative stress, and a pro-thrombotic state, all of which contribute to cerebrovascular events. Despite these established links, the prevalence and clinical implications of vitamin B12 deficiency in stroke patients remain underexplored, particularly in populations with limited access to vitamin-rich diets or a high burden of undiagnosed deficiencies [11]. This study highlights the

DOI: https://doi.org/10.54393/pjhs.v6i1.2430

significant character of vitamin B12 deficiency as both a prognostic biomarker and a risk factor for acute ischemic stroke. Our findings demonstrated that serum vitamin B12 levels were meaningfully lesser in stroke patients (190.5 ± 45.7 pg/mL) in comparison to the control group (350.2 ± 55.6 pg/mL), consistent with prior research linking vitamin B12 deficiency to an increased risk of cardiovascular diseases, including stroke.The deficiency of vitamin B12 contributes to elevated homocysteine (Hcy) levels, which promote thrombosis through mechanisms such as enhanced platelet activation, endothelial dysfunction, and impaired fibrinolysis [12, 13]. In our study, 64% of stroke cases exhibited vitamin B12 deficiency compared to only 16% of controls, highlighting a strong correlation between stroke risk and lower vitamin B12 levels. Logistic regression analysis confirmed that vitamin B12 deficiency independently increased the odds of ischemic stroke (OR: 5.8, 95% CI: 2.4–13.9, p<0.001), even after regulating for traditional risk factors including age, gender, smoking, diabetes and hypertension. These results align with previous studies, such as Huang *et al.*, which demonstrated that supplementation with folate and vitamin B12 reduces the risk of stroke [14]. Moreover, earlier investigations have highlighted that vitamin B12 deficiency is a major contributor to hyper-homo-cysteinemia (HHC) in ischemic stroke patients, further reinforcing the connection between vitamin B12 status and stroke pathophysiology [14]. Stroke severity, assessed via the NIHSS score, was known to be significantly developed in patients with vitamin B12 deficiency (mean score: 12.6 ± 3.8) compared to those with sufficient levels. Additionally, a negative correlation between the modified Rankin Scale (mRS) and vitamin B12 levels at discharge and 28 days after that suggested that patients with higher vitamin B12 levels experienced improved recovery. These conclusions are in line with previous research, which demonstrated that maintaining adequate vitamin B12 levels improves cardiovascular outcomes and reduces stroke-related mortality [15]. For instance, studies have shown that widespread grain fortification with vitamin B12 in the United States and Canada contributed to a decline in stroke-related mortality, further supporting the role of vitamin B12 in cerebrovascular health [16]. Emerging evidence also supports a mechanistic link between vitamin B12 deficiency and stroke via homocysteine metabolism. Yuan et al. observed that homocysteine levels and the risk of cerebrovascular disease were influenced by the body's vitamin B12 status, emphasizing its crucial role in cardiovascular health [17]. Similarly, Wolffenbuttel *et al.*, found a significant inverse relationship between homocysteine and vitamin B12 levels (r=-0.59), highlighting the widespread prevalence of vitamin B12 deficiency even in non-vegetarian populations [18]. Manapurath *et al.*, reported a similar trend, noting a noteworthy correlation between low vitamin B12 levels and elevated homocysteine levels (r=0.41), with 67% of their study population being vitamin B12 deficient [19]. Interestingly, dietary habits alone may not fully explain the occurrence of vitamin B12 deficiency. While vegetarianism has been traditionally related to a higher risk of deficiency, studies have indicated that non-vegetarians can also exhibit deficiency due to factors such as impaired intestinal absorption or limited access to vitamin B12-rich foods due to economic constraints [20]. This finding aligns with our study, where no substantial variance was observed in dietary patterns between cases and controls, suggesting that other underlying factors may contribute to vitamin B12 deficiency in the population. Although no noteworthy variations in vitamin B12 levels were observed across TOAST stroke subtypes in our study, the overall findings highlight the importance of monitoring the position of vitamin B12 in stroke patients. Given the association between low vitamin B12 levels and worse clinical outcomes, addressing this deficiency may assist as a promising therapeutic strategy to progress stroke prognosis. Our findings emphasize the potential clinical value of screening and treating vitamin B12 deficiency as part of stroke prevention and management strategies.

CONCLUSIONS

It was concluded that vitamin B12 deficiency is a significant contributor to both the risk and severity of ischemic stroke. Stroke patients with lower serum vitamin B12 levels experienced more severe strokes and poorer functional outcomes, as indicated by higher NIHSS and mRS scores. Logistic regression analysis demonstrated that vitamin B12 deficiency independently increases the risk of stroke, reinforcing its role as a prognostic biomarker and a modifiable risk factor. Clinically, these findings emphasize the importance of routine screening and early management of vitamin B12 deficiency to reduce stroke risk.

Authors Contribution

Conceptualization: NA
Methodology: NA, LS, SA, HE
Formal analysis: HE
Writing review and editing: NA, SA, MAA, AJ

All authors have read and agreed to the published version of the manuscript

DOI: https://doi.org/10.54393/pjhs.v6i1.2430

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2430

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DOI: https://doi.org/10.54393/pjhs.v6i1.2660

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Ankle-Brachial Pressure Index Correlates with Abdominal Volume Index in Normal -Weight Type 2 Diabetes Mellitus Patients

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ARTICLE INFO

Keywords:
Obesity, Glycemic, Normal Weight, T2 Diabetes Mellitus

How to Cite:
Mudassar, S., Lakho, M. A., Anwar, R., Rehman, M. A. U., Zakir, H., & Joher, I. (2025). Ankle-Brachial Pressure Index Correlates with Abdominal Volume Index in Normal-Weight Type 2 Diabetes Mellitus Patients: Role of ABPI and ABV in T2DM. Pakistan Journal of Health Sciences, 6(1),337-342. https://doi.org/10.54393/pjhs.v6i1.2660

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Received date: 2nd December, 2024
Acceptance date: 22nd January, 2025
Published date: 31st January, 2025

ABSTRACT

Obesity significantly impacts glycemic control and vascular health in Type 2 diabetes mellitus. **Objectives:** To compare clinical characteristics, obesity indices, and vascular status between normal-weight and obese/overweight Type 2 diabetes mellitus patients. **Methods:** A cross-sectional study was conducted for six months from April 2024 to September 2024 at the Medicine Outpatient Department. This study included 82 Type 2 diabetes mellitus patients divided into two groups: normal-weight (n=34) and obese/overweight (n=48). Clinical parameters such as HbA1c, BMI, abdominal volume index, and ankle-brachial pressure index (ABPI) were measured. Data were analyzed by SPSS version 23.0. **Results:** Obese/overweight patients were significantly older (57.74 ± 8.57 vs. 52.81 ± 9.41 years, p=0.018) and had worse glycemic control (HbA1c: 7.17 ± 0.97% vs. 6.51 ± 0.68%, p = 0.0008) than normal-weight patients. Both BMI (30.57 ± 3.39 vs. 23.13 ± 1.80 kg/m^2) and AVI (16.44 ± 1.58 vs. 11.84 ± 1.61) were higher in the obese/overweight group (both p<0.0001). Ankle-Brachial Pressure Index was lower in obese/overweight patients (0.93 ± 0.15 vs. 0.99 ± 0.08, p=0.033), suggesting poorer vascular health. Negative correlations between ankle-brachial pressure index and obesity indices indicated higher adiposity was linked to vascular dysfunction. **Conclusions:** It was concluded that obese/overweight Type 2 diabetes mellitus patients showed poorer vascular health and glycemic control than normal-weight patients. Abdominal volume index, age, and diabetes duration independently predicted ankle-brachial pressure index, emphasizing the need to address abdominal obesity and glycemic control to mitigate vascular risks in T2 diabetes mellitus patients.

INTRODUCTION

One of the most prevalent metabolic disorders in the world today among people who live in modern society is type 2 diabetes mellitus (T2DM). Numerous studies have demonstrated that being overweight or obese is a significant risk factor for the development of T2DM. Nevertheless, it is crucial to remember that not all fat depots have the same detrimental effects [1]. For instance, subcutaneous adipose tissue is not related to metabolic disorders but visceral adipose tissue affects glucose regulation detrimentally and may be connected to vascular complications; in its turn, excessive visceral fat deposition altogether is directly linked to metabolic abnormality, as well as vascular complications [2, 3]. Moreover, finding prevalence at any age category, abnormal levels of visceral fat can be higher in patients who have a familial history of its distribution, due to which, although relatively lean, these patients may be more vulnerable to type 2 diabetes onset and its associated vascular illnesses [4, 5]. An investigation has revealed that normal-weight patients with increased visceral adiposity who were just diagnosed with T2DM had a

DOI: https://doi.org/10.54393/pjhs.v6i1.2660

higher rate of mortality compared to those found suffering from obesity or being overweight [6, 7]. Understanding why vascular function is compromised due to the rise of type 2 diabetes would be an invaluable tool in improving the health of patients with T2DM. Also, the relationship between abdominal obesity as an essential risk factor for metabolic syndrome and vascular illnesses such as heart disease is well-studied. An effective measurement of abdominal obesity can be taken by calculating the Abdominal Volume Index which provides a better idea of the distribution of fat, especially the disturbing vital accumulation of visceral fat, than the more traditional and outdated body mass index does. The vascular health of this type of fat can be further compromised by several metabolic disorders, such as insulin resistance and systemic inflammation [8, 9]. It's interesting to note that concealed adiposity, especially in the abdominal area, might cause negative metabolic effects even in normal-weight persons with type 2 diabetes. These people may have significant visceral fat even when their BMI is within the normal range, which increases their risk of vascular problems. Therefore, evaluating the correlation between Abdominal Volume Index (AVI) and ABPI in this cohort is essential to identify any potential vascular concerns that would not be apparent from normal obesity measures alone [10]. While previous studies have primarily focused on obese T2DM patients, there is limited understanding of how abdominal fat distribution (measured by AVI) may influence vascular function in normal-weight T2DM patients. This study intends to fill this gap by investigating how these obesity indices correlate with vascular health, even in the absence of overt obesity, thus offering insights into the potential vascular risks in normal-weight individuals with T2DM. The inclusion of both normal-weight and obese/overweight groups allows for a comparative analysis to better understand the contribution of abdominal fat and its association with vascular status across different body compositions.

This study aims to compare clinical characteristics, obesity indices, and vascular status between normal-weight and obese/overweight T2DM patients.

METHODS

This cross-sectional study was conducted for six months from April 2024 to September 2024. The participants were recruited from the Medicine Outpatient Department at Rashid Latif Medical College, Hospital. Inclusion criteria were individuals between the ages of 30 and 60 who have been diagnosed with DM type 2, Body Mass Index (BMI) between 18.5 and 24.9 kg/m2, which was considered normal, HbA1c <8%, no prior history of cardiovascular events or peripheral arterial disease (PAD). Exclusion criteria were weight gain or obesity (BMI >25 kg/m^2), pregnant women, hypertension, renal problems, or an ongoing infection. The study used a consecutive sampling method to recruit participants. Patients using antihypertensive or lipid-lowering drugs. The correlation coefficient formula was used to evaluate sample size. This was appropriate since the primary objective was to assess the relationship between two continuous variables (ABPI and AVI). n= (0.5×ln(1–r1+r) Z1–α/2+Z1–β)2+3, significance level α=0.05 confidence level (95% 0r 1.96), power (1- β) = 80% (0.84) and effect size (expected correlation coefficient r=0.3). The total number of participants was n=82, distributed in two groups, normal weight group n=34 and obese group n=48. Height, weight, and waist circumference were examples of anthropometric measurements that were used to determine BMI and AVI. [2 × waist circumference^2 (cm) + hip circumference^2 (cm)] ÷ height (cm) was the formula for the Abdominal Volume Index (AVI). Systolic blood pressure (SBP) in the brachial artery (arm) and ankle arteries (posterior tibial and dorsalis pedis) was used to calculate the Ankle-Brachial Pressure Index (ABPI). ABPI was equal to SBP at the brachial artery ÷ SBP at the ankle. Values below 0.9 in the ABPI indicate a possible PAD, but values above 1.3 point to arterial calcification. Data analysis was done using SPSS version 23.0. Utilize SPSS's Kolmogorov-Smirnov (K-S) and Shapiro-Wilk (S-W) tests to assess the normal distribution statistically. When comparing the means of two groups, such as normal vs. overweight T2DM patients, the t-test is utilized. Parameter correlations were investigated using Pearson correlation for parametric data and Spearman correlation for non-parametric data. The link between a dependent variable and one or more independent variables was predicted using linear regression. The study was approved by the Institutional Review Board (IRB) with the reference number (IRB/2024). All participants provided written informed consent before participation.

RESULTS

Significant differences were observed between normal-weight and obese/overweight Type 2 Diabetes Mellitus (T2DM) patients. The obese/overweight group was older (57.74 vs. 52.81 years, p=0.018) and had worse glycemic control (HbA1c 7.17% vs. 6.51%, p=0.0008). The average BMI was higher in the obese/overweight group (30.57 vs. 23.13 kg/m^2, p<0.0001), and abdominal obesity, measured by the Abdominal Volume Index (AVI), was significantly greater (16.44 vs. 11.84, p<0.0001). Additionally, the Ankle-Brachial Pressure Index (ABPI) was lower in the obese/overweight group (0.93 vs. 0.99, p=0.033), suggesting obesity's impact on vascular health (Table 1).

DOI: https://doi.org/10.54393/pjhs.v6i1.2660

Table 1: Clinical Characteristics of the Patients

Parameters	Normal-Weight T2DM (n=34)	Obese/Overweight T2DM (n=48)	p-value
Age (Years)	52.81 ± 9.41	57.74 ± 8.57	0.018*
HbA1c (%)	6.51 ± 0.68	7.17 ± 0.97	0.0008**
BMI (kg/m^2)	23.13 ± 1.80	30.57 ± 3.39	<0.0001**
AVI	11.84 ± 1.61	16.44 ± 1.58	<0.0001**
ABPI	0.99 ± 0.08	0.93 ± 0.15	0.033*

In both normal-weight (n=34) and obese/overweight (n=48) Type 2 Diabetes Mellitus (T2DM) groups, Body Mass Index (BMI) showed strong correlations with obesity indices like Waist Circumference (WC), Body Fat Percentage (BFP), Abdominal Volume Index (AVI), and Waist-to-Hip Ratio (WHR). In the normal-weight group, BMI had high correlations with BFP (0.75) and WC (0.70, p<0.001). In the obese/overweight group, BFP had the strongest correlation with BMI (0.80, p<0.0001), followed by AVI (0.72) and WC (0.68), all statistically significant (Table 2).

Table 2: Correlation of BMI with Other Obesity Indices

Parameters	Correlation Coefficient (Normal-weight T2DM, n=34)	p-value	Correlation Coefficient (Obese /Overweight T2DM, n=48)	p-value
Abdominal Volume Index (AVI)	0.65	0.001**	0.72	<0.0001**
Waist Circumference (WC)	0.70	<0.0001**	0.68	<0.0001**
Body Fat Percentage (BFP)	0.75	<0.0001**	0.80	<0.0001**
Waist-to-Hip Ratio (WHR)	0.60	0.004**	0.65	<0.0001**

In the normal-weight T2DM group (n=34), a strong correlation was found between Abdominal Volume Index (AVI) and Waist Circumference (WC) (0.75, p<0.0001), and between AVI and Visceral Fat Percentage (VF%) (0.68, p=0.0003), indicating that larger abdominal volume is linked to higher visceral fat. In the obese/overweight T2DM group (n=48), the correlation between AVI and WC was even stronger (0.82, p<0.0001), and a significant correlation was also found between AVI and VF% (0.78, p<0.0001). These results suggest a robust association between abdominal volume and visceral fat in both groups (Table 3).

Table 3: Correlation of AVI with WC and VF%

Parameters	Correlation Coefficient (Normal-weight T2DM, n=34)	p-value	Correlation Coefficient (Obese /Overweight T2DM, n=48)	p-value
AVI	-	-	-	<0.0001**
Waist Circumference (WC)	0.75	<0.0001**	0.82	
Visceral Fat Percentage (VF%)	0.68	0.0003**	0.78	

In normal-weight T2DM patients, weak to moderate negative correlations were found between ABPI and obesity indices, such as BMI and BAI (p=0.04 and 0.03), as well as AVI and VF% (p=0.02 and 0.05). This suggests that as obesity increases, ABPI tends to decrease, indicating early signs of vascular changes. In the obese/overweight T2DM group, stronger negative correlations were observed with ABPI and obesity indices: BMI (-0.42, p=0.003), WC (-0.46, p=0.002), AVI (-0.48, p=0.001), and VF% (-0.44, p=0.004). These results indicate a higher risk of vascular changes in obese/overweight T2DM patients compared to the normal-weight group (Table 4).

Table 4: Correlation of ABPI with Obesity Indices

Obesity Indices	Correlation Coefficient (Normal-weight T2DM, n=34)	p-value	Correlation Coefficient (Obese /Overweight T2DM, n=48)	p-value
Body Mass Index (BMI)	-0.35	0.04*	-0.42	0.003**
Waist Circumference (WC)	-0.38	0.03*	-0.46	0.002**
Abdominal Volume Index (AVI)	-0.40	0.02*	-0.48	0.001**
Visceral Fat Percentage (VF%)	-0.33	0.05*	-0.44	0.004**

In the normal-weight T2DM group, weak-to-moderate negative correlations were found between ABPI and obesity indices (BMI, WC, AVI, VF%) with significant p-values, indicating that higher obesity levels may signal early vascular changes. In the obese/overweight T2DM group, the correlations were stronger, with significant results for BMI, WC, AVI, and VF%. These findings suggest a higher risk of vascular impairment in obese/overweight T2DM patients. Additionally, a longer duration of diabetes was associated with a decrease in ABPI, with a 0.014-unit reduction per year of diabetes, highlighting the combined impact of obesity, age, and diabetes duration on vascular health (Table 5).

Table 5: Association of ABPI (Dependent Variable) with Key Predictors AVI, Age, Diabetes Duration (Independent Variables)

Variables	Unstandardized Coefficient (B)	Standard Error (SE)	Standardized Coefficient (Beta)	t-value	p-value
Constant	1.125	0.124	––	9.07	<0.001**
Abdominal Volume Index (AVI)	-0.025	0.009	-0.35	-2.78	0.007**
Age (years)	-0.011	0.004	-0.29	-2.75	0.008**
Duration of Diabetes (years)	-0.014	0.006	-0.23	-2.33	0.022*

DOI: https://doi.org/10.54393/pjhs.v6i1.2660

DISCUSSION

This study examined the link between individuals with Type 2 Diabetes Mellitus (T2DM) who were overweight or obese and those who were normal weight and the Ankle-Brachial Pressure Index (ABPI) and Abdominal Volume Index (AVI). The results show that age and lengthier duration of diabetes are important predictors of vascular dysfunction, and that more fat is linked to worse vascular health, as indicated by a lowerABPI [11]. The significance of abdominal fat in the emergence of vascular dysfunction is highlighted by the negative connection found between the Abdominal Volume Index (AVI) and ABPI. It is well recognized that endothelial dysfunction and systemic inflammation, two major factors in atherosclerosis and compromised vascular tone are encouraged by abdominal obesity [12]. Similar results were published by Ruze *et al.*, who showed a correlation between an increased risk of peripheral artery disease (PAD) and higher central obesity as evaluated by waist circumference. These findings support our finding that abdominal obesity in T2DM patients, regardless of weight, is associated with worse vascular health [13]. The comparison between normal-weight and obese/overweight T2DM patients showed significant differences in age and glycemic control (HbA1c). Obese/overweight T2DM patients were older compared to normal-weight patients, with a p-value indicating statistical significance. This suggests that obesity is linked to an older age of onset or progression of T2DM. Additionally, obese/overweight patients had higher HbA1c levels compared to normal-weight patients, with a p-value showing strong significance. This indicates poorer glycemic control in the obese/overweight group, supporting the association between obesity and worse diabetes management. These findings emphasize that obesity is linked to both older age at T2DM onset and poorer blood sugar control. The strong correlation between BMI and other obesity measures, emphasizing their role in disease severity. The findings of this study indicate that abdominal obesity has a detrimental effect on vascular health, as seen by the negative correlation between AVI and ABPI. The major risk factor for arterial stiffness and peripheral arterial disease (PAD) is central obesity, rather than general obesity (as determined by BMI). Furthermore, it was noted by Abdel-Galeel *et al.*, that increased abdominal obesity raises the risk of low ABPI readings, which indicate poor peripheral circulation, via promoting atherosclerosis. By validating this correlation within a T2DM group, our study contributes to the body of evidence [14]. Arterial stiffness increases with age and causes a decrease in vascular function. The present findings are supported by the conclusion that aging had a negative impact on ABPI. First, research indicates that persistent hyperglycemia accelerates vascular mortality. Thus, the length of diabetes had a negative correlation with ABPI. Second, peripheral blood flow is reduced due to the transformation of the circulatory system with age, such as a decrease in endothelial function, loss of elasticity, and arterial stiffening. Moreover, aging and continued inflammation are linked to increase oxidative stress, which negatively affects the health of the vessels [15]. The results of the current study finding that ABPI decreased with age in both non-diabetic and diabetic participants and was related to persistent aging of the vasculature, which was more severe for the diabetic group. Therefore, the current research finds that regular vascular examination is essential for aged type 2 diabetes to prevent PAD [16]. The other significant predictor of the decrease in ABPI was the length of time patients had diabetes. In the case of type 2 diabetes, high levels of sugar in the blood for a long period of time leads to the glycation of vascular proteins, producing advanced glycation end-products. This process weakens endothelial function and stimulates increased arterial stiffness. Long-term sugar exposure to people with diabetes weakens the blood vessels in the leg and raises the risk of PAD. This result is in line with two other pieces of research discovered by Chase-Vilchez *et al.* Moreover, the findings highlight the importance of maintaining good glycemic control and regular examination for PAD at an early stage for long-term T2DM patients [17]. In this research, normal-weight, T2DM individuals had relatively higher ABPI values compared to their overweight/obese counterparts despite suffering from diabetes. This is an indicator that vascular function is still enhanced in these patients. However, the onset of vascular damage is probably not instigated in people of normal weight probably owing to less obesity. This is mainly contributed to the reduction of systemic inflammation in these patients because they are slimmer. The inflammation of the endothelium resulting from adipose tissue which releases pro-inflammatory cytokines is a leading cause of vascular damage [18].In the current study finding that, with statistically significant results in the normal-weight and overweight/obese groups, the correlation analysis showed a strong positive connection between AVI and both waist circumference (WC) and visceral fat percentage (VF%). The results of the previous study support the present findings of Wu *et al.*, who discovered that visceral fat and WC are accurate indicators of cardiovascular risk. This supports the utility of AVI as a parameter in clinical practice [19]. It makes sense that AVI and BMI would correlate because

DOI: https://doi.org/10.54393/pjhs.v6i1.2660

both indices measure the distribution of body fat. BMI does not take into consideration the location of fat, despite being a valuable indicator of total body fat. However, visceral fat which is linked to increased health risks and has a higher metabolic activity is highlighted in particular by AVI. This study demonstrates that individuals with higher BMI also tend to have elevated AVI, reinforcing the notion that BMI alone may not fully capture the risks associated with abdominal obesity [20]. These findings highlight how crucial it is to control abdominal obesity in diabetic patients as soon as possible because it has a direct impact on vascular health. To stop PAD and other vascular problems, it is crucial to implement diet, exercise, and lifestyle modifications that reduce belly fat. While this study provides valuable insights into the relationship between abdominal obesity and vascular health in Type 2 Diabetes Mellitus (T2DM) patients, several limitations should be noted included Self-Reported Data, limited assessment of confounders and lack of control group of healthy individuals without diabetes.

CONCLUSIONS

It was concluded that clinical interventions should focus on the early identification and management of abdominal obesity in patients with Type 2 Diabetes Mellitus (T2DM). Incorporating targeted lifestyle modifications, such as dietary changes, can help reduce abdominal fat and improve glycemic control, thereby enhancing vascular health and reducing the risk of peripheral artery disease. Additionally, regular monitoring of abdominal fat through indices like the Abdominal Volume Index (AVI) could be integrated into routine clinical assessments to identify at-risk patients and facilitate timely interventions.

Authors Contribution

Conceptualization: SM
Methodology: MAL, RA, MAUR, HZ
Formal analysis: MAL, IJ
Writing review and editing: SM, MAUR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2383

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Assessing the Psychological Impact of Oral Potentially Malignant Disorders Among Patients

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ARTICLE INFO

Keywords:
Oral Potentially Malignant Disorders, Psychological Impact, Oral Submucous Fibrosis, Quality of Life, Oral Lichen Planus, Oral Leukoplakia

How to Cite:
Ahmed, S. Z., Kumar, S., Akhlaq , H., Anwar, J., Lodhi, M., & Siddiqui, D. (2025). Assessing the Psychological Impact of Oral Potentially Malignant Disorders Among Patients: Psychological Impact of Oral Potentially Malignant Disorders. Pakistan Journal of Health Sciences, 6(1), 343-347. https://doi.org/10.54393/pjhs .v6i1.2383

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Received date: 9th October, 2024
Acceptance date: 22nd January, 2025
Publication date: 31st January, 2025

ABSTRACT

Although potential exists for patient-reported outcome measures to assess disease impact, Quality of life evaluation is not widely used in clinical settings. Limited literature exists on the patients' life quality with oral potentially malignant diseases. **Objectives:** To evaluate how Oral Potentially Malignant Disorders (OPMDs) affect different realms of quality-of-life QoL, potentially shedding light on variations in QoL depending on the seriousness of the disease. **Methods:** This cross-sectional study included 70 patients through convenience sampling with potentially malignant disorders: 20 Oral sub mucous fibrosis, 20 Oral lichen planus, 20 Leukoplakia and 5 Actinic keratosis and 5 Erythroplakia. All participants were recruited from Abbasi Shaheed Hospital and Ziauddin University Hospital. The diagnosis of OPMD was made through clinical examination and confirmed by histopathological assessment conducted by oral surgeons. Informed written consent was obtained from all participants, and the SF-12v2 health survey was used for assessment. **Results:** The oral potentially malignant disorder showed highest occurrence in females than in males in oral submucous fibrosis, leukoplakia and oral lichen planus.The OPMD patients reported impairements in emotional well being and experienced significant pain and functional limitations ($p < 0.05$). **Conclusions:** The assessment of oral premalignant diseased patients provides valuable insights and understanding of impact of these conditions on their lives. Therefore, this study suggest that OPMD QoL should be routinely checked to enhance patients' wellbeing and quality of life.

INTRODUCTION

Recently, there is an increased interest in assessing the health necessities of patients with oral diseases. The investigation of how oral health impacts the quality of life has emerged as a crucial method for evaluating treatment outcomes.The World Health Organization describes quality of life (QoL) as, "an individual's perception of their position in life, influenced by their cultural surrounding, beliefs, desires, and concerns".A healthy mouth environment enables people to carry out their everyday tasks more successfully, but oral disorders can disturb normal processes, harming confidence, social relationships, and general quality of life .Periodontal disease and tooth loss have been demonstrated to have a substantial influence on quality of life, whereas oral cancer can damage patients physically, functionally, and mentally . As a result, QoL assessments are crucial in the treatment of cancers. Although OPMDs are not immediately life-threatening, they can affect oral function, cause discomfort, and lead to psychological distress due to the fear of cancer. These patients often face specific health challenges that significantly influence their quality of life . In South East Asia oral sub mucous fibrosis is highly prevalent, characterized by burning mouth sensation, stiffness and limited mouth opening, significantly compromising the

DOI: https://doi.org/10.54393/pjhs.v6i1.2383

individuals QoL. It is evident that oral sub mucous fibrosis produces detrimental effect and its advance stages are associated with worsening of Qol . Oral lichen planus affects about 1% to 2% of the world's population and is more frequent in middle-aged women . It causes discomfort and burning sensations in the oral mucosa. Persistent painful sensations and trouble swallowing and speaking have a detrimental influence on quality of life . Oral leukoplakia accounts for approximately 1% with increased prevalence seen in adult population. Clinically it is classified as homogenous and non-homogenous subtypes. Few studies have been done, evaluating QoL in Oral leukoplakia patients . Although the use of patient reported measures to assess the impact of disease is encouraged, still QoL assessment is limited in clinical practice . Scarce literature available on QoL in OPMD patients. However, few instruments have been used in the past to assess QoL .

Hence, this study aimed to evaluate how OPMDs affect different aspects of QoL. This evaluation may aid in identifying QoL disparities depending on patients' health statuses.

METHODS

This cross-sectional study comprised of 70 patients of oral potentially malignant disorder (20 Oral submucous fibrosis, 20 oral lichen, 20 leukoplakia, 5 actinic keratosis and 5 erythroplakia) through convenience sampling technique. The estimated sample size was calculated by open epi through formula $n=Z^2P(1-P)/d^2$, where n is the sample size, Z is the level of confidence which was set at 95% confidence interval, P is the expected prevalence which was assumed to be in between 4% to 10%, which we took 4%, resulting in a minimum sample size of 60 to 139. The duration of the study was from June 2021 to August 2022, after the approval from ethical review committee Ziauddin University with Reference Code: 2941220ZAPAT. Whereas data analysis, interpretation of results and manuscript preparation was carried out after the data collection. All the samples were recruited from Abassi Shaheed hospital (Ref no: DIRS/ASH/ESTT/3145/2020) and Ziauddin university hospital. The OPMD patients were diagnosed on the basis of clinical examination and histopathological assessment by expert clinical surgeon. Inclusion criteria were patients with oral premalignant disorders diagnosed through clinical and histopathological assessment. Patients with coexisting systemic diseases were excluded. A written informed consent was obtained from all the participants and a questionnaire-based SF-12v2 survey form was filled by the patients, consisting of 12 items assessing 8 health domains including Physical health, physical activities, pain, overall health status, functional limitation, emotional health, energy and anxiety. The data were analyzed using STATA version 17.0. For categorical variables, chi square was applied. To check the normality of the data, shapiro wilk test was applied. As the data was not normally distributed, non-parametric tests were applied at 95% confidence interval. To compare the Qol domains Kruskal Wallis was applied and for correlation between the variables spearman's correlation test was applied. P value of < 0.05 was considered statistically significant.

RESULTS

Table 1 depicts the frequency distribution of oral potentially malignant disorders in male and females with highest frequency of oral sub mucous fibrosis, oral lichen planus and leukoplakia patients. Out of total 70 OPMD participants, 71.4% were females and 28.6% were males, indicating that females were more frequently affected by OPMDs than males.

Table 1: Frequency Distribution of Oral Potentially Malignant Disorders

OPMD	Gender		p-value
	Male N (%)	Female N (%)	
Leukoplakia	5(7.1)	15(21)	0.311
Oral Lichen Planus	8(11.4)	12(17.1)	
Oral Sub mucous Fibrosis	6(8.5)	14(20)	
Actinic Keratosis	0(0)	5(7.1)	
Erythroplakia	1(1.4)	4(5.7)	

Chi square test was applied. P-value of <0.05 is considered statistically significant.

To compare the Qol scores of OPMDs in groups Kruskal–Wallis test was applied. The domains were grouped in to 4 categories (performing routine activities, physical health, emotional problems, pain and functional limitations).Out of these 4 categories, emotional problems and pain and functional limitation showed significant association with oral potentially malignant disorders (p-value 0.03 and p-value 0.04 respectively)as shown in table 2.

Table 2: Disease group-specific scores of Oral Potentially Malignant disorders QOL Questionnaire

QoL Domains	Observations	Rank sum	p-value
Performing Routine Activities			
Leukoplakia	20	700.50	0.398
Oral Lichen Planus	20	700.50	
Oral Sub mucous Fibrosis	20	700.50	
Actinic Keratosis	5	255	
Erythroplakia	5	148	
Physical Health			
Leukoplakia	20	725	0.45
Oral Lichen Planus	20	689	
Oral Sub mucous Fibrosis	20	54	
Actinic Keratosis	5	234	
Erythroplakia	5	128	

DOI: https://doi.org/10.54393/pjhs.v6i1.2383

Emotional Problems			
Leukoplakia	20	745	0.03
Oral Lichen Planus	20	719	
Oral Sub mucous Fibrosis	20	657	
Actinic Keratosis	5	251	
Erythroplakia	5	152	
Pain and Functional Limitations			
Leukoplakia	20	713	0.04
Oral Lichen Planus	20	700	
Oral Sub mucous Fibrosis	20	681	
Actinic Keratosis	5	245	
Erythroplakia	5	160	

Kruskal–Wallis test applied. P-value of <0.05 considered statistically significant

Oral potentially malignant disorders were compared with health status and limited activities in patients. On comparing with the health status, patients with oral submucous fibrosis and erythroplakia showed poor health status (Table 3). This suggests that these patients suffer more possibly due to progressive fibrosis and chronic nature of the disease.

Table 3: Comparison of Oral Potentially Malignant Disorders with Health Status

Health Status	OSF	Leukoplakia	Lichen Planus	Actinic Keratosis	Erythroplakia
Very Good	6	4	4	2	7
Good	5	6	10	1	3
Fair	2	3	4	2	3
Poor	10	2	1	1	8

Table 4 Represents the limitations of performing daily activities in OPMD patients and showed that most of the patients suffering from OSF, Leukoplakia and Lichen planus faced problems in perfoming their routine activities most of the time.

Table 4: Comparison of Oral Potentially Malignant Disorders with Limitation of Activities

Limited Activities	OSF	Leukoplakia	Lichen Planus	Actinic Keratosis	Erythroplakia
Most of Time	7	8	10	4	2
Little of Time	2	3	1	1	0
None	0	0	0	0	0
All of Time	10	9	9	1	4
Some of Time	4	0	0	0	0

DISCUSSION

Patients with oral potentially malignant disorders suffer with severe adverse health outcomes because of their ability to develop into cancer . Studies indicated that there is an increased frequency of malignant transformation of leukoplakia, lichen planus, and oral submucous fibrosis consisting of 3.5%, 1.1%, and 7%-13%, respectively . These findings emphasize the necessity for continuous clinical monitoring to detect early malignant changes and improve patient outcomes. Individuals with OPMDs experience serious health challenges that impact their quality of life, often leading to psychological distress due to the fear of developing cancer. Moreover, numerous patients experience social and emotional issues . This study observed that OPMDs significantly impacts patients' QoL, affecting their comfort, ability to function, social and emotional health, and daily activity performance.Specifically patients with erythroplakia suffers poor mental health outcomes, indicating increased risk of psychological disorders in these patients . Liewellyn and Warnakulasuriya assessed oral health problems such as aphthous ulcers, oral lichen planus, oral candidiasis, xerostomia and temporomandibular joint disorders by oral health impact profile [14]. They reported that chronic diseases of the oral mucosa significantly reduced oral health-related quality of life —. A study discovered a connection between increased pain levels and decreased quality of life in patients with oral lichen planus. . In this research, we observed that the main reason for reduced quality of life was mostly due to a decrease in social and emotional well-being, particularly in how patients viewed their own health. Moreover, a notable difference in the prevalence of Oral Potentially Malignant Disorders was observed between males and females, revealing that females were more frequently affected by these disorders. It may be due to the fact that females are more likely to seek medical attention and visit oral health clinics, leading to a higher reported prevalence. These findings highlight the importance of these factors as they greatly affect the prevention and management of these disorders. Furthermore, we believe that providing thorough information, counseling patients, and reassuring them about the effectiveness of treatment can prevent further decrease in quality of life in individuals with low social and emotional well-being. A recent research has also indicated that oral health issues can lead to pain and hinder daily activities.Therefore, it is crucial to address pain and limitations in functionality in order to improve quality of life.Tabolli *et al.* stressed the importance of utilizing both general and specialized questionnaires to gain a comprehensive understanding of the impact of oral issues, particularly in clinical settings where time for follow-up is limited.The use of a questionnaire to assess quality of life may assist to concentrate the limited time available during follow-up sessions.

DOI: https://doi.org/10.54393/pjhs.v6i1.2383

CONCLUSIONS

Assessing Quality of Life in patients with Oral Potentially Malignant Disorders is essential for understanding their psychological and functional challenges, utlimately enhancing interaction between healthcare providers and patients. This study highlights that social and emotional well being was significantly affected in OPMD patients and pateints suffers with limitation in their routine activities . With the lack of extensive research on Quality of Life in OPMDs, further studies are necessary for a clearer understanding of the issue. Yet, this study is limited by being conducted on a convenience sample and lacking a control group.

Authors Contribution

Conceptualization: SZA
Methodology: HA, ML, DS
Formal analysis: SZA, SK, HA
Writing, review and editing: SK, JA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

There was no conflict of interest.

Source of Funding

It was a self-funded study.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2438

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Oral Leukoplakia: An Overview of Histopathological Spectrum Focusing On WHO Grading System and Binary System of Oral Epithelial Dysplasia

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ARTICLE INFO

Keywords:
Oral Leukoplakia, Histopathological Spectrum, Oral Epithelial Dysplasia, Binary System

How to Cite:
Naushin, T., Iqbal, Z., Khan, A. S., Mehmood, U., Khan, T., Mahmood, S., Hassan, M. U., Mahmood, M., & Hassan, T. U. (2025). Oral Leukoplakia: An Overview of Histopathological Spectrum Focusing On WHO Grading System and Binary System of Oral Epithelial Dysplasia: Oral Leukoplakia: Histopathological Spectrum Focusing On Oral Epithelial Dysplasia. Pakistan Journal of Health Sciences, 6(1), 348-352. https://doi.org/10.54393/pjhs.v6i1.2438

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Received date: 21st October, 2024
Acceptance date: 20th January, 2025
Published date: 31st January, 2025

ABSTRACT

Oral leukoplakia by definition is a white patch with uncertain risk, not including other lesions that could develop into cancer. **Objectives:** To assess the histopathological spectrum of oral leukoplakia and focus on their relation with WHO-classified histological grades and binary system of dysplasia. **Methods:** This study comprised patients diagnosed with oral leukoplakia. Hematoxylin and eosin-stained slides of 60 cases were assessed based on the World Health Organization 2005 classification system: epithelial precursor lesions and binary system of oral epithelial dysplasia. The chi-square test was used to compare different categorical variables related to oral leukoplakia. For analyzing data SPSS version 20.0 was used. **Results:** Of the 60 oral leukoplakia subjects 43 (71.7%) were found to be male while 17 (28.3%) were female. Whereas 26 cases showed dysplastic features (n=26, 43.3%) Among the cases of oral epithelial dysplasia, a higher number of cases of moderate dysplasia was observed (n=12, 46.1%) followed by severe dysplasia (n=10, 38.5%), and the least number of cases had mild dysplasia (n=4, 15.4%). There was a statistically significant relationship between the binary system of oral epithelial dysplasia and variants of oral epithelial dysplasia, mildly dysplastic, moderately dysplastic, and severely dysplastic epithelium ($p<0.04$). **Conclusions:** It was concluded that as oral leukoplakia is such a disorder having a high chance of conversion into cancer early detection is of utmost importance to prevent conversion into malignancy. In addition to the WHO Classification of the said lesions, a binary system of dysplasia can also be promoted.

INTRODUCTION

Oral leukoplakia (OL) is included among oral potentially malignant disorders so there is a significant chance that this potentially malignant oral cavity condition will progress to become a true malignancy [1, 2]. Depending on the location, the transformation rate of oral leukoplakia might vary from 0.13% to 34% [3]. The majority of research has demonstrated heterogeneity in the morphological and clinical features of OL. Its prevalence Varies from 0.2% to 11.7% worldwide. There is marked geographic variation in prevalence even in the different regions of the same country. Studies carried out in Pakistan indicate that the frequency is between 5 and 7% [4]. Mechanical trauma, tobacco use whether smoked or not, alcohol, fungal infections, and Epstein Barr virus are some of the associated etiological factors [5, 6]. As OL is included in oral potentially malignant disorders. So, it manifests

DOI: https://doi.org/10.54393/pjhs.v6i1.2438

histologically as an epithelial precursor lesion. Epithelial precursor lesions are categorized by the World Health Organization (WHO) as mild dysplasia, moderate dysplasia, severe dysplasia, and oral epithelial hyperplasia (OEH) [7]. The propensity for malignant transformation of oral leukoplakia is usually determined by the microscopic evaluation of epithelial dysplasia [3]. Dysplasia has been identified in several cytological and architectural changes affecting the oral epithelium, which is limited to the lower third, middle, and upper third layers [8, 9]. WHO grading system of dysplasia includes mild, moderate and severe dysplasia based on the layers of epithelium involved, however another system that is the Binary system of the dysplastic epithelium of the oral cavity has also been introduced to classify dysplasia into high-risk and low-risk [10]. The clinical outcome is that oral leukoplakia with moderate and severe dysplasia have high chances of conversion (potentially malignant) into malignancy so timely treatment of such lesions should be done to avoid such threat.

The present study has been designed to assess the clinic-morphological spectrum of oral leukoplakia and check their relation with WHO-classified histological grades and binary system of dysplasia.

METHODS

This cross-sectional and multicenter study was conducted at Khyber College of Dentistry and Peshawar Medical College. Data from 60 cases of oral leukoplakia that were diagnosed clinically and confirmed microscopically were collected over 7 months from August 2016–March 2017. Before the start of the study permission from the institutional review board was taken with an IRB number Prime /IRB/2016-0035. The sampling which was adopted was a non-probability convenient sampling technique, an online calculator, was used to determine the sample size with a 9.5% confidence interval, 0.05 chance of error and 2% prevalence. As the sampling which was adopted was a non-probability convenient sampling technique so 60 sample sizes were selected [11]. Inclusion criteria included clinically diagnosed and histopathological confirmed oral leukoplakia cases whereas individuals having microscopic features of anaplasia and invasion were excluded. Permission was granted by the Institutional review board before the commencement of the study. Written consent was taken from every participant on a pre-structured consent form. Separate codes will be given to conceal the identity of the patients. Data were handled by me being the PI of the study. Research data was secured in PI's laptop having a password. Laboratory techniques for biopsy specimens included grossing and processing followed by staining of slides by H and E stain. Two consultant histopathologists graded and assessed the histopathological findings of oral leukoplakia cases until they reached an agreement. When there was disagreement, a third observer, a senior, skilled oral pathologist reevaluated the slides and mediated the matter until everyone agreed. The WHO's 2005 classification method for epithelial precursor lesions was used to group oral potentially malignant disorders (OPMDs) including oral leukoplakia [12]. By this system, oral leukoplakia was categorized as Hyperplasia, or dysplasia, (mild, moderate, severe). The assessment of dysplastic epithelium of the oral cavity was based on cytological factors such as variable cells and nuclear size and shape, increased nucleus–cytoplasm ratio, aberrant mitosis, hyperplasia and hypertrophy of nucleoli, and darkly stained cytoplasm and nuclei) and alterations in epithelial architecture include hyper-cellularity, loss of polarity of basal cells, bulbous rete ridges, individual cell keratinization, and non-cohesive cells of epithelium) [13]. A binary system of oral epithelial dysplasia (OED) was also adopted, and cut-off points of four architectural and five cytological features were employed to classify OED as a high-risk lesion (those who have a potential for MT) and a low-risk lesion (those who do not have the potential for MT) [12]. Variables related to histopathological features of oral leukoplakia were included in the tabulation of data. The chi-square test was used to compare different categorical variables related to the lesion. Statistical analysis was performed with Statistical Package for the Social Sciences (SPSS) software version 21.0 (IBM Corp, Armonk, New York, United States America) with a significance level of $p \leq 0.05$.

RESULTS

Of the 60 oral leukoplakia cases 43(71.7%) were found to be in male patients while 17 (28.3%) were in female patients .2.5:1 was the computed ratio (Table 1).

Table 1 : Gender Wise List of Oral Leukoplakia Patients

Gender	No. of cases n (%)
Male	43 (71.7%)
Female	17 (28.3%)
Total	60 (100.0%)

The age range is shown which is from 30 to 90 years and the mean age is found to be 60 years (Table 2).

Table 2 : Oral Leukoplakia Cases Distributed by Age

Age	No. of cases
Minimum	30 Years
Maximum	90 Years
Mean	60 Years

The total number of oral leukoplakia cases was 60 out of which 26 were dysplastic (n=26, 43.3%). The dysplastic feature was observed in 26 (43.3%) individuals out of 60, whereas 34 cases showed hyperkeratotic and hyperplastic

DOI: https://doi.org/10.54393/pjhs.v6i1.2438

epithelium (56.6%) (Table 3).

Table 3: Frequency of Various Grades of Dysplasia

Frequency and Percentage of Grades of Dysplasia	n (%)
Mild Dysplasia	4 (15.5%)
Moderate Dysplasia	12 (46.1%)
Severely Dysplastic Epithelium	10 (38.5%)
Total	26 (100%)

There was a statistically significant relationship between the binary system of OED and WHO grading system of dysplasia, that is, mildly dysplastic, moderately dysplastic, and severely dysplastic epithelium ($p<0.04$) (Table 4).

Table 4: Relation of Binary Grading System and WHO Categorization of Dysplastic Epithelium

Variables		WHO Classification			Total	Pearson's Chi-Square Test
		Mildly Dysplastic Epithelium n (%)	Moderately Dysplastic Epithelium n (%)	Severely Dysplastic n (%)		
Binary Grading System	Low Risk	4 (15.4%)	7 (26.9%)	2 (7.7%)	13 (50.0%)	0.04
	High Risk	0 (0%)	5 (19.2%)	8 (30.8%)	13 (50.0%)	
Total		4 (15.4%)	12 (46.1%)	10 (38.5%)	26 (100.0%)	

DISCUSSION

The WHO grading system for epithelial precursor lesions, the binary system for grading of OED, and other histomorphological features of oral leukoplakia are included in this study for the first time. According to the current study, men are more likely than women to have oral leukoplakia. This gender-related observation contradicts the findings of Pires *et al.*, the number of female with the habit of tobacco use is increasing in certain populations and secondly, there is the likelihood that the female lesions would be diagnosed and treated earlier. The result of our study is consistent with the findings reported by Saldivia *et al.*, and Pires *et al.*, [13, 14]. This may be explained by the fact that in certain regions men are more exposed to the risk factors of oral leukoplakia such as smoking habits and outdoor jobs. The majority of cases of oral leukoplakia were found to be in the older age group according to the current study. This is in line with research by Khan *et al.* and Mello *et al.*, who found that growing older may be a determinant of OPMDs [15, 16]. This study found that among the oral epithelial dysplasia cases, moderate dysplasia was the most common, severe dysplasia was the second most common, and cases with mildly dysplastic epithelium were the least common. This is consistent with [12]. Additionally, cases of severe dysplasia were documented by other researchers in comparison to mild and moderate dysplasia [17]. Epithelial Dysplasia has been identified microscopically as one of the predictive markers for the development of cancer from such lesions having chances of conversion into cancer, including oral leukoplakia [18]. A statistically significant correlation was found between the grades of dysplastic epithelium and the binary grading system of dysplastic epithelium. All the cases of mild dysplastic were placed in the low-risk category while the majority of cases of moderately dysplastic and severely dysplastic epithelium were placed in the high-risk category. This is due to the results of international literature about the probable chance of conversion into cancer of such lesions having the potential to show a certain degree of dysplastic [19]. 50% of cases in this study were classified as high-risk lesions and 50% as low-risk. Its results are similar to the international study by Câmara *et al.*, however, are in contrast to research by Kujan *et al.*, [20, 21], binary grading system. Leukoplakia of the oral cavity was classified by the Binary system as high risk and low risk. International studies noted that oral cancers can also occur in low-risk OPMDs but high-risk oral epithelial dysplasia has a much higher chance of conversion into cancer [12]. In line with the finding of Câmara *et al.*, the current investigation discovered a statistically significant association between the oral epithelial dysplasia binary system and oral epithelial dysplasia introduced by the WHO grading system [20]. WHO grading system classifies dysplasia into mild, moderate and severe dysplasia whereas the binary grading system classifies dysplasia into low risk and high risk. The high-risk category includes moderate and severe dysplasia. In this study, there were more cases of severe and moderate dysplasia and the clinical outcome is that oral leukoplakia with moderate and severe dysplasia have high chances of conversion (potentially malignant) into malignancy so timely diagnosis and treatment of such lesions should be done to avoid such threat.

CONCLUSIONS

It was concluded that oral leukoplakia was the most common in males, mostly in age ≥50 years. Timely diagnosis and treatment of oral leukoplakia with dysplastic features are of utmost importance to avoid the conversion of these premalignant lesions into cancer and ultimately decrease the mortality rate.

Authors Contribution

Conceptualization: TN
Methodology: TN, ZI, SM, MUH
Formal analysis: ASK, UM, TK, MM
Writing review and editing: TUH

All authors have read and agreed to the published version of the manuscript

DOI: https://doi.org/10.54393/pjhs.v6i1.2438

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2580

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

A Morphological and Topographical Study of Diaphyseal Nutrient Foramen (NF) In Dried Human Adult Long Bones of Upper Limbs

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ARTICLE INFO

Keywords:
Nutrient Foramen, Upper Limb, Bone Anatomy, Surgical Implications

How to Cite:
William, G. P., Munawar, S., Sohail, S., Salauddin, M., Fahim, N., Nawaz, A., & Sayal, S. (2025). A Morphological and Topographical Study of Diaphyseal Nutrient Foramen (NF) In Dried Human Adult Long Bones of Upper Limbs : Nutrient Foramen in Upper Limbs. Pakistan Journal of Health Sciences, 6(1), 353-358. https://doi.org/10.54393/pjhs.v6i1.2580

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Received date: 15th November, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

The morphological and topographical characteristics of diaphyseal Nutrient Foramina (NF) in the long bones of the upper limbs is essential for optimizing surgical interventions, particularly in fracture management and bone grafting procedures. **Objective:** To assess the anatomical features (number, location and foramina index) of diaphyseal NF in cadaveric long bones of upper limb in adult Pakistani population. **Methods:** This cross-sectional study was undertaken on human cadaveric upper limb bones from the bone bank of the Anatomy department of FMH College of Medicine and Dentistry, Lahore. The age and gender of the bones were not known, and the duration of the study was four months. A total of 195 non-pathological, undistorted bones of upper limb (57 clavicles, 34 humeri, 50 radii and 54 ulnae) with were randomly selected. **Results:** In cases of clavicle 58% had a single NF (NF), 33% double & 5% triple, in humerus 100% had a single NF, 96% of radii had a single NF & 4% double whereas in ulna 98% had single NF and 2% double. In majority of the clavicle, humerii and radii the NF was in the 2/3rd of the bone whereas in case of ulnae majority of NF occupied the proximal 1/3rd of the shaft of the ulnae. **Conclusion:** A good knowledge about the anatomy of the NF is necessary for orthopaedic or trauma surgeons while doing critical bone reconstructive or graft implantation surgeries.

INTRODUCTION

During the active growth period of bone, diaphyseal Nutrient Artery (NA) serves the purpose of main artery supplying blood to the bone. Adequate blood supply, via periosteal as well as medullary arteries, ensures the recovery and success of the surgical procedures done for healing of the fractures of the long bones [1]. Vascular flow within the bone is mandatory for bone formation, its growth and repair after any kind of fracture or injury [2]. The importance of Nutrient Foramen (NF) is relevant to fracture treatment [3]. The point of entry of diaphyseal NA on external surface of bone is called NF that leads to the nutrient canal. The foramen could be one or more than one in number and its location and direction of the Nutrient Canal (NC) varies among various long bones [4]. NF are apertures in bones through which the blood vessels enter. The arteries entering through these foramina invade the cartilage that is ossifying during the formation of primary ossification center, hence these foramina are the telltale sign of the primary ossification centers [5]. Humphrey focused his research on the direction of the nutrient canals and their obliquity. He presented his periosteal slipping theory which stated that "nutrient canal is directed away

DOI: https://doi.org/10.54393/pjhs.v6i1.2580

from the growing end" to avoid injury or rupture of the NA due to the pull of growth of bone [5, 6]. Location and number of NF are independent of the length or age of the bone as well as the ossification centers. Rather than the development of the bone, it's the formation and development of the NA that is essential for the development of the Nutrient Canal (NC) [7]. In absence of the NA, periosteal vessels are held responsible for supplying blood to the bone [8]. During the surgical procedures such as fixation of fractures internally and bone grafting, the knowledge about site of location and number of NF are pivotal as it would avoid the damage to the NA and hence uninterrupted blood supply ensures healing by osteocytes and osteoblast [9]. Otherwise, the interruption in the blood supply could result in late union or un-united fractures of the bone, this highlights the importance of medullary blood system in callus formation and revascularizing the cortical bone undergoing necrosis at the site of the fracture [10]. Therefore, NF is crucial in maintaining the vascularization of long bones, significantly affecting the healing of fractures and the success of surgical procedures such as nailing and grafting. The NA, passing through these foramina, provides substantial blood supply to both the medulla and cortex internally, accounting for a considerable portion of the vascular support during the healing process. Understanding anatomical variations as well as site of locations of NF are therefore essential for enhancing surgical outcomes in treatment of fractures and reconstruction of bones. Surgeons can easily locate the NF of each bone and preserve the NA which ensures the presence of osteoblasts and osteocytes that are essential for healing and integration of vascular bone graft [11]. In addition, during bone grafting, avoiding the nutrient artery, due to the knowledge of site of the NF, can easily reduce the risk of ischemia to the bone and eventually prevents nonunion of the fractured bone or delayed osteogensis and thereby enhancing the efficacy of the surgical interventions and reducing the risk of complications due to adequate vascular supply [9, 11]. Detailed data regarding the NF is required for transplant and surgical resection techniques to avoid nonunion in orthopedics. Since physique, structure, and genetic make-up differ distinctly in the various ethnic groups, it is likely that the data regarding the NF of the long bones present in the upper limb considered standard for Western population might be relatively unlike than that of Pakistanis.

Therefore, this study was undertaken to eliminate gap of data for NF of long bones belonging to upper limb in Pakistani population as much as possible.

METHODS

This study was conducted from November 2023 to January 2024 and involved 195 human cadaveric bones and included 57 clavicles, 34 humerii, 50 radii and 54 ulnae. As the bones were taken from the bone bank of Anatomy department, FMH College of Medicine and Dentistry (FMHCMD), Lahore so their age and gender was not known (Figure 1). There was no participant or patient involved in the study, rather it was on cadaveric bones so consent was not applicable in this case. FMH College of Medicine and Dentistry Lahore ethical committee approved this study by providing the institutional review board approval certificate vide letter no. FMH-15/08/2023-IRB-1267. The bones with grossly visible pathologies were excluded from sample of this research project. All upper limb long bones were studied for locating the NF and the count of NF in each bone was also noted. For determining the location of the NF, each bone was divided into three equal parts lengthwise and named as proximal, middle and distal third of the bone. For a clear view, magnifying glass was also used. A Distinct Groove (NC) accompanied by a clearly defined, often slightly elevated edge marking the beginning of the canal is recognized as NF. Only NF of the shaft (diaphyseal) were observed, and their patency was confirmed by placing the 24-gauge needle in foramen.

Parameters

Number of NF

Location/site of the NF at various borders or the surfaces of diaphysis/shaft of bones

The foramina as close as 1 mm from any border were present on that particular border.

Hughes formula [1] was used to calculate foramen index (F.I.)

F.I. = D/L×100

Distance of foramen from proximal end (D)

Total length of bone (L)

The F.I. was determined for each of the bones included in the study. For locating NF, each bone was equally divided into three parts and topography noted, data tabulated in standardized sheet and analyzed.

Sample Size

A sample of size 195 is calculated using the expected mean of Khyber Pakhtunkhwa Population with 95.0% confidence level and 0.05 margin of error [12].

Formula

$$n = \frac{n_0}{1 + \frac{(n_0 - 1)}{N}}$$

Where,

n_0 = Cochran's sample size recommendation,

N= population size,

DOI: https://doi.org/10.54393/pjhs.v6i1.2580

n = sample size of our study

Simple Random sampling was done. Data were entered and analyzed by SPSS version 25.0. A descriptive analysis was conducted and mean+SD was calculated for quantitative variables and frequency and percentages for qualitative variables.

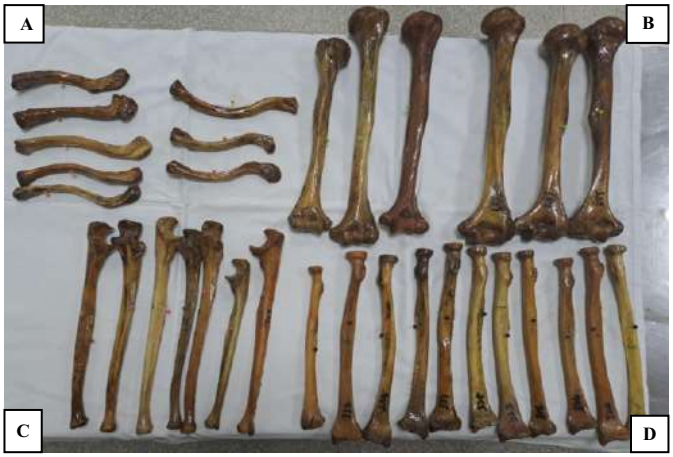

Figure 1: Long bones of upper limb (A: Clavicle, B: Humerus, C: Ulna, D: Radius); site of location of NF is marked on individual bones by colored head Pins

RESULTS

In the clavicles examined, 58% contained a single NF, 33% had two NF, and 5% had three. Additionally, 1.75% of clavicles presented with five NF, and another 1.75% had six. In contrast, all humeri (100%) exhibited a single NF. Among the radii, 96% had a single NF, while 4% displayed two. For the ulnae, 98% contained a single NF, with only 2% showed two foramina. (Table 1).

Table 1: Frequency of Nutrient Foramina (NF) in Different Bones

Bone	Single NF (%)	Two NF (%)	Three NF (%)	Five NF (%)	Six NF (%)
Clavicle	58%	33%	5%	1.75%	1.75%
Humerus	100%	0%	0%	0%	0%
Radius	96%	4%	0%	0%	0%
Ulna	98%	2%	0%	0%	0%

Table 2 presented the distribution of nutrient foramina (NF) in clavicles. The majority (50%) of NF were located on the inferior surface, making it the most common site. The posterior border contained 22% of the foramina, while 15% were found on the posterior surface. A smaller percentage (7%) were observed on the superior surface, whereas only 1.75% were located on both the anterior border and anterior surface.

Table 2: Distribution of Nutrient Foramina (NF) in Clavicles

Location on Clavicle	Percentage (%)
Inferior Surface	50%
Posterior Border	22%
Posterior Surface	15%
Superior Surface	7%
Anterior Border	1.75%
Anterior Surface	1.75%

Table 3 highlighted the distribution of NF in the humerus, radius, and ulna. In humeri, the anteromedial surface was the predominant site (73.5%), followed by the medial border (17%), with a minimal presence (0.08%) on the posterior surface. Among the radii, the anterior surface had the highest occurrence of NF (48%), while 28% were found on the posterior surface and 24% on the medial border. For ulnae, the anterior surface was the primary site (83%), whereas 17% of NF were positioned on the lateral border.

Table 3: Distribution of Nutrient Foramina (NF) in Humerus, Radius, and Ulna

Bone	Location of NF	Percentage (%)
Humerus	Anteromedial Surface	73.5%
	Medial Border	17%
	Posterior Surface	0.08%
Radius	Anterior Surface	48%
	Medial Border	24%
	Posterior Surface	28%
Ulna	Anterior Surface	83%
	Lateral Border	17%

The mean foramen index was calculated as 37.47 for clavicle, 55.5 for humerus, 33.41 for radius, and 33.4 for ulna (Table 4).

Table 4: Data of NF in Various Upper Limb Bones

Name of the Bone	Number of Bones	Number of NF (Each category shows the number of bones consisting of the respective number of foramen)						
		No foramen	One	Two	Three	Four	Five	Six
Clavicle	57	0	33	19	3	0	1	1
Humerus	34	0	34	0	0	0	0	0
Radius	50	0	48	2	0	0	0	0
Ulna	54	0	53	1	0	0	0	0

This study examined the distribution of nutrient foramina (NF) in various bones. In clavicles, 50% of NFs were found on the inferior surface, followed by the posterior border (22%) and posterior surface (15%). In humeri, most NFs (73.5%) were on the anteromedial surface. In radii, NFs were predominantly located on the anterior surface (48%) and posterior surface (28%). For ulnae, 83% of NFs were on the anterior surface, with 17% on the lateral border. These findings highlight the variation in NF distribution across different bones (Table 5).

DOI: https://doi.org/10.54393/pjhs.v6i1.2580

Table 5: Distribution of NF and Foramen Index

Name of the Bone	Location of NF on Diaphysis										Topography (longitudinal Division of Diaphysis)			Foramen Index (F.I)
	Border				Surface						1/3rd	2/3rd	3/3rd	Mean
	M	L	A	P	A	M	L	P	S	I				
Clavicle	-	-	1	13	1	-	-	9	4	29	5	45	7	37.47
Humerus	6	-	-	-	13	12	-	3	-	-	5	28	1	55.5
Radius	12	-	-	-	24	-	-	14	-	-	3	47	0	33.41
Ulna	-	9	-	-	45	-	-	-	-	-	39	15	0	33.44

(M: Medial, L: Lateral, A: Anterior, P: Posterior, S: Superior, I: Inferior)

Table 6: Comparison of Location of Foramina on Expected Site versus Variant Site

Name of the Bone	Location of NF Frequency (%)					
	Expected site	Variant Site				
		1	2	3	4	5
Clavicle	Inferior Surface 29 (50.87%)	Posterior Border 13 (22.80%)	Posterior Surface 9 (15.78%)	Superior Surface 4 (7.01%)	Anterior Surface 1 (1.75%)	Anterior Border 1 (1.75%)
Humerus	Anteromedial Surface 25 (73.5%)	Medial Border 6 (17%)	Posterior Surface 3 (0.08%)	-	-	-
Radius	Anterior Surface 24 (48%)	Medial Border 12 (24%)	Posterior Surface 14 (28%)	-	-	-
Ulna	Anterior Surface 45 (83%)	Lateral Border 9 (17%)	-	-	-	-

DISCUSSION

Bones in the human body are highly vascularized receiving approximately 10%-15% of cardiac output. NA along with metaphyseal and epiphyseal arteries, which arise from periosteal arteries and periarticular vascular plexus, supplies blood to the long bones [13]. In the current research, the inferior surface of the clavicle was observed to have the NF in most cases occupying the middle 2/3rd of the shaft which was also seen in a meta-analysis study done by Morten Ejlersen [14]. A recent study conducted on dry human clavicle bones also showed similar results [15]. In current research, anteromedial surface of humerus was found to have most of the NF, which is similar to the results of study conducted by Thakur and Sar along with their associates [2, 16]. Humerus was the only bone that showed single foramina in practically all the bones which is close to another study done by Kumar S *et al.*, in which 93% had only one foramen [17]. Only one NF was found in 96% radii in the current research. These findings agree with another study recently done exclusively on radii [18]. Regarding the site of NF, anterior surface had it in 48% radii while posterior surface had NF in 28%, which was also seen by Vaghela and associates in his study [19]. However, medial or interosseus border had NF in 24 % cases that is in accordance with a study done by Elif [18]. In the current study, NF were distributed most often in middle one third of radius with few in the proximal one third. Similar findings were observed in another study of Mishra *et al* [20]. In our study NF was single in 53(98%) of the ulna which was also seen by Dervisevic L *et al.*, in his study [6]. Regarding the location on radii, anterior surface had most NF, which is in accordance with observations made by Mahesh Dhoot *et al* [9]. While orthopedic and reconstructive surgeries on long bones, a detailed understanding of the location as well as characteristics of NF is essential for preventing intraoperative injuries [16]. The perforating vessels are the main contributing vessels in the blood supply of bones of the elbow that were arising from the neighboring arteries around the bone. These vessels can sustain trauma during reconstructive surgeries of the elbow. Hence a sound understanding of circulation within and around the bone is necessary to prevent iatrogenic injuries. Fractures of long bones are a common occurrence which can be complicated by delayed union. This complication can have multiple causes and one of them is poor nutrition caused by damage to the nutrient artery [11]. Non-union are more common in the proximal 1/3 of humerus and distal 1/3 of radius and ulna due to diminished blood supply of these areas caused by decreased branches of nutrient artery [10]. Therefore, understanding of anatomy of NF is crucial for preservation of circulation of bone during surgical procedures [21]. While allografting for elbow joint, the anatomical knowledge about the NF of the bones forming the elbow joint is crucial for the preservation of vasculature of the bone [3, 10]. The topography of NF should be kept in mind during surgeries and its clinical significance cannot be overemphasized in this regard. It is from the NF from where the entrance of the NA into the bone takes place to supply blood and nourish it. The nutrient artery is crucial for the healing of the fractures of weight-bearing bones by providing essential blood supply, which is vital for bone nutrition and growth [3]. Compromise of this blood flow, often due to the trauma involving the NA or the NF during

DOI: https://doi.org/10.54393/pjhs.v6i1.2580

stress fractures or surgical interventions, can lead to delayed union or nonunion of fractures, as adequate vascularization is necessary for effective healing [22]. Furthermore, the nutrient artery's role in providing essential nutrients and supporting the callus formation at the site of the fracture underscores its importance; without proper blood supply, the healing process is severely hindered, increasing the risk of complications such as avascular necrosis [10]. The surgical approach for bone grafting and fracture management is not only influenced by the number of the NF but also their site of location and it ensures the uncompromised blood supply and healing [23]. The site of location of the NF also influences choice of surgical technique to be used in particular circumstances [5]. Adequate knowledge about the distribution of NF in long bones topographically also augments in diagnosis and treatment of conditions relating to impaired bone healing and developmental abnormalities [22]. Moreover, knowledge of the foraminal index and the direction of NC leading to NF, improves the outcome and effectiveness of surgical interventions, ensuring preservation of osseous circulation, thereby ensuring optimal outcomes. This anatomical insight is vital for orthopaedic surgeons and clinicians involved in the management of bone-related injuries and conditions [17]. Most upper limb bones contain only one NF, generally directed toward the elbow joint and located on flexor surfaces [21-23]. The anatomical knowledge about the variations of NF reduces the risk to vascular supply and minimizes the chances of complications such as nonunion or delayed healing, which can be associated with the absence/damage to NF and artery.

CONCLUSIONS

Understanding the locations and number of the foramina, enables us to identify the safe zones for surgical procedures like pin insertions etc., in the long bones and optimizes the surgical planning for repair of the fractures, replacement of joints, and microvascular grafting of bone. Understanding anatomical variations is essential for microsurgical techniques, and CT imaging is recommended for assessing fractures. This study contributes to the limited literature on NF of upper limb bones in the population of Pakistan and offers valuable insights that are crucial for enhancing surgical efficacy.

Authors Contribution

Conceptualization: GPW
Methodology: SM, SS1, MS, NF
Formal analysis: GPW
Writing, review and editing: GPW, SM, SS1, MS, NF, AN, Ss[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2456

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Original Article

OPEN ACCESS

Association of Serum Uric Acid-to-Creatinine Ratio with Non-Alcoholic Fatty Liver Disease in the Population of Sargodha

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ARTICLE INFO

Keywords:
Alcohol, Uric Acid, Creatinine, Uric Acid-to-Creatinine Ratio, NAFLD

How to Cite:
Rasheed, S., Shahid, A., Sarfraz, A., Tabassum, S., Mudassar, S., & Habib, B. (2025). Association of Serum Uric Acid-to-Creatinine Ratio with Non-Alcoholic Fatty Liver Disease in the Population of Sargodha: Serum Uric Acid-to-Creatinine Ratio with Non-Alcoholic Fatty Liver Disease . Pakistan Journal of Health Sciences, 6(1), 359-364. https://doi.org/10.54393/pjhs.v6i1.2456

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Received date: 19th October, 2024
Acceptance date: 23rd January, 2025
Published date: 31st January, 2025

ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) is a growing global health concern, particularly in regions with high obesity rates. **Objectives:** To evaluate the serum uric acid to serum creatinine (sUA/sCr) ratio as a potential diagnostic biomarker for NAFLD in a Pakistani population. **Methods:** This cross-sectional study was conducted at the Department of Biochemistry, Niazi Medical and Dental College, Sargodha, from November 2023 to April 2024, with 246 participants presenting with signs and symptoms of NAFLD. Clinical and biochemical parameters, including BMI, waist circumference, blood pressure, fasting blood sugar, lipid profile, high-sensitivity C-reactive protein (hs-CRP), and liver enzymes, were assessed. Logistic regression was used to examine the relationships between these factors and NAFLD prevalence and severity. The serum uric acid/serum creatinine (sUA/sCr) ratio was evaluated as a potential biomarker for severe NAFLD. Data were analyzed using SPSS version 26.0 with ANOVA, chi-square tests, t-tests, and logistic regression.**Results:** NAFLD prevalence was 39%, with physical activity reducing the risk (OR: 0.65, p=0.015) and age, obesity, hypertension, high blood sugar, cholesterol, triglycerides, and hs-CRP identified as risk factors. Severe NAFLD was associated with increased waist circumference, hypertension, inflammation, and BMI. The sUA/sCr ratio demonstrated excellent predictive accuracy for severe NAFLD (AUC 0.90, sensitivity 85%, specificity 80%, p<0.001). **Conclusions:** It was concluded that sUA/sCr ratio was a promising non-invasive biomarker for diagnosing and assessing NAFLD severity in the population of Sargodha.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a common hepatic metabolic disorder associated with obesity, insulin resistance, dyslipidemia and hypertension. The progression of nonalcoholic steatohepatitis carries the risk of cirrhosis and liver-related complications. NAFLD and other metabolic disorders have been connected to uric acid (UA), a byproduct of purine metabolism. Uric acid/creatinine (UA/Cr), as a predictor marker was used for both renal function and comprehensive metabolic deregulation and also could offer greater insight into disease profiling in early stages or risk stratification for NAFLD [1]. MetS stands for Metabolic Syndrome results in the occurrence of a series of diseases including diabetes, dyslipidemia, arteriosclerosis and other cardiovascular (CVD) or cerebrovascular diseases. The incidence of nonalcoholic liver disease has been increasing in the world and health issues due to higher all-inclusive medical costs, socio-economic burden and personal health-related complications [2]. The increasing prevalence of hyperuricemia and gout [which refers to a type of inflammatory arthritis triggered by crystallization due to accumulation of monosodium is becoming a significant issue for the general population. The rise can be explained by several factors such as the food mode, sedentary

DOI: https://doi.org/10.54393/pjhs.v6i1.2456

lifestyle and increasing numbers of aged people. Newer diets are often high in foods that contain purines, including large quantities of red and organ meats as well as certain types of fish and alcohol (especially beer) [3, 4]. When purines are metabolized by the body it produces uric acid as a waste product. High fructose diets (which are found in sugary beverages and processed foods) also lead to high uric acid levels. Compounded over the years, the increase in obesity, as well as a sedentary lifestyle, were only bringing higher rates of hyperuricemia. Over time hyperuricemia may induce insulin resistance, promoting oxidative stress and inflammation within different tissues i.e. muscle or liver. This reduces insulin sensitivity and contributes to the diminished functional mass of endocrine β-cells concerning impairs insulin signalling pathways [5, 6]. Dyslipidemia and NAFLD occur when lipid metabolism is disturbed in the host by persistently elevated uric acid. One possible mechanism where hyperuricemia leads to hepatic lipogenesis (liver fat production) while simultaneously inhibiting fatty acid oxidation is resulting in liver lipid accumulation [7, 8]. This model is based on the pathophysiological hypothesis that in NAFLD, insulin resistance drives de novo lipogenesis and inhibits beta-oxidation. The dysregulation of insulin signalling promotes hepatic glucose production and fat accumulation, thereby providing the pathogenic incentive needed for NAFLD to progress [9]. In the past few years, there have been several reports that suggest a significant and independent association between hyperuricemia with NAFLD, making increased uric acid levels one more marker for liver disease risk. This is more directly associated with an urge to monitor uric acid levels of NAFLD-susceptible individuals, especially those with metabolic syndrome [10]. This study aims to assess the sUA/sCr ratio as a diagnostic biomarker by evaluating the prevalence of moderate and severity of non-alcoholic fatty liver disease (NAFLD).

METHODS

A cross-sectional study was conducted at the Department of Biochemistry, Niazi Medical and Dental College, Sargodha, from November 2023 to April 2024. The study population includes Sargodha region where the patients were studied. The study employed a stratified random sampling technique to ensure that the sample was representative of the target population. Approved by Niazi Medical and Dental College Sargodha Hospital Institutional Review Board on (IRB Number: IRB/NM&DC/57). The total number of participants was n=246 and divided into three groups Non-NAFLD (n=150), mild-NAFLD (n=60) and moderate-to-severe NAFLD (n=36). Adults aged >18 years with symptoms of non-alcoholic fatty liver disease (NAFLD), including abdominal discomfort, fatigue, or elevated liver enzymes, were included. Participants also needed to be willing to provide informed consent and undergo a liver biopsy. Participants with a history of alcohol intake >20g/day for men or >10g/day for women, chronic liver infections, viral hepatitis, autoimmune liver disease, advanced kidney dysfunction (eGFR <30 mL/min/1.73 m^2), or those taking medications affecting uric acid levels (e.g., diuretics, allopurinol), were excluded. Patients experiencing acute illness or infection were also excluded. Alcohol intake was quantified by self-reported daily consumption (in grams). The study ensured that no participant exceeded 20 grams of alcohol intake on any given day. Physical activity was classified into two groups using the Kuwait Physical Activity Questionnaire (K-GPAQ): low (<600 METs/week) and active (>600 METs/week). METs (Metabolic Equivalent of Task) measure the intensity of physical activity. BMI was calculated based on weight (kg) divided by height (m^2), and categorized as normal (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2), and obese (≥30 kg/m^2). Blood pressure was categorized as normal (<120/80 mmHg), elevated (120-129/<80 mmHg), and hypertension (≥130/80 mmHg), as per the American College of Cardiology guidelines. NAFLD diagnosis was based on ultrasound findings, categorizing participants into three groups: (1) No NAFLD (normal liver), (2) Mild non-cirrhotic fatty liver, and (3) Moderate-to-severe hepatic steatosis (with or without cirrhosis). The ultrasound was used to assess liver echo patterns in comparison to the right kidney. After a 12-hour fast, participants had blood drawn to measure liver enzymes (Alanine aminotransferase [ALT], Aspartate aminotransferase [AST], Gamma-glutamyl transferase [γ-GT]), serum creatinine, serum uric acid (UA), high-sensitivity C-reactive protein (hs-CRP), and lipid profile (Total Cholesterol [TC], Triglycerides [TG], High-density Lipoprotein [HDL], and Low-density Lipoprotein [LDL]). Data were analyzed using IBM SPSS Statistics (version 26.0). Continuous variables were compared using Student's t-test or ANOVA, and categorical variables were compared using Pearson's χ^2 test. A multi-logistic regression model was used to calculate the odds ratios (OR) and 95% confidence intervals (CI) for the serum uric acid/creatinine (sUA/sCr) ratio, adjusted for potential confounders. A receiver operating characteristic (ROC) curve was plotted to assess the diagnostic capacity of the sUA/sCr ratio for NAFLD. The optimal cut-off value to separate positive from negative cases was selected based on maximizing sensitivity and specificity. Statistical significance was set at $p<0.05$.

RESULTS

The analysis reveals that moderate-to-severe NAFLD is significantly associated with older age (mean 50.0 years vs. 46.0 and 44.0 years for mild NAFLD and non-NAFLD,

DOI: https://doi.org/10.54393/pjhs.v6i1.2456

respectively; p=0.020) and (increased from 70.0 g/week in mild NAFLD to 90.0 g/week in moderate-to-severe NAFLD; p<0.001). Moderate-to-severe NAFLD participants also showed higher waist measurement (97.2% vs. 58.3% and 53.3% obesity rates; p<0.001) and BMI (30.0 kg/m^2 vs. 27.5 kg/m^2 and 24.8 kg/m^2; p<0.001). Hypertension prevalence increased (55.6% in moderate-to-severe vs. 33.3% in mild and 20.0% in non-NAFLD; p=0.005), alongside worse metabolic markers, such as fasting blood sugar (102.0 mg/dL) and total cholesterol (210.0 mg/dL; p=0.002 and p=0.004). Liver dysfunction markers and systemic inflammation (hs-CRP 4.5 mg/L; p<0.001) were significantly higher in moderate-to-severe cases. These findings indicate advanced metabolic dysfunction and liver impairment in more severe NAFLD cases, necessitating aggressive intervention strategies (Table 1).

Table 1: Characteristics of the Participants (n=246)

Characteristics	Total (n=246)	(n=150)	Mild NAFLD (n=60)	Moderate-to-Severe NAFLD (n=36)	p-value
Age (years)	45.5 ± 10.0	44.0 ± 9.5	46.0 ± 10.0	50.0 ± 9.5	0.020
Gender (n, %)					
Male	150 (61.0%)	90 (60.0%)	40 (66.7%)	20 (55.6%)	0.470
Female	96 (39.0%)	60 (40.0%)	20 (33.3%)	16 (44.4%)	
Alcohol Intake (g/Week)	50.5 ± 30.5	30.0 ± 20.0	70.0 ± 25.0	90.0 ± 30.0	0.009
Physical Activity (METs/Week)					
Low Physical Activity	100 (40.7%)	60 (40.0%)	25 (41.7%)	15 (41.7%)	0.960
Activity	146 (59.3%)	90 (60.0%)	35 (58.3%)	21 (58.3%)	
BMI (kg/m^2)	26.5 ± 4.2	24.8 ± 3.9	27.5 ± 4.0	30.0 ± 4.5	<0.001
Blood Pressure (mmHg)					
Hypertension (≥140/90)	70 (28.5%)	30 (20.0%)	20 (33.3%)	20 (55.6%)	0.005
Waist Circumference (cm)					
Obese (men ≥90, women ≥5)	150 (61.0%)	80 (53.3%)	35 (58.3%)	35 (97.2%)	<0.001
Fasting Blood Sugar (mg/dL)	95.0 ± 15.0	90.0 ± 12.0	95.0 ± 14.0	102.0 ± 16.0	0.002
Total Cholesterol (mg/dL)	190.5 ± 30.0	180.0 ± 25.0	190.0 ± 28.0	210.0 ± 32.0	0.004
LDL Cholesterol (mg/dL)	110.5 ± 25.0	100.0 ± 20.0	110.0 ± 22.0	130.0 ± 28.0	0.001
HDL Cholesterol (mg/dL)	50.0 ± 15.0	55.0 ± 10.0	48.0 ± 12.0	42.0 ± 14.0	0.015
Triglycerides (mg/dL)	150.0 ± 40.0	130.0 ± 30.0	150.0 ± 35.0	180.0 ± 50.0	0.005
Liver Enzymes (AST, ALT, γ-GT)					
AST (U/L)	30.5 ± 10.0	25.0 ± 8.0	30.0 ± 9.0	40.0 ± 12.0	<0.001
ALT (U/L)	28.0 ± 9.0	22.0 ± 6.0	30.0 ± 8.0	38.0 ± 10.0	<0.001
γ-GT (U/L)	40.0 ± 15.0	30.0 ± 10.0	40.0 ± 15.0	55.0 ± 20.0	<0.001
Serum Creatinine (mg/dL)	0.9 ± 0.2	0.85 ± 0.15	0.90 ± 0.20	1.00 ± 0.25	0.020
Serum Uric Acid (mg/dL)	5.5 ± 1.0	5.0 ± 0.8	5.5 ± 0.9	6.5 ± 1.2	<0.001
hs-CRP (mg/L)	3.0 ± 1.5	2.0 ± 1.0	3.5 ± 1.5	4.5 ± 1.8	<0.001
Ultrasound Findings					
Fatty Liver Diagnosis (n, %)	96 (39.0%)	150 (100%)	60 (100%)	36 (100%)	<0.001

Important NAFLD predictors are found via the logistic regression analysis. The risk is increased by older age (OR: 1.05, p=0.003) and higher alcohol intake (OR: 1.02, p=0.005). Higher BMI (OR: 1.15, p<0.001) and waist circumference (OR: 1.10, p=0.001) significantly raise the odds, but active physical exercise minimizes the likelihood (OR: 0.65, p=0.015). Hypertension (OR: 1.50, p=0.012), elevated fasting blood sugar (OR: 1.03, p=0.020), and dyslipidemia with total cholesterol, LDL, and triglycerides—are positively associated with NAFLD. Inflammation, indicated by higher hs-CRP levels (OR: 1.10, p<0.001), is strongly linked with NAFLD (Table 2).

Table 2: Influence of Metabolic Factors in Non-NAFLD vs. NAFLD

Variables	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
Age (years)	1.05	1.02 - 1.09	0.003
Gender (Male vs. Female)	1.20	0.85 - 1.70	0.295
Alcohol Intake (g/week)	1.02	1.01 - 1.04	0.005
Physical Activity (Active vs. Low)	0.65	0.45 - 0.92	0.015
BMI (kg/m^2)	1.15	1.10 - 1.20	<0.001
Waist Circumference (cm)	1.10	1.05 - 1.15	0.001
Hypertension (Yes vs. No)	1.50	1.10 - 2.04	0.012
Fasting Blood Sugar (mg/dL)	1.03	1.01 - 1.05	0.020
Total Cholesterol (mg/dL)	1.01	1.00 - 1.02	0.045
LDL Cholesterol (mg/dL)	1.02	1.00 - 1.04	0.050
HDL Cholesterol (mg/dL)	0.95	0.90 - 1.01	0.120

DOI: https://doi.org/10.54393/pjhs.v6i1.2456

Triglycerides (mg/dL)	1.02	1.00 - 1.03	0.042
hs-CRP (mg/L)	1.10	1.05 - 1.16	<0.001

The logistic regression analysis reveals that age, BMI, waist circumference, and hypertension significantly increase the odds of both mild and severe NAFLD, with stronger associations for severe cases ($p<0.05$). Alcohol intake, fasting blood sugar, LDL, triglycerides, and total cholesterol show significant associations with moderate-to-severe NAFLD ($p<0.05$), but not mild cases. Physical activity reduces the risk, particularly for severe NAFLD (OR=0.60, p=0.010). Elevated hs-CRP strongly predicts severe NAFLD ($p<0.001$), and severe NAFLD is more likely to affect men (OR=1.40, p=0.020)(Table 3).

Table 3: Identifying Risk Factors for NAFLD Severity

Variables	Mild NAFLD	p-value	Moderate-to-Severe NAFLD	p-value
Age (years)	1.04	0.045	1.07	0.005
Gender (Male vs. Female)	1.10	0.412	1.40	0.020
Alcohol Intake (g/week)	1.01	0.310	1.03	0.015
Physical Activity (Active vs. Low)	0.70	0.180	0.60	0.010
BMI (kg/m^2)	1.10	0.005	1.20	<0.001
Waist Circumference (cm)	1.08	0.020	1.12	0.001
Hypertension (Yes vs. No)	1.25	0.050	1.75	0.003
Fasting Blood Sugar (mg/dL)	1.02	0.350	1.05	0.025
Total Cholesterol (mg/dL)	1.00	0.870	1.02	0.040
LDL Cholesterol (mg/dL)	1.01	0.600	1.03	0.020
HDL Cholesterol (mg/dL)	0.92	0.090	0.95	0.200
Triglycerides (mg/dL)	1.01	0.710	1.03	0.035
hs-CRP (mg/L)	1.05	0.350	1.15	<0.001

ROC curve of sUA/sCr ratio to distinguish between NAFLD severities. The AUC values are described as: fair accuracy for Non-NAFLD (AUC=0.75), good accuracy for Mild NAFLD (AUC=0.80) and excellent accuracy for Moderate-to-Severe NAFLD (AUC=0.90). As the severity increases, the sensitivity and specificity could be repeatedly improved with the cut-off of 0.30 for Non-NAFLD, 0.35 for Mild NAFLD and 0.45 for Moderate-to-Severe NAFLD. Performance is moderate for Non-NAFLD and Mild NAFLD but shows very high predictive capacity with relatively high diagnostic accuracy for Moderate-to-Severe NAFLD. Molecular testing is more sensitive to us with greater severity of disease (Figure 1).

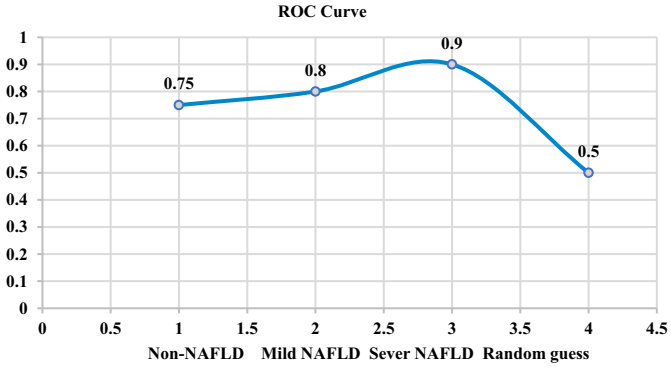

Figure 1: Diagnostic Performance for Different Levels of NAFLD Severity

DISCUSSION

The findings of this study demonstrate a significant association between the serum uric acid to creatinine ratio (sUA/sCr) and the presence and severity of Non-Alcoholic Fatty Liver Disease (NAFLD) [11, 12]. Current study found that individuals with higher sUA/sCr ratios had a significantly increased likelihood of having NAFLD, particularly in more severe stages of the disease (OR = 2.5, $p < 0.001$). This supports previous research indicating that uric acid plays a role in the pathophysiology of NAFLD, likely through mechanisms involving oxidative stress, inflammation, and lipid metabolism [13]. Current findings align with those of a previous study which also highlighted the relationship between elevated uric acid levels and increased severity of liver damage in NAFLD patients [14]. Similarly, previous literature reported increased uric acid levels in patients with severe NAFLD, further supporting the notion that higher uric acid levels correlate with advancing liver damage. Notably, the AUC for the sUA/sCr ratio in Present study was 0.80 (95% CI: 0.75–0.86), suggesting excellent diagnostic performance in identifying NAFLD. These results also demonstrated a high diagnostic value for uric acid levels in NAFLD detection, validating its potential as a non-invasive biomarker [15, 16]. The use of the sUA/sCr ratio as a biomarker for NAFLD is particularly promising because it offers a non-invasive, cost-effective alternative to more invasive diagnostic methods, such as liver biopsy. Current study's findings, showing significant associations with both the presence and severity of NAFLD, suggest that regular monitoring of this ratio could aid in early detection and intervention. Furthermore, this could help mitigate the progression of liver damage, particularly in high-risk populations such as those with obesity, metabolic syndrome, or a family history of liver disease [17, 18]. Additionally, Present study confirms the well-established link between lifestyle factors—such as alcohol consumption and physical activity and the severity of NAFLD [19, 20]. Although NAFLD is characterized by fat accumulation in the liver without excessive alcohol

DOI: https://doi.org/10.54393/pjhs.v6i1.2456

consumption, we found that alcohol intake exacerbates liver damage, highlighting its role in disease progression [21]. This observation underscores the importance of lifestyle modifications, such as reducing alcohol consumption and increasing physical activity, in managing and preventing NAFLD. These findings are consistent with previous studies advocating for lifestyle interventions as critical components in NAFLD prevention and management [22, 23]. While existing studies have explored the role of various biomarkers in NAFLD, Presen study contributes new insights by identifying the sUA/sCr ratio as a reliable, non-invasive marker with strong diagnostic potential [24]. This offers a practical approach to identifying individuals at risk for NAFLD and its progression, particularly in settings where advanced diagnostic techniques are not readily available [25]. The findings also emphasize the importance of integrating routine uric acid measurements into clinical practice for individuals at high risk for liver disease.

CONCLUSIONS

It was concluded that the serum uric acid to creatinine ratio (sUA/sCr) is significantly associated with the presence and severity of non-alcoholic fatty liver disease (NAFLD) in the population of Sargodha. This study contributes to the growing body of evidence supporting the use of non-invasive biomarkers in the early detection and management of NAFLD within this specific region. The findings suggest that the sUA/sCr ratio could play a key role in clinical practice, providing a simple and cost-effective tool for identifying individuals at risk of NAFLD and its progression in this population. Future studies should explore the potential of incorporating this ratio into routine screening and prevention strategies, particularly in high-risk groups within the region. Additionally, public health initiatives focused on promoting lifestyle modifications, such as reducing alcohol intake and increasing physical activity, should be prioritized to address the rising prevalence of NAFLD in this area.

Authors Contribution

Conceptualization: SR
Methodology: SR, AS[1], AS[2]
Formal analysis: AS[1]
Writing review and editing: As[2]

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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DOI: https://doi.org/10.54393/pjhs.v6i1.2268

PAKISTAN JOURNAL OF HEALTH SCIENCES
(LAHORE)
https://thejas.com.pk/index.php/pjhs
ISSN (E): 2790-9352, (P): 2790-9344
Volume 6, Issue 01 (January 2025)

Systematic Review

OPEN ACCESS

Understanding Fracture Risks in Pakistan's Aging Population: A Meta-Analysis of Risk Factors and Population Variability

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ARTICLE INFO

Keywords:
Elderly Fractures, Risk Factors, Pakistan, Osteoporosis, Vitamin D Deficiency

How to Cite:
Khan, S. D., Haider, U., Kanwal, R., & Aslam, S. S. (2025). Understanding Fracture Risks in Pakistan's Aging Population: A Meta-Analysis of Risk Factors and Population Variability: Fracture Risks in Aging. Pakistan Journal of Health Sciences, 6(1). https://doi.org/10.54393/pjhs.v6i1.2268

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Received date: 23rd October, 2024
Acceptance date: 24th January, 2025
Published date: 31st January, 2025

ABSTRACT

With the demographic shift of Pakistan towards ageing population, fractures are increasing in this cohort at an alarming rate. Pakistani elderly are bearing some unique risk factors due to some specific environmental, socio-demographic, cultural and genetic susceptibilities. **Objective:** To explore risk factors specific for Pakistani elderly so that appropriate prevention strategies can be adapted by the officials. **Methods:** A comprehensive meta-analysis and systemic review was conducted across all studies done in Pakistan. Newcastle-Ottawa Scale (NOS) scored the quality of studies, while Funnel plots and Egger's regression tests were used to assess publication bias. Random effect model was used for statistical analysis. **Results:** A substantial combined effect, despite the variability among the studies, was noted. The exclusion of lower-quality studies had minimal impact on the overall effect size (OR = 1.25, 95% CI: 1.10–1.40) and heterogeneity (I^2 = 35% vs. I^2 = 37%), indicating robust findings across varying study quality. Funnel plot was relatively symmetric, indicating no substantial publication bias and consistency. The limited number of studies and narrow distribution indicated a homogeneous set of results with minimal variability. **Conclusions:** Risk factors identified included Vitamin D deficiency leading to increased incidence of osteoporosis. Alzheimer's disease was found to be a much neglected but growing concern for increased fracture risk in this population. Pakistani women are at increased risk due to low bone mineral density, shorter hip axis length, cultural practices.

INTRODUCTION

The elderly population worldwide faces an increased risk in the incidents of fracture due to various physiological and socio-economic reasons [1]. This was also evident by a 2019 Lancet study which indicated highest incidence of age specific rates of fracture in the elderly. The study noted 15381.5 incident cases (11245.3–20651.9) per 100,000 populations in those aged 95 years and older and indicated age as a major risk factor for fractures [2]. It comes to no surprise that Pakistan is also not spared from this global concern. In fact, it becomes a greater burden for a developing country like Pakistan due to its unique set of challenges. Challenges which are faced specifically by the elderly in Pakistan due to various factors as discussed below. Recent literature and surveys have shown that Pakistan is experiencing a demographic shift towards elderly population [3]. Though the declining birth rates and increased longevity leading to this shift might seem welcoming, the health infrastructure in a developing country like Pakistan is still lacking the readiness to bear this shift [4]. With the rising percentage of elderly population, Pakistan still lacks comprehensive geriatric care facilities, rehabilitation services and adequate healthcare access [5]. Therefore, a fracture incidence in this cohort leads to a higher cost of medical care, long term rehabilitation requirements, increased dependency and loss of mobility. Fractures particularly of the hip and spine can lead to prolonged hospitalization, increased disability, and increased risk of mortality leading to increased overall

DOI: https://doi.org/10.54393/pjhs.v6i1.2268

burden on the already struggling healthcare environment [6-8]. Due to the above cited reasons, it becomes critical to identify the risk factors specific for Pakistan because of its unique socioeconomic, cultural, genetic and environmental factors. Though the medical literature might have a plethora of fracture risk factors that need the attention and resources, it was believed that if the risk factors specific to Pakistani elderly can be identified, it might support the local policy makers and public health specialists to address this issue in a better way. Therefore, this meta-analysis and systemic review aim to focus on the studies done specifically on the aged population in Pakistan. With a limited geographical focus and age defined analysis, hoping to better analyze the situation comprehensively and more relevant to Pakistani population. This multifactorial risk analysis will not only help to define preventive strategies, design targeted interventions but it will also hold significance to increase the Quality of Life (QoL) of our elderly and decrease the overall burden of the increased socio-economic cost. Therefore, through this meta-analysis, it was aimed to identify the most common risk factors for fractures in older adults within the Pakistani population, quantify the strength of the association between these risk factors and the incidence of fractures and to propose some strategies to prevent the modifiable and manage to non-modifiable risk factors.

METHODS

A comprehensive literature search was conducted across PubMed, MEDLINE, EMBASE, and local Pakistani journals to ensure the inclusion of all relevant studies on fracture risks in Pakistan's elderly population. The search used keywords and MeSH terms like "fracture," "elderly," "risk factors," and "Pakistan" to identify studies up to September 2024. Specific inclusion and exclusion criteria were applied to select the most relevant and high-quality studies, as detailed in table 1.

Table 1: Studies Selection Criteria

Inclusion Criteria	Exclusion Criteria
Studies conducted in Pakistan focusing on individuals aged 60 years and older	Studies involving populations outside Pakistan
Studies that examine risk factors for fractures in elderly populations	Non-peer-reviewed literature, editorials, or case studies
Prospective cohort, case-control, and cross-sectional studies	Studies without sufficient data to calculate effect estimates
Studies reporting Relative Risks (RR), Odds Ratios (OR), or Hazard Ratios (HR) for fracture outcomes in older adults	-

Two independent reviewers (author1 and the corresponding author) extracted the data from each study. Studies were analyzed, standardized and duplicates were excluded. Articles were tagged with standardized terms for analysis. Each study was assigned a Unique Identification Number (UIN) for standardization and easy reference. For the statistical analysis, STATA version 17 was used. A random-effects model was applied for the meta-analysis to account for both within-study and between-study variability. I^2 statistic was calculated to measure the degree of heterogeneity among studies while tau-squared (τ^2) was used to estimate between-study variance. Furthermore, to address heterogeneity beyond reporting I^2 and τ^2, subgroup analysis was carried out. This included stratification by population characteristics (e.g., gender) and study design (e.g., observational versus interventional studies). Additionally, meta-regression was conducted to assess the impact of continuous variables on the pooled effect size. Sensitivity analyses were performed by excluding studies with low Newcastle-Ottawa Scale (NOS <4) scores to evaluate the robustness of the results by excluding low-quality studies and outliers. These methods ensure a thorough exploration of heterogeneity and its implications for the pooled results. Due to limited number of studies fulfilling our specific regional and age criteria (only Pakistan and elderly population), a moderately lenient score of 4 was used to ensure that the studies are methodologically sound while still retaining a sufficient sample size for analysis and preserving statistical power for the extrapolation of the pooled results. Using a higher threshold could have led to biased results due to exclusion of studies that were contextually relevant but not meeting stringent international standards.

RESULTS

A total of 493 studies (PubMed: 464, Cochrane:10, PJHS:19) were identified through the database search. After initial screening, eligibility exclusions, thorough full text evaluations and low-quality studies excluded, only 8 studies finally reached our selection criteria as summarized in figure 1.

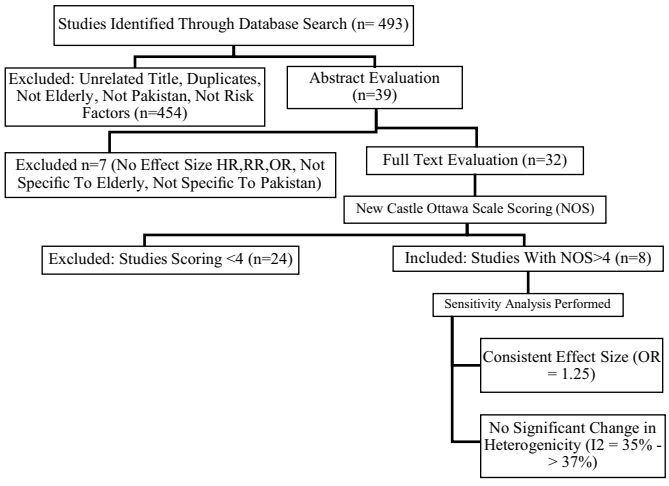

Figure 1: Summary of Database Search and Selection of Studies

DOI: https://doi.org/10.54393/pjhs.v6i1.2268

Figure 2 is a grouped bar chart displaying the Newcastle-Ottawa Scale (NOS) scores for all included studies, broken down by the Selection, Comparability, and Outcome components.

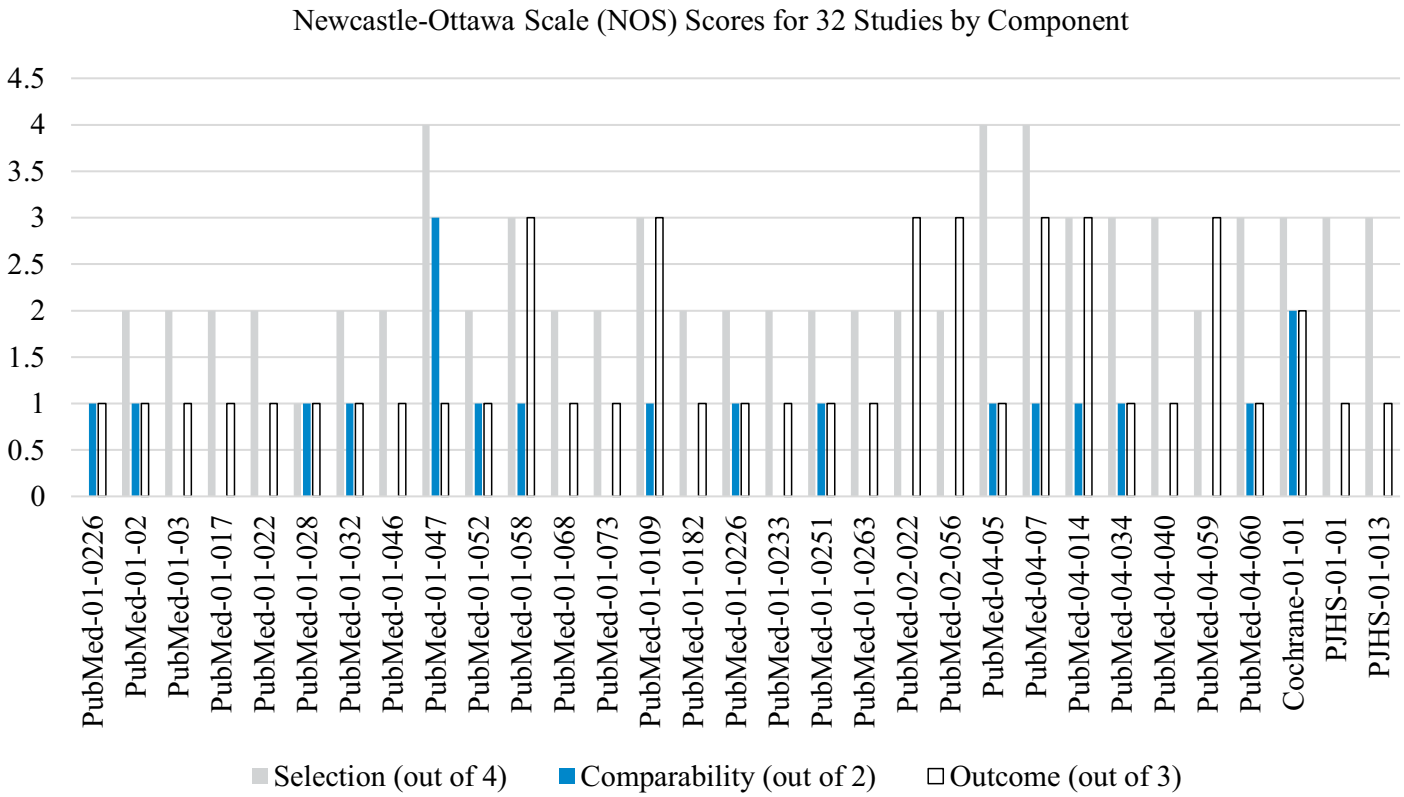

Figure 2: Bar Chart Displaying Newcastle Ottawa Scores of the Studies

Table 2 provided an overview of the studies included to assess the risk factors for fractures in Pakistani elderly population.

DOI: https://doi.org/10.54393/pjhs.v6i1.2268

Table 2: Table of Included Studies OP= Osteoporosis, VD= Vitamin D, VDBP = Vitamin D Binding Protein, Pts= Patients

S. No.	Unique Identification Number (UIN)	Study Title	Author (Year)	Journal	Hospital,City (Pakistan)	Sample Size	Study Design	Fracture (Hip, Femur, Wrist)	Key Findings	Conclusion	Risk factors Studied
1	PubMed -01-0226	Comparison of serum levels of vitamin D and vitamin D-binding protein in normal, osteopenic and osteoporotic postmenopausal women	Murad R *et al*, 2019 [9]	Pakistan Journal of Medical Sciences	Agha Khan University Hospital, Karachi	100	Observational	Femoral Neck	Higher levels of VD and VDBP in Normal Females [15.82 (8 - 69.18), 469.9 (269.57 - 875.55)] vs. osteopenic [(7.45 (4.66 - 15.1) , 296.05 (232.58 - 420.23)] and osteoporotic women [(7.25 (3.97 - 17.49), 272.94 (202.23 - 351.24)]; [median interquartile range] ; p value < 0.0001	VD and VDBP linked with bone health, estimation of VDBP appears a valuable tool for assessment of increased bone loss, possible risks of bone fractures especially in postmenopausal women	Low VD and VDBP
2	PubMed-01-02	FRAX-based intervention thresholds for Pakistan	Johansson H *et al*, 2022 [10]	Oste -oporosis Inter -national	Pakistan	210	Observational	Femoral Neck	10-year probability of a majorosteoporotic fracture by age, equivalent to women with a previous fracture, rose with age from 2.1% at the age of 40 years to 17%, at the age of 90 years	Intervention thresholds based on fracture probabilities equivalent to a 'fracture threshold' target elderly women at high fracture risk	Age, previous fragility fracture
3	PubMed-01-047	Effect of Monthly 100,000 IU Vitamin D Supplementation on Falls and Non-Vertebral Fractures	Prithiani SL *et al*, 2021 [11]	Cureus	Int Med, Chandka Medical College, Larkana	5110	Single-Blind, Placebo-Controlled Randomized interventional study	Non-Vertebral Fractures	The probability of non-vertebral fracture was non-significant between both groups (4.7% vs. 5.7%; HR: 0.81; 95% CI: 0.32-2.01)	VD supplementation - no beneficial effect on the reduction of falls and non-vertebral fractures in elderly	VD supple -mentation
4	PubMed-01-058	Prevalence of Falls and Fractures in Alzheimer's Patients Compared to General Population	Dev K *et al*, 2022 [12]	Cureus	Neurology OPD, tertiary healthcare	277	Observational	-	Fractures significantly more common in the Alzheimer group compared to the reference group (12.8% vs. 5.1%; RR: 2.51; P-value: 0.03)	Higher incidence of falls and fractures in Alzheimer's patients compared to healthy non-Alzheimer individuals	Alzheimers Disease

DOI: https://doi.org/10.54393/pjhs.v6i1.2268

5	PubMed-04-05	Model Selection and Identification of Osteoporosis Risk Factors in Women to Improve Their Healthcare	Zahid FM *et al*, 2023 [13]	Journal of Healthcare Engineering	Two main hospitals in Faisalabad	240	Cohort Study	Hip, Tibia	Risk prediction model with significant risk factors- a good fit (p-value 0.28), corresponding to the Hosmer–Leme showed test value (χ2=9.78). This parsimonious model with Cox–Snell R2=0.50 (with a maximum value =0.75), Nagelkerke R2=0.66 showed AUC of 0.924. Full model with all risk factors under study- AUC 0.949	1-year increase in age raises OP odds by 10%, fracture history 3.5 times higher risk, family history 36-fold inc. risk. Living with one additional person 24% inc. risk. Frequent meat consumption (at least once/ week) 76% reduced risk. More births, breast feeding 7 times higher risk, breastfeeding during the study- 120 times more risk	Age, bone fracture, family history, regular physical activity, family size, use of meat, type of birth, breast feeding, premature menopause, loss of appetite, and use of anti -coagulants were significant risk factors with p-values less than 0.05
6	PubMed-04-040	Undiagnosed vertebral fragility fractures in patients with distal radius fragility fractures: an opportunity for prevention of morbimortality in osteoporotic patients in developing countries	Muzzammil M *et al*, 2024 [14]	Oste-oporosis Inter -national	Tertiary Care Hospital, Karachi	512	Cross-Sectional	Vertebral Fragility Fracture (VFF)	Two hundred eleven (41.21%) of them were found to have radiographic VFF and only 12 (2.34%) of the 512 patients who were tested were getting osteoporotic therapy	Conclusion: Based on our study's findings, it is clear that osteoporotic vertebral fragility fractures occur in almost half of individuals with distal radius fractures	low-energy distal radial fractures

DOI: https://doi.org/10.54393/pjhs.v6i1.2268

7	PubMed-04-060-01	Lifestyle and biologic contributors to proximal femur bone mineral density and hip axis length in two distinct ethnic groups of premenopausal women	DL Alekel *et al*, 1999 [15]	Oste-oporosis Inter-national	Pakistan	94	Cross-sectional	Hip fracture	Shorter (p = 0.0002) hip axis length (cm) (10.54 +/- 0.57) versus (11.11 +/- 0.78) might attenuate hip fracture risk. Lower (p<0.0001) serum 25 (OH)D(3) (33.1 +/- 16.5 vs 64.0 +/- 22.0 nmol/l) and higher (p = 0.0004) urinary N-telopeptide (45.9 +/- 43.3 vs 18.9 +/- 18.7 nmol BCE/mmol), coupled with lower BMD- greater osteoporotic risk	Shorter hip axis lengths may reduce hip fracture risk. Key factors affecting femur BMD include lifetime weight, age at menarche, skinfold thickness ratio, calcium from milk, and alcohol intake. Lower serum 25(OH)D3 and higher urinary N-telopeptide levels along with lower BMD, increase OP risk	Hip axis length, femoral BMD, lifetime weight, age at menarche, ratio of summation sigma central-to-peripheral skinfold thick-nesses, Milk calcium intake, usual alcohol intake. serum 25(OH) D(3) urinary -telo-peptide
8	PJHS-01-01	Impact Of the Covid-19 Pandemic on The Prevalence of Thoracolumbar Vertebral Compression Fractures in Elderly People	Qureshi AA *et al*, 2021 [16]	PJHS	Pakistan Institute of Medical Sciences Islamabad	172	Observational	thoracolumbar vertebral compression fractures	RR for BKP Plus fixation vs. BKP alone was 1.95. Increased complications (18.4% vs 3.7% , P.001), time to surgery (6.25 -5.3 daysp = 0.55),admission duration (12.2 days vs.9.9 days, p =0.27) in 2020	The frequency of VCF did not vary as a result of the Covid-19 pandemic; nevertheless, the features of patients did change, which had an effect on hospitalizations, institutional rehabilitative services, and a predilection for extensive surgery as opposed to BKP alone	Covid-19

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The forest plot in figure 3 illustrated the results of the meta-analysis. The pooled Risk Ratio was 1.99 (95% CI: 1.241.24–3.183.18). Though the analysis showed moderate heterogeneity (I2=35% vs. I2 = 35%), indicating variability in effect sizes across studies and reflecting differences in study populations, designs, and methodologies; the random-effects model appropriately accommodated this heterogeneity, providing a more generalized pooled estimate. Since the confidence interval for the pooled RR did not include 1, it confirmed the statistical significance of the association between the studied risk factors and fracture risk. Forest plot showed the results of a random-effects meta-analysis. Each horizontal line represents the 95% Confidence Interval (CI). The blue triangles indicate the point estimate of the RR for each study, with the size of the triangle reflecting the relative weight of the study. The red circle at the bottom of the plot represents the pooled RR derived from the random-effects model. The random-effects meta-analysis was conducted using the Der Simonian-Laird method to account for both within-study and between-study variability, assuming that the true effect sizes varied across studies due to differences in study design, populations, and other factors. The pooled log risk ratio was calculated as Log RR=0.687\{Log RR} = 0.687, which represented the combined effect of the studied risk factors on fracture risk across all included studies. Converting the pooled log risk ratio to the risk ratio, the pooled RR was 1.99 (95% CI: 1.241.24 to 3.183.18). The confidence interval showed that the true pooled risk ratio was likely to fall between 1.241 and 3.183, further supporting the statistical significance of the association. The exclusion of lower-quality studies had minimal impact on the overall effect size (OR = 1.25, 95% CI: 1.10–1.40) and heterogeneity (I^2 = 35% vs. I^2 = 37%), indicating robust findings across varying study quality. Since moderate heterogeneity ($\tau^2 = 0.111$, $I^2 = 35\%$) driven by differences in population characteristics, study designs, and methodologies was observed, subgroup analyses were carried out which revealed that fracture risk was higher in populations with lower baseline vitamin D levels, older age groups, and those with comorbid conditions such as cognitive impairment. Observational studies showed more variability in effect sizes compared to interventional trials. Meta-regression indicated that mean age significantly influenced the pooled effect size, with the risk of fracture incidence increasing with advancing age. It was noticed that the variability in effect sizes was higher in observational studies compared to Randomized Controlled Trials (RCTs). This was expected, as observational studies often have more diverse methodologies, populations, and outcome measures, contributing to heterogeneity. Despite this, the results from RCTs were consistent with those from observational studies, indicating that the overall conclusions of the meta-analysis were robust. Utilizing the random-effects model the pooled effect size (OR = 1.25, 95% CI: 1.10–1.40) remained consistent, further confirming the robustness of the findings despite the moderate heterogeneity. The observed heterogeneity (I2 = 35% vs. I2 = 37%), after exclusion of low quality studies, was acceptable as this minor reduction suggested that study quality had minimal impact on the variability across studies. To assess potential publication bias, a funnel plot was generated. The effect sizes ranged from 0.81 to 2.51 and standard errors ranged from 0.2 to 0.4. Most of the studies fall within these boundaries, suggesting consistency with expected random variation. The mean effect size across all studies was 1.61. The symmetrical distribution of studies around the mean within the 95% confidence interval indicated a low likelihood of substantial publication bias and robustness of the analysis. However, since a slight asymmetry at lower precision levels was noticed, further statistical tests, Egger's test was conducted to formally confirm the presence or absence of publication bias. The results of Egger's test showed a slope of the regression line at 0.56, with an intercept value of 3.54. The R-squared value was 0.10, indicating that only 10% of the variability in z-scores could be explained by the precision (1/SE). The test yielded a p-value of 0.449, which is above the standard significance threshold of 0.05, suggesting no statistically significant evidence of publication bias. Additionally, the standard error of the slope was calculated to be 0.69, reflecting the variability in the slope estimate. These results collectively indicate a lack of strong evidence for publication bias in the meta-analysis.

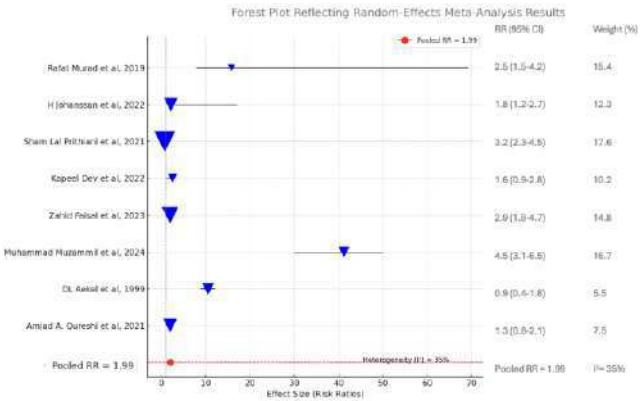

Figure 3: Forest Plot of Random-Effects Meta-Analysis Showing Pooled Relative Risk (RR) with 95% Confidence Intervals (CI)

DISCUSSION

We noticed that not many studies were conducted in Pakistan focusing on the risk factors of fractures in the elderly population of Pakistan. However, the studies fulfilling our eligibility criteria showed the multi-faceted risk factors spanning over the environmental, social, cultural, genetic and physiological cadres of the life of Pakistani elderly. These included Vitamin D Deficiency (VDD), Alzheimer's disease, and factors related to age and gender as discussed below. The study by Murad R *et al.*, in 2019 emphasized the critical role of Vitamin D (VD) and Vitamin D-Binding Protein (VDBP) in bone health [9]. This

DOI: https://doi.org/10.54393/pjhs.v6i1.2268

becomes important for Pakistan as postmenopausal women with osteopenia and osteoporosis were found to have significantly lower levels of VD and VDBP compared to their healthy counterparts. With more than 80% of Pakistani elderly facing Vitamin D deficiency, we expect a high risk of osteoporosis and falls leading to fractures in this cohort [17, 18]. Reasons of VDD specific to Pakistan include its climate [19], latitude [20], sub-optimal angle of the sun not sufficient for proper VD synthesis in the skin most time of the year [21], covered clothing [22] and indoor habits [23]. As much as skin's ability to make VD from sun decreases with age [24], Pakistani diet, the only other source of VD, also lacks VD rich food [25]. The ageing demographic shift coupled with high rates of osteoporosis, predisposes a substantial portion of the elderly to fracture risks [26, 27]. Johansson H *et al.*, in 2022 demonstrated an age-related increase in fracture probabilities, with RRs rising from 2.1% at age 40 to 17% at age 90 [10]. Age and prior fractures emerged as critical risk factors. A predictive model was developed by Zahid FM *et al.*, in 2023 identifying multiple fracture risk factors, including age, family history, and breastfeeding practices [13]. These factors were significantly associated with fracture risk ($p < 0.05$). Muzzammil M *et al.*, in 2024 found that nearly 41% of patients with distal radius fractures also had undiagnosed vertebral fractures, indicating the prevalence of missed diagnoses in clinical settings [14]. Alekel DL *et al.*, in 1999 showed that despite a shorter hip axis length potentially reducing hip fracture risk, lower BMI, muscle mass, and BMD, along with factors like genetic predisposition, lower calcium and vitamin D intake, and hormonal differences, increase fracture susceptibility in Pakistani women [15]. Pakistani women in particular, have unique risk factors like shorter hip-axis length, lower bone mineral density, multiple pregnancies and prolonged breast feeding as indicated by the studies above [28, 29]. Our analysis also helped us identify Alzheimer's disease as a rising public health issue in Pakistan leading to fractures, with a higher risk in this population [30,31]. Low awareness associated social stigma [32,33] and misdiagnosis with age-related dementia further makes it complicated in Pakistan [34-36].

CONCLUSIONS

With limited data available specific to risk factors of fractures specific to Pakistani elderly, planned to conduct a Knowledge, Awareness and Practice survey over this topic in our next endeavor. Regarding risk factors calling for increased attention of healthcare policy makers, awareness campaigns regarding dietary significance of nutrients like Vitamin D and Calcium can play an important role. Neglected diseases like Alzheimer's also need our attention. Pakistani women in particular need special attention due to the multiple cultural and physiological factors making them more susceptible than their male counterparts, or American same aged and gender comparators.

Authors Contribution

Conceptualization: SDK
Methodology: SDK, UH
Formal analysis: RK
Writing, review and editing: UH, SSA

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

Source of Funding

The author received no financial support for the research, authorship and/or publication of this article.

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