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Abstract should include a brief content of the article. It should be structured and not more than 250 words. It should include following sub headings: Objective, Methods, Results and Conclusions.

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INTRODUCTION
Provide a context or background for the study (i.e.,the nature of the problem and its significance). State the specific purpose or research objective, or hypothesis tested the study or observation; the research objective is often more sharply focused when stated as a question. Both the main and secondary objectives should be made clear and any pre-specified subgroup analysis should be described. Give only strictly pertinent references and do not include data or conclusions from the work being reported.

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The methods section should include only information that was available at the time or plan of the protocol. All information gathered during the conduct of study should be included in the result section.
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Cook NR, Rosner BA, Hankinson SE, Colditz GA. Mammographic screening and risk factors for breast cancer. American Journal of Epidemiology. 2009 Dec;170(11):1422-32. doi: 10.1093/aje/kwp304.

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Conclusion should elucidate how the results communicate to the theory presented as the basis of the study and provide a concise explanation of the allegation of the findings.

ACKNOWLEDGEMENT

Provide the list of individuals who contributed in the work and grant details where applicable.

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Breaking Boundaries: Advancements in Stem Cell Therapy for Lymphoma

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Stem cell transplantation (SCT) has broken significant boundaries, marking a pivotal advancement in oncology. Healthcare professionals use stem cell transplantation methods to treat blood disorders or various kinds of cancer or autoimmune diseases. SCT may be used if other treatments aren't effective or if blood cancer comes back (recurs). Lymphoma is a type of cancer that affects the immune system. It refers to a collection of cancers originating from lymphocytes, a type of white blood cell found in the lymphatic system. The lymphatic system is a network of body germs and a disease-fighting immune system. Hematopoietic stem cells are found in bone marrow. They are immature cells that are capable of dividing and producing more blood-forming stem cells or mature blood cells that circulate in the bloodstream.

Patients undergoing stem cell transplants go through intensive chemotherapy before treatment. For individuals with lymphoma, a combination of radiation and chemotherapy frequently eradicates the cancerous white blood cells within the body. Regrettably, these treatments also eliminate some healthy cells, including the patient's stem cells.

High-dose chemotherapy can effectively eliminate cancer cells, but it is not generally administered alone, because the body requires a sufficient number of stem cells to regenerate blood. Healthcare professionals will evaluate whether a person will manage stem cell transplantation side effects or not. There are two primary types of SCT: autologous (uses the patient's stem cells, which lower the risk of graph-versus-host-disease) and allogeneic (the donor is genetically similar to the patient but with a higher risk of graph-versus-host-disease).

When donated cells successfully engraft in the patient, they become part of the patient's immune system and target the remaining cancerous cells. It is one of the benefits of allogeneic stem cell transplantation. This condition is known as the graph-versus-lymphoma effect (GVLE). However, in certain instances, the donor's stem cells may erroneously attack the patient's healthy cells and tissues, resulting in graft-versus-host disease (GVHD).

Ongoing research focuses on strategies to mitigate GVHD while preserving its beneficial graph versus tumor effects by enhancing the new conditioning regimens and transplant protocols. SCT represents a transformative leap forward in lymphoma treatment and offers new avenues of hope for patients facing a challenging diagnosis. As medical technology and research continue to advance, SCT in lymphoma treatment remains promising, with enhancing efficacy, minimizing complications, and improving quality of life.

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Original Article

Hypertriglyceridemia in Patients with Ischaemic Heart Disease

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ABSTRACT

Cardiovascular Diseases (CVD) have been the main cause of mortality in non-communicable diseases. Managing hypertriglyceridemia is crucial for lowering the risk of cardiovascular disease. **Objective:** To find out the frequency of increased triglycerides in the local population of patients with ischemic heart disease. **Methods:** A descriptive study design was conducted from October 16, 2020, to April 15, 2021, at the Lady Reading Hospital Department of Medicine in Peshawar. A total of 182 patients were enrolled using non-probability consecutive sampling calculated by WHO sample size calculator, with ages being of 20 years and 60 years, irrespective of gender. The presence or absence of hypertriglyceridemia was stratified according to different age groups, gender, height, weight, Body Mass Index (BMI), presence/absence of hypertension, diabetes and smoking history and a level of 150 mg/dl was deemed necessary to confirm the existence of hypertriglyceridemia. Post-stratification chi- squared test was applied in which a p-value of ≤0.05 was considered significant. **Results:** The average age, weight, height and BMI were 50 ± 7.5 years, 75.14 ± 5.8 kg, 172.89 ± 6.4 cm and 25.204 ± 2.29 kg/m^2 respectively. Patients with the history of diabetes, hypertension and smoking were 32.4%, 47.3%, and 40.1% accordingly and when comparing these parameters with hypertriglyceridemia produced highly significant results (p-value 0.001- 0.002). **Conclusions:** It was concluded that patients with history of smoking, hypertensions and BMI of more than 25kg/m^2 are more likely to have hypertriglyceridemia, and hence more likely to be linked to cardiovascular events.

INTRODUCTION

The most frequent fatalities in non-communicable diseases are now because of cardiovascular disease (CVD), with the World Health Organization (WHO) reporting a total of 17.6 million deaths because of CAD [1]. Heart disease, cancer and accidents are the top three causes of death between 2011 and 2018 in a United States (U.S) based study, with 600,000 or more deaths per year from each of these three diseases, cancer and heart disease are likely to continue to be the top two causes, respectively and serve as a sobering reminder of the ongoing social challenges posed by these non-communicable diseases [2]. In a similar instance, ischemic heart disease accounted for 22.7% of fatalities in Pakistan and 27.4% of deaths in India in 2021 [3]. An increase in triglycerides in the blood is referred to as hypertriglyceridemia [4, 5]. Patients with type II diabetes mellitus frequently have hypertriglyceridemia, which has been linked to an increased risk of ischemic heart disease [6, 7]. Triglyceride rich in Very Low-Density Lipoproteins (VLDL), chylomicrons and similar fragments known to be associated with athrosclerosis [8]. Hypertriglyceridemia is one of the risk factors for coronary heart disease in the younger Pakistani population [9]. Consequently, managing hypertriglyceridemia is crucial for lowering the risk of

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cardiovascular disease [10]. In patients with increased triglycerides, medications that lower triglycerides and triglycerides-rich lipoprotein cholesterol may be beneficial to the cardiovascular system [11, 12]. Tobacco consumption, diet of higher saturated fats and less physical activity have been associated with deaths in non-communicable diseases with global mortality being 7.2 million, 3.9 million and 3.2 million respectively; additionally, alcohol consumption, hypertension, hyperglycemia and hypercholesterolemia attributed to 0.32 million, 9.4 million, 3.4 million and 2.0 million global deaths respectively [13]. However, there is scarcity of data regarding the frequency of hypertriglyceridemia in our local population.

We aimed to find out the frequency of increased triglycerides in the local population of patients with ischemic heart disease.

METHODS

A descriptive design was used in the study, which was conducted from October 16, 2020, to April 15, 2021, at the Lady Reading Hospital Department of Medicine in Peshawar, after the approval from the Ethical Review Board (IRB) with Reference Number 459/LRH/MTI. A sample size of 182 with a 95% confidence level and a 5% margin of error were calculated using the WHO sample size methodology. The sample selection process involved non-probability consecutive sampling, with a focus on patients with ischemic heart disease between the ages of 20 years and 60 years, irrespective of gender. After taking written informed consent, a total of 182 patients were enrolled if their medical history suggested they had ischemic heart disease and had symptoms such as chest discomfort, shortness of breath treated with nitrates and confirmed by a coronary angiography, exercise tolerance test, or electrocardiogram. Based on the measurement of triglycerides in the patient's fasting blood sample, hypertriglyceridemia was diagnosed. A level of 150 mg/dl was deemed necessary to confirm the existence of hypertriglyceridemia. The data were analyzed using SPSS version 23.0. Frequencies and percentages were used to describe categorical variables. Mean and standard deviation were calculated for the numerical variables. The presence or absence of hypertriglyceridemia was stratified according to different age groups, gender, height, weight, Body Mass Index (BMI), presence/absence of hypertension, diabetes and smoking history. Post-stratification chi- squared test was applied in which a p value of ≤0.05 was considered significant.

RESULTS

Among the total 182 patients, the average age, weight, height and BMI were 50 ± 7.5 years, 75.14 ± 5.8 kg, 172.89 ± 6.4 cm and 25.204 ± 2.29 kg/m^2 respectively. The gender, age groups and BMI of patients are represented in table 1, with history of diabetes mellitus, hypertension, smoking and hypertriglyceridemia also being represented as shown in table 1.

Table 1: Distribution of Different Parameters in the Study Population

S.No.	Variables		Frequency (%)
	Category	Sub-Category	
1	Gender	Male	136 (74.7)
		Female	46 (25.3)
2	Age Groups	20-40 Years	26 (14.3)
		41-60 Years	156 (85.7)
3	BMI (Kg/m^2)	Healthy (18-25)	84 (32)
		Overweight (25.1-30)	92 (11)
		Obese (>30)	6 (4)
4	Hx of Diabetes Mellitus	-	59 (32.4)
5	Hx of Hypertention	-	86 (47.3)
6	Hx of Hypertriglyceridemia	-	73 (40.1)

BMI-body mass index,
Hx-history

Although comparing age groups, gender and history of diabetes with hypertriglyceridemia did not produce any significant results, yet comparing history of other study parameters produced highly significant (p-value 0.001-0.002) results, represented as shown in table 2.

Table 2: Comparison of Hypertriglyceridemia with the Study Parameters

S.No.	Variables		Hypertriglyceridemia		p-Value
			Present	Absent	
1	Gender	Male	59	77	0.310
		Female	24	22	
2	Age Group	20-40	8	18	0.101
		41-60	75	81	
3	Diabetes	Present	22	37	0.119
		Absent	61	62	
4	Hypertension	Present	57	29	0.001
		Absent	26	70	
5	Smoking	Present	22	51	0.001
		Absent	61	48	
6	BMI	Healthy (18-25Kg/m^2)	31	53	0.002
		Overweight (25.1-30Kg/m^2)	52	40	
		Obese (>30Kg/m^2)	6	0	

BMI-body mass index

DISCUSSION

The association between triglyceride rich particles and coronary ischemic disease was reported for the first time by Gofman and colleagues when they reported a significant increase in the concentration of triglyceride-rich lipoprotein particles in patients with Ischemic Heart Disease (IHD) aged 40 to 59 years compared with age and sex-matched control subjects [14]. In this study, 45.6% of patients with ischemic heart disease had hypertriglyceridemia. The findings of this investigation are

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somewhat better than those of Aryal B and associates' study, which revealed hypertriglyceridemia in 36.48% of ischemic heart disease patients [12]. The higher percentage of male candidates (74.7%) in this study compared to Aryal B *et al.*, study (64% male participation) may be the reason for the higher percentage of hypertriglyceridemia [12]. The distribution of ischemic heart disease in the population is substantially influenced by gender. Gheisari, F *et al.*, show that men had a higher risk of ischemic heart disease than women, with a male to female ratio of 19.1% to 14.2% [15]. Despite the inability of this study to show a significant correlation between hypertriglyceridemia (p-value 0.310), male patients were more likely than female patients to have higher lipid levels because of social, cultural and religious restrictions on physical activity, women in our society burn less calories than men do. This could be the cause of their higher cholesterol levels. Although there was no significant correlation found in this study between age and hypertriglyceridemia (p-value 0.101), there was an increasing trend in the prevalence of hypertriglyceridemia as people aged. Of the 83 hypertriglyceridemia patients in total, 75 patients (90.36%) belonged to the 40-60 age range. Growing older and adopting a more sedentary lifestyle could be the cause of this decrease in physical activity. The decrease in hormone levels that protect against IHD after the age of 50 has an additional effect in female patients. Dyslipidemia prevalence varied considerably with age in a cross-sectional study by Cho SM *et al.*, An increased odds ratio (OR = 2.31, p-value 0.008) for dyslipidemia was seen in the elderly group [16]. A significant correlation between smoking and hypertriglyceridemia was found (p-value 0.001). There has never been a thorough investigation of how smoking and quitting affect lipoprotein levels in a sizable modern smoker population. Two randomized controlled trials found that quitting smoking enhanced HDL-C, total HDL, and large HDL particles even in the face of weight gain, notably in women. LDL or LDL size was not impacted by quitting smoking. Reductions in the risk of cardiovascular disease upon quitting smoking may be partially mediated by increases in HDL [17]. Through risk factors such raised fasting plasma triglycerides, high LDL cholesterol, low HDL cholesterol, elevated blood glucose and insulin levels, and high blood pressure, obesity raises the risk of cardiovascular disease [18]. Similar outcomes were seen in this investigation as well, obesity and hypertriglyceridemia were found to be positively correlated in patients with ischemic heart disease (p-value 0.002). Cardiovascular diseases mediated by triglycerides have been associated with aortic valve stenosis and adverse cardiac remodeling, hence lifestyle modification and pharmacotherapy should be directed towards hypertriglyceridemia and its treatment should reasonably be cost effective [19, 20].

CONCLUSIONS

Hypertriglyceridemia is a frequent finding in patients presenting with ischemic heart disease. It was more commonly observed in patients with advanced age irrespective of the gender of the patient. Patients with history of smoking, hypertension and BMI of more than 25kg/m^2 are more likely to have hypertriglyceridemia.

Authors Contribution

Conceptualization: MKK
Methodology: MKK, MZ, AG, MH
Formal analysis: MKK, MZ, AG, MT, MF
Writing, review and editing: MKK, MZ, AG, MT, MH, MF

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Frequency of Hearing Impairment in School-Going Children of District Hyderabad, Sindh, Pakistan

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ABSTRACT

Hearing impairment is prevalent disability in the general population; early intervention facilitates proper development. Without hearing rehabilitation, hearing impairment can cause detrimental effects on speech, language, developmental, educational and cognitive outcomes in children. **Objective:** This study aimed to document the frequency of hearing impairment in school-aged children of District Hyderabad, Sindh, Pakistan. **Methods:** This cross-sectional study was carried out in school-going children to find out the frequency of hearing loss of district Hyderabad, Sindh, Pakistan. The study was conducted from July 2023 to December 2023. The hearing threshold was assessed by a Type 2 audiometer (Manufactured by, Interacoustics A/S, Denmark). Hearing impairment was defined as ≥ 20 dB Hearing level. The results of hearing levels were independently documented in left and right ears, better and worse ears. The data obtained were analyzed on SPSS version 26.0. Statistical significance was set at $P<0.05$. **Results:** In this study, 1520 school-aged children were recruited. The mean age was 9.56 ± 1.56 years and most of the children were between 8 to 12 (85.7%) years. The frequency of hearing impairment was found 1.97%, and no age difference was found among participants. A positive relationship of neonatal icterus, and otitis media was found in participants. **Conclusions:** In this study, hearing loss was found in 1.97% of the population. It is suggested that the screening of children for hearing impairment is compulsory for diagnosis and treatment.

INTRODUCTION

Hearing loss is an invisible disability present in every region of the world. Approximately 10% of the world population has been affected by Hearing loss to some extent [1]. In developed countries, at birth 3 per 1000 children and > 6 per 1000 children in developing countries are affected. Approximately 1.5 billion people (about 20% of the world population) live with hearing disability. It is estimated that > 700 million people may have a disability of hearing loss by 2050 [2]. Hearing impairment in children is a prevalent condition that can have significant impacts on their development, communication, and overall well-being. According to the World Health Organization, it is expected that approximately 60% of children will experience some degree of hearing loss, spending a third of their time unable to hear within normal thresholds [3]. This can greatly affect their ability to learn and interact with others in school and social settings. Furthermore, research has shown that teachers often overlook the importance of sound quality in classrooms, which further exacerbates the challenges faced by children with hearing loss [4]. This article suggests that there are practical, low-cost actions that teachers can take to improve the hearing environment in

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classrooms, thereby decreasing stress levels for both students and teachers [5]. According to a study conducted in Rasht, Iran, the incidence of hearing loss in elementary school-age children was found to be approximately 2%. The study used audiometry to screen the hearing thresholds of 2019 children. This study found that the frequency rates of hearing loss greater than 15 dB in the low-frequency range (500-8000 Hz) were 1.94% in the right ear and 1.68% in the left ear [3, 5]. Research from Pakistan reported 7.9% of prevalence in school-going children. This research also reported that parents were late in noticing hearing problems in their children, with only 35% reporting it before 6 months, 14.3% between the age of 13-18 months, and the remaining 50.7% even later [6]. Generally hearing loss increases with the increase of age, and it is 3% in people aged 20 to 35, 11% in people aged 44 to 55, and 43% aged 65 to 85 years of age [7]. In adults irrespective of age, extended exposure to loud noise is the major cause of hearing impairment, other causes include wax and ear infections that blockage the ear passage, which cause temporary hearing loss which can be corrected by professional treatment. In most cases, hearing loss may be permanent due to damage to the auditory nerve or inner ear [8]. In particular, the burden of hearing impairment during life is important and it may be worse by harmful attitudes and behavior of the society with the particular individual [9]. Generally hearing loss has negative impacts on interpersonal communications, mental health, quality of life, and economics. In children, unaddressed hearing loss mainly damages the development of language, lack of schooling, social, and mental problems [10]. Continuing these problems in adulthood may cause a decreased connection with society that leads to isolation, anxiety, depression, disgrace, and mental and physical health problems. These individuals find it very hard to develop relationships with partners, and children. These individuals also have limited job opportunities and comparatively low income [11]. Since 2007, the World Health Organization has promoted higher public awareness of hearing loss by World Hearing Day on 3rd March each year. This program aims to decrease the cases of hearing impairment and to better the quality of life of individuals who were suffering from hearing loss [12]. Progress is inadequate in low and middle-income countries because of a lack of capability to coup up the established intervention at all levels healthcare delivery system. This shortening is mostly due to a lack of funding support and initiatives like screening newborns for suspected cases of hearing loss that is mostly carried out in high-income countries [13].

This study aimed to document the frequency of hearing impairment in school-aged children of District Hyderabad, Sindh, Pakistan. It is necessary to identify the early detection that is crucial for timely intervention.

METHODS

This cross-sectional study was conducted in school-going children to find out frequency of hearing loss in the district of Hyderabad, Sindh, Pakistan. After approval from institutional research ethics committee letter no. DRGS/Physio-152. The sample size was calculated by using Epi info software and non-probability convince type of sample was done to collect the data. Inclusion criteria included the participants aged between 6 to 13 years of age, participants who were enrolled in school, participants who were residents of district Hyderabad. Exclusion criteria included those participants who were not aged between 6 to 13 years, not enrolled in schools, not residents of district Hyderabad and diagnosed case ear discharge/ or any disease of ear. A self-designed questionnaire was used to collect the data including sociodemographic, and health status of the participants. Type 2 audiometer used for hearing threshold in participants. The study was conducted from July 2023 to December 2023. Sampling was done using multistage random cluster sampling method from different schools of district Hyderabad. A total of 1700 children were approached aged from 06 years to 13 years old. Informed written consent was taken from parents of all children before recruitment. Parents were volunteers to assess the hearing of their children and to provide necessary information. The response rate was 89.41%. The remaining 10.59% of parents were unwilling to participate in this study hence, the total number of 1520 children recruited in this study (Boys 925 and girls 592). Two sittings were carried out, in the first sitting parents also participated to provide complete information, in the pre-designed questionnaire, and in the second sitting hearing loss were assessed by the audiologist. A general medical examination was conducted by general practitioners; the ear examination was conducted by an ENT specialist with an otoscope. Any foreign material, wax, or impacted debris was removed. Any children having acute or chronic ear infections, or effusion were not included in this study. The audiometry was done in a quiet room of each school with <45 dB noise level. A calibrated Type 2 audiometer (Manufactured by, Interacoustics A/S, Denmark) was used with Radio Ear 3045 earphones and audiocups for extra attenuation. The threshold for hearing level was assessed by the standard of different frequency levels of 500Hz, 1000Hz, 2000Hz, and 4000Hz. Type 2 audiometer was classified into two levels, one is Low-Frequency Pure Tone (LPTA), and the other is High-Frequency Pure Tone (HPTA) and their mean hearing threshold were 0.5-2, and 4-8 kHz, respectively. Hearing impairments were categorized into three groups, including unilateral (less than 20 dB Hearing Level in the better ear and equal or more than 35dB Hearing Level in the bad ear), mild (20 to 34 dB Hearing Level), and moderate (equal or more than35 dB Hearing Level). Hearing loss was classified into sensorineural hearing loss and

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conductive hearing loss if the air-bone gaps were less than 15dB and more than 15 dB, respectively. In mixed types of hearing loss, both air-bone gap and bone conduction thresholds were more than 15 dB. The hearing level was documented in the right and left, and worse and better ears. The frequency of hearing loss was calculated in percentages with a 95% Confidence Interval. Logistic regression tests were used to examine the relationship between hearing loss and possible risk factors. T test was used to measure mean between groups including age, hearing threshold. A P <0.05 considered statistically significance was set. The data obtained were first via Microsoft Excel and later confirmed through SPSS version 26.0.

RESULTS

In this study, 1520 school-aged children including; boys were 755 (49.67%) and girls were 765 (50.32%) recruited. The mean age was 9.56 ± 1.56 years most of the children were between 8 to 12 years (85.7%), and 76% of participants had a history of neonatal icterus in 76 participants (5%), and otitis media was found in 3 participants. In this study, both ears of all participants were assessed; the socio-demographic characteristics were shown in table 1 in which Boys were 755 and Girls were 765.

Table 1: Sociodemographic Characteristics of Participants (n=1520)

Variables	Total	Boys	Girls
Age < 10 Years	990	465	525
Age ≥ 10 Years	530	290	240
Neonatal Icterus	76	11	65
Middle Ear Infection	3	1	2
Family History (Hearing Loss)	113	43	70
Socioeconomic Status			
Moderate to Low	1201	532	669
High	319	118	201
Audiometry (Mean ± SD)			
Mean Audiometry	4.9 ± 3.2	4.9 ± 2.9	5.0 ± 3.3

The frequency of hearing impairment was found 1.97%, a total of 30 participants (i.e., 15 boys and 15 girls). The most common type of hearing impairment was found conductive deafness (unilateral or bilateral). Furthermore, 18 children were found affected with conductive hearing impairment (Unilateral/Bilateral), 10 children were found to have a sensorineural hearing impairment (unilateral/bilateral) and 2 children were found to have a mixed type (Unilateral). Furthermore, one participant had conductive hearing loss in one ear and in other sensorineural hearing loss. Binary logistic regression revealed a significant effect for a history of otitis media (OR=7.9, P=0.008). However, there was no significant effect for age, gender, family history, or socioeconomic status. When the effects of various factors on conductive and sensorineural hearing loss were separately assessed, the results showed only a strong association between the history of otitis media and sensorineural hearing loss (adjusted odds ratio: 11.8; 95% CI 1.4-102.7) as shown in table 2 in which Boys were 925 and Girls were 592.

Table 2: Type of Hearing Loss (n=1520)

Variables	Total	Boys	Girls
Bilateral Conductive	11	4	7
Bilateral Sensorineural	5	3	2
Unilateral Conductive	7	5	2
Unilateral Sensorineural	5	2	3
Unilateral Conductive/ Sensorineural	2	1	1

Depending on the LPTA, in the right ear in 2.1% of children and the hearing level in the left ear in 1.7% of children were equal or more than 20 dB. In HPTA, in the right ear, 1.5% and in the left ear 1.4% hearing impairment was found as seen in table 3.

Table 3: Hearing Levels Depending on HPTA and LPTA among Participants for Right and Left Ears

Audiometry	Normal N (%)	Mild N (%)	≥ Moderate N (%)
Low Frequency			
Right Ear	1488 (97.9)	26 (1.7)	6 (0.4)
Left Ear	1494 (98.3)	21 (1.4)	5 (0.3)
High Frequency			
Right Ear	1497 (98.5)	18 (1.1)	5 (0.4)
Left Ear	1499 (98.6)	15 (1)	6 (0.4)

DISCUSSION

Hearing loss in school-going children can have significant impacts on their academic performance, language development, social interactions, and overall quality of life. The literature review on hearing loss in school-going children provides valuable insights into the frequency, causes, and impact of hearing impairment in this population. It emphasizes the importance of early screening and identification of hearing loss to provide appropriate interventions and support for affected students. The study found that the overall frequency of hearing impairment was 1.97% among the participants, which is relatively low compared to some other studies conducted in different regions and countries. Awais M *et al.*, conducted a study in Lahore that reported an 11.3% prevalence in school-aged children, this higher prevalence may be due to low sample size of only 142 participants [14]. Maharjan M *et al.*, found a 5.37% prevalence in Nepal, this study was conducted in children studying in government schools from grade 1 to grade 10 and also concluded the highest incidence of conductive hearing loss and the main cause documented chronic otitis media. This study was conducted on a larger scale and recruited 79340 participants in 509 different government schools [15]. Jalali MM *et al.*, found similar findings with a frequency of

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1.5% and 1.0%. Consistent with this study documented the same trends and found conductive and sensorineural hearing impairment in 0.9% and 0.4% of participants. In this study, the reduced frequency of hearing impairment may be due to wax in participants who were removed, rescreened and counted as normal. Furthermore, wax was considered a cause of conductive hearing impairment in previous studies [5]. Furthermore, the study found that conductive deafness was the major type of hearing loss, affecting both boys and girls in similar proportions. The study also explored the association between risk factors and hearing loss. The relationship between otitis media and sensorineural or conductive hearing impairment was found to be strong, highlighting the importance of early detection and management of otitis media in children. These results have important implications for the screening and management of hearing loss in school-aged children. Similarly, Intakorn P *et al.*, conducted a study to find an association between a middle ear infection and bacteria in Thailand, and they documented that 18% of the participants were affected with Haemophilus Influenza type b (Hib) in countries of Eastern Mediterranean [16]. However, immunization against Hib is not in the immunized program in Pakistan. It was found that middle ear infection is the major reason for hearing loss in school-aged children. This result was found in consistent with the other studies of underdeveloped countries [17-19]. In this study, there is no significant gender difference; however, the result of this study is not in agreement with the past studies [16]. This result may be recognized as a pattern of exposure to noise-induced hearing loss that requires more investigation. Also, no significant relationship was found between socioeconomic status and hearing impairment. Jalali MM *et al.*, and Youngs R suggested that poor hygiene conditions, decreased vaccination rate and needless consumption of ototoxic drugs were the factors related to hearing impairment [5, 20].

CONCLUSIONS

Hearing impairment in children is a significant health concern that can have detrimental effects on their overall development and well-being. In this study, the overall frequency was 1.97% among school-going children. Also, it is suggested to screen children for hearing through Public Health centers and this should be compulsory medical inspection. This program helps to find hearing impairment in children so that may be further referred to audiological/ otolaryngological assessment. Also recommended for childhood immunization against Haemophilus influenza immunization that may decrease the frequency of childhood hearing impairment due to otitis media.

Authors Contribution

Conceptualization: SAS
Methodology: MAB
Formal analysis: SFM, KA, AR, HS
Writing, review and editing: SAS, SFM, KA

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Role of Fine Needle Aspiration Cytology (FNAC) In Evaluation of Thyroid Nodules

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ABSTRACT

Fine-Needle Aspiration Cytology (FNAC) is a practical and low-cost preoperative method for evaluating thyroid gland neoplasms that provides a correct diagnosis fast and with minimal hazards. Thyroid nodules are communal, being existing in up to 50% of the aged populace. The mainstream are benign with thyroid cancer representing an uncommon clinical problem. **Objective:** To assess the role of FNAC of thyroid gland cancers in our environment and the diagnostic performance of the FNAC in identifying these conditions. **Methods:** A retrospective analysis was conducted on 120 individuals who had thyroid swelling when they were first seen and who had surgery between January 2020 and December 2022. Patients with findings from postoperative surgical histopathology and preoperative fine needle aspiration cytology were included in the research. The FNAC's diagnostic accuracy, positive and negative predictive values, sensitivity, and specificity were all calculated. **Results:** Out of 120 patients, 18(15%) were male and 102 (85%) were female. Out of 120 cases, by histopathological examination FNAC showed 79 cases as benign and 41 cases as malignant lesions. **Conclusions:** According to this research, FNAC is a reasonably accurate approach for identifying thyroid gland cancers, with good sensitivity and specificity. Thus, it can be a useful resource for preoperative counselling on the characteristics of the neoplasms and their outcomes as well.

INTRODUCTION

In the general population, 4%–5% of people have thyroid swellings that are clinically noticeable [1]. The majority of these enlargements are benign in origin, with goiter being the most prevalent. More than 40 million people in India and more than 2 billion people worldwide suffer with goiter [2]. Thyroid cancer in nodules is found in people ranging from 0.1% in the general population to 20% in nodules that are surgically biopsied. With an annual incidence of 1-2/100,000, thyroid cancer accounts for 0.5% of cancer-related deaths, 1% of all human cancers and 90% of all endocrine system cancers [3]. Across the world, thyroid nodules are a common clinical issue. Alongside establishing the presence of thyroid nodules and evaluating their size, texture and vascularity, since ultrasound has provided valuable information regarding the qualitative classification of thyroid nodules based on benign or malignant characteristics, it has a wide range of applications. The most sensitive, precise, and economical way to investigate thyroid nodules is through fine needle aspiration cytology [4]. For thyroid nodules bigger than 0.5

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cm and a high-risk history, such as exposure to ionizing radiation as a child or adolescent, or a history of thyroid cancer in one or more first-degree relatives, Fine Needle Aspiration Cytology (FNAC) is recommended., along with a previous hemithyroidectomy where thyroid cancer was found to be suspect based on sonographic features such as micro-calcifications, hypo-echogenicity, enhanced nodular vascularity, infiltrative margins, absence of halo, and taller than wide on transverse view [5, 6]. As the initial diagnostic test for preoperative patient selection in thyroid lesions, FNAC is widely and safely advised. These days, referring physicians can manage patients more effectively thanks to the flexible reporting framework provided by the Bethesda system for reporting thyroid cytology 2007, which offers clinically relevant data [7]. Definitive diagnosis of malignancy, together with the kind of tumors, can be made via thyroid cytology, allowing for one-stage therapeutic surgery. Consequently, in recent years, the incidence of malignancy in thyroidectomy specimens has risen from 5–10% to 30–50%. A nodule with micro calcifications measuring 1 cm or more, a solid nodule measuring 1.5 cm or more with coarse calcifications, and a nodule measuring 2 cm or more with mixed solid and cystic components or connected to abnormal cervical lymph nodes should all undergo FNAC [8]. According to a different research, FNAC has a sensitivity of 84.48% and the corresponding positive and negative predictive values were 78.26%, 90.74% and 66.67% for specificity. Prior to now, thyroid FNAC reporting was complicated by the variety of category definitions. To address this issue, the 2007 Bethesda, Maryland The Bethesda System for reporting Thyroid Cytopathology was developed as a result of the "Thyroid Fine Needle Aspiration State of the Science Conference", which harmonizes nomenclature and morphologic criteria along with the corresponding risk of malignancy [9-11].

Analyzing the diagnostic accuracy of FNAC in the diagnosis of thyroid nodule in our population was the rationale of this study. As large number of populations in Pakistan belongs to poor socio-economic status, mostly diagnostic tool which are available for diagnosis of thyroid nodule are invasive and expensive. FNAC test is comparatively very easy, cheap, and non-invasive and also no hospitalization nor general anesthesia required for the same. In the future, this non-invasive test will be suggested as the first line of investigation to decrease the number of patients who are exposed to biopsy if the results of my study demonstrate that FNAC has good diagnostic accuracy in the detection of thyroid disease for other healthcare professional in future. Additionally, this research will offer a practical and effective clinical tool for early suspect surgical decision-making to prevent delays in diagnosis. To assess the role of FNAC of thyroid gland cancers in current environment and the diagnostic performance of the FNAC in identifying these conditions.

METHODS

This retrospective analysis was conducted in the ENT Head and Neck Surgery Department of the SHED Hospital in Karachi, Pakistan. Using a non-probability consecutive sampling technique, 120 patients who were presented in our department between January 1, 2020, and December 31, 2022, and had both preoperative FNAC and postoperative histopathology results and Patients between 20 years to 75 years of age. The patient had been experiencing thyroid swelling for more than three months. The patient's history, clinical examination, and ultrasound revealed a thyroid nodule with multiple suspicious features, including Extra Thyroidal Extension (ETE), deformed nodular architecture, uneven margins, hypo echogenicity, and micro calcifications (stippled rim calcifications). Only euthyroid patients were selected, assessed by clinically and normal thyroid function test i.e. (TSH level = 0.2-4.00 m IU/l, T3 level = 2.5-5.8pmol/l, T4 level =11.5-23.0pmol/l) were included in this study. Individuals exhibiting diffuse thyroid swelling. Every case of toxic and multinodulargoitres was verified through clinical assessment. Individuals who have previously undergone thyroid surgery of any kind (lobectomy or total thyroidectomy) were excluded from the study. SPSS version 23.0 was used for data analysis and ethical approval of study was obtained from the Supporting Health and Education Deserving fellow (SHED) foundation hospital (00IRB-SH/Approval/2022/050). The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) guidelines have an impact on thyroid cytology diagnosis. All reports should be categorized into one of the following six diagnostic categories: I stand for non-diagnostic or unsatisfactory; II for benign; and III for Atypia of Undetermined Significance (AUS) or Follicular Lesion of Unclear Significance (FLUS). IV: a follicular tumor or any symptoms that point to one; V: a malignancy; VI: a malignant [13]. Utilizing a 5cc or 10cc syringe, a 22-gauge needle was employed to perform FNAC. In the radiology suite, ultrasound guidance was used for all FNAC procedures. In the nodule, at least two passes were made. The specimen that was collected was placed onto a glass slide and treated with either Giemsa or Papanicolaou stain. Diagnostic accuracy, sensitivity, specificity, NPV, PPV were computed.

RESULTS

In this study of 120 subjects there were 18 (15%) males and 102 (85%) were females. Age range was 15 to 75 years old and mean age standard deviation was calculated as 39.83 ± 12.09 years. Majority of the patients belongs to 36-45 years old (31.7%) followed by 26–35 years old (i.e., 36 cases), and the age group of 66–75 years old (i.e., 4 instances) had the fewest patients as indicated in table 1.

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Table 1: Demographic Distribution of the Subjects

Variables	Frequency (%)
Mean ± SD	39.83 ± 12.09
Age (Years)	
15-25	15 (12.5)
26-35	36 (30)
36-45	38 (31.7)
46-55	16 (13.3)
56-65	11 (9.2)
66-75	4 (3.3)
Gender	
Male	18 (15)
Female	102 (85)

Table 2 indicated postoperative histopathology reports of FNAC the results of benign and malignant lesions with Bethesda classification in which majority of cases belongs to class II classification (71) while most of the cases belongs to benign category (79) and 41 are malignant lesions.

Table 2: Post-Operative Histopathology of Thyroid Lesions

FNAC		Histopathological Examination	
Bethesda Classification	Total no. of Cases	Benign N (%)	Malignant N (%)
I	4	4 (100%)	-
II	71	66 (93%)	5 (7%)
III	4	3 (75%)	1 (25%)
IV	5	3 (60%)	2 (40%)
V	25	3 (12%)	22 (88%)
VI	11	-	11 (100%)

Table 3 classified discordant cases (total11) in which most of the cases belongs to papillary carcinoma (36.4%) followed by benign (27.3%) and medullary carcinoma (18.2%) while follicular carcinoma and other carcinomas are up to 9.1% respectively.

Table 3: Details of the Discordant Cases

Bethesda Classification	No. of Cases	Histopathological Result				
		Benign	Papillary Carcinoma	Follicular Carcinoma	Medullary Carcinoma	Other Thyroid Carcinomas
I	0 in 4	-	-	-	-	-
II	5 in 71 (7%)	-	3	1	-	1
III	1 in 4 (25%)	-	-	-	1	-
IV	2 in 5 (40%)	-	1	-	1	-
V	3 in 25 (12%)	3	-	-	-	-
VI	0 in 11	0	-	-	-	-
Total Discordant Cases in 120 Cases	11 (9.16%)	3 (2.5%)	4 (3.33%)	1 (0.83 %)	2 (1.66%)	1 (0.83 %)
% Distribution of Discordant Cases Total 11 Cases	100%	27.3%	36.4%	9.1%	18.2%	9.1%

Table 4 showed the distribution of thyroid cancers found in each Bethesda scoring grade. Out of 41 most of the cases are papillary carcinoma (80.5%), Follicular carcinoma (7.3%), medullary carcinoma (7.3%) and other thyroid carcinomas are (4.9%).

Table 4: Distribution of the Thyroid Cancers

Bethesda Classification	Histopathology Report N (%)			
	Papillary Carcinoma	Follicular Carcinoma	Medullary Carcinoma	Other Thyroid Carcinoma
I	-	-	-	-
II	3	1	-	1
III	-	-	1	-
IV	1	-	1	-
V	21	1	-	-
VI	8	1	1	1
Total from 120 Cases	33 (27.5%)	3 (2.5%)	3 (2.5%)	2 (1.7%)
% Distribution Total no. of Cancers=41	80.5%	7.3%	7.3%	4.9%

DISCUSSION

The primary diagnosis of thyroid swellings was made through an outpatient procedure called Fine Needle Aspiration Cytology (FNAC). The American Thyroid Association and National Comprehensive Cancer Network have established practice guidelines that recommend FNAC as the first diagnostic test before thyroid scintigraphy and ultrasonography due to its higher diagnostic accuracy and cost-effectiveness [12-13]. Since FNAC can distinguish between benign and malignant lesions fairly well, its application has led to a notable drop in the number of surgeries carried out, but it has also increased the number of malignant lesions in patients who have had surgery. Clinically, thyroid nodules are frequently observed, with a reported prevalence of 4-7% in the adult population. Nonetheless, the majority of adult thyroid nodules are benign neoplasms or non-neoplastic lesions, with less than 5% being malignant. Therefore, to avoid needless surgery and potential complications, it is preferable to only operate on patients who have a suspicion of cancer. Nevertheless, the clinical appearance by itself cannot be a reliable indicator of whether these benign lesions are benign or malignant nodules [14]. Today, a variety of imaging methods, including high-resolution ultrasonography and radio nucleotide scanning are utilized to diagnose thyroid nodules. However, FNAC is still thought

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to be the most accurate technique, particularly when ultrasound is utilized as a guide to ensure better sample collection, particularly in cases of cystic lesions [15]. According to published data, the overall accuracy rate of FNAC in detecting thyroid cancer is approximately 95% [15-16]. The identified pitfalls include those involving inadequate specimens, collection methods, the aspiration technique used by the doctor, the pathologist's experience reading the aspirate and the fact that certain benign and malignant thyroid tumors have intermingling cytological characteristics [17]. FNAC has a number of limitations when it comes to diagnosing thyroid nodules, despite its reputation for having high diagnostic accuracy. In 4-21% of cases, inadequate sampling is the cause and indeterminate diagnosis in 3–18% even with the benefit of ultrasound guidance. The best way to manage thyroid nodules is still beset by unresolved issues such as inconclusive diagnosis, inadequate sampling, indeterminate results and potential FNAC misdiagnosis. When done by skilled professionals, ultrasound guided FNAC has a diagnostic sensitivity and specificity of about 83% and 92%, respectively [18]. In our study, the mean age was 39.83 ±12.09 years. The study of Basharat R *et al.*, noted age as 44 years whereas Sharma C, noted as 33.04 ± 12.29 years [19, 20]. In this study, 18 (15%) were male while 102 (85%) were female. Erkinuresin T, reported that 48 cases (16.2%) were male and 248 cases (83.8%) were females. Sharma C noted to have 18% males and 82% females [21]. According to Sharma C, the results of the FNAC were as follows: 80%, 97.7%, 80%, 97.7% and 96% for sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy, respectively [20]. As indicated in a study by Erkinuresin T [21]. The sensitivity of thyroid FNAC for malignant cases was 57.89%, specificity was 88.10%, false-positive rate was 11.90%, false-negative rate was 42.11%, positive predictive value was 52.38%, negative predictive value was 90.24% and accuracy rate was 82.52%.

CONCLUSIONS

FNAC detects both benign and malignant thyroid lesions with excellent sensitivity and specificity, it should be performed in all thyroid nodule cases. Facility of cytopathological diagnosis of thyroid disease should also be available in all secondary and tertiary health centers. This strategy is both dependable and economical in detecting malignant thyroid gland tumors and provides the surgeon with valuable information in preoperative diagnostics.

Authors Contribution

Conceptualization: MMUK

Methodology: SFA

Formal analysis: MWUK

Writing, review and editing: MWUK, SFA, TGA, SS, AAA

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

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Original Article

Investigation of Total Knee Arthoplasty Failure Factors and Evaluating Functional Outcomes after Revision Surgery

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ABSTRACT

Total Knee Arthroplasty (TKA) is an effective surgical procedure for treating severe knee arthritis. However, certain factors can lead to failure of TKA necessitating the revision surgery. **Objective:** To evaluate the factors of TKA failure along with assessment of functional outcomes after revision surgery. **Methods:** It was a prospective cohort study conducted at Pak International Medical College, Hayatabad, from June 2022 to July 2023. A consecutive number of 67 patients admitted in orthopedics surgery department during the selected timeframe were screened. 40 patients aged 25 years and older with Total Knee Arthroplasty (TKA) failure requiring revision surgery were included in this study. Each patient was assessed to find the causes of total knee arthroplasty failure. The American Hospital for Special Surgery Knee Score and Visual analog scale scores was used preoperatively, at three and six months after surgery to assess the functional outcomes after revision surgery. **Results:** The mean age of the sample was 49.2 ± 5.4years with 57.5% males and 42.5% females. The causes of failure were aseptic loosening (12.5%), periprosthetic fracture (2.5%) and patellofemoral extensor mechanism insufficiency (50%). The pre-operative (HSS) data score was 59.44 ± 5.99, at the 3-month post-operative mark 73.17 ± 3.85The mean pre-operative VAS score was determined to be 3.71 ± 0.97 and at 6-month post-operative 1.49 ± 0.79 (p-value < 0.01). **Conclusions:** The factors leading to failure of primary knee replacement includes patellofemoral extensor mechanism insufficiency, infection and malalignment, with revision knee surgery effectively leading to better patient outcomes.

INTRODUCTION

Total Knee Arthroplasty (TKA), also known as total knee replacement, is a highly effective surgical procedure for treating severe knee arthritis. This intervention aims to relieve pain, improve function and enhance the quality of life for patients suffering from conditions such as osteoarthritis, rheumatoid arthritis and post-traumatic arthritis [1]. Recent studies show the majority of sufferers from pain, register an improvement in the mobility and the better quality life after undergoing surgery with patient satisfaction rates of 80% [2]. Furthermore, there were excellent postoperative functional outcomes that can last up to 5 years after surgery [3]. Several patient-specific factors affect the success of TKA. Therefore, the success of TKA was determined by patient-specific factors. Additionally, higher wear rates on implants and earlier revisions may be experienced by younger and more active patients. Furthermore, surgical technique and implant design also influence the outcome [4]. One of the key factors that have contributed to improved outcomes of TKA was advances in minimally invasive surgical techniques and better implant materials [5]. There were failures even though the primary TKA (Total knee arthroplasty) has high success rates. Revision surgery was therefore needed for such occasions. PJI accounts for a

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major contribution towards failure of TKA at 1% to 2% rates which were reported during primary total knee replacement surgeries. Such factors as diabetes, obesity, rheumatoid arthritis, and immunosuppression enhance susceptibility to PJI hence different strategies such as Debridement Antibiotics and Implant Retention (DAIR) must be employed or a two-stage revision for chronic infections [6, 7]. Aseptic loosening was also one of the most common long-term causes of TKA failure, accounting for up to 40% of revisions [8]. Mechanical wear, osteolytic activity and biological factors contribute to implant loosening [9]. Other factors that contribute to failure in total knee arthroplasty include instability, wear and osteolysis and peri-prosthetic Fractures [10]. Revision surgeries were a necessary component of knee replacement surgery. In total knee arthroplasty, any complications arising after the initial operation were direct reasons for this decision. The decision was made by assessing traditional symptomatic, radiographic or functional impairment [11]. Studies have shown that revision surgery in TKA can lead to significant improvements in pain relief, functional outcomes, and patient satisfaction [12]. In the last few years, the success rates of revision surgery in TKA have been further improved by advances in surgical techniques, implant designs, and perioperative management. Wear rates for polyethylene have decreased and implant failures induced by polyethylene wear osteolysis have been countered with the help of highly cross-linked polyethylene and different bearing surfaces [13]. Additionally, better functional outcomes and implant longevity have been achieved by improved accuracy of revision surgeries which were as a result of innovative approaches like bone-preserving techniques, computer-assisted navigation, and patient-specific instrumentation [14]. We have yet to resolve a persistent discrepancy around the assessment techniques like Knee Rating Scale (KRS), Oxford Knee Score (OKS) or Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) as researchers have yet to determine the best approach to determining post-revision functional outcomes and their relationship to a patient's quality of life even if seventeen studies have attempted it so far. Even though the present knowledge on reasons behind failed TKA, as well as its effects on subsequent surgeries, seem quite considerable, there were certain knowledge gaps present [15]. The study populations were variable and studies were usually single-centered thus may not be applicable to all healthcare facilities. An important way through which these gaps can be addressed was through promoting longitudinal researches with patient centered outcomes comparison analyses and taking into account individual patient attributes that will assist us improve on how we manage patients requiring revision Total Knee Arthroplasty (TKA) [16, 17].

The aimed of this study was to evaluate the leading factors of TKA failure in an all-encompassing manner, which includes assessing the infection rates, aseptic loosening, instability, wear and periprosthetic fractures among other variables. Additionally, the research would evaluate how patients who have previously undergone TKA would perform in terms of general health following revision surgeries. This should be placed within a wider lens considering the potential disparities in the availability of health resources and frequency of arthritis of the knee in Pakistan among other regions. This research could guide in creating evidence-based clinical practices guidelines on how to do TKA operations in Pakistan

METHODS

It was a prospective cohort study conducted at Pak International Medical College, Department of Medical Research, Hayatabad, from June 2022 to July 2023 for duration of one year after taking approval from the ethical review committee (PIMC/DMR/3). A consecutive number of 67 patients who were admitted in orthopedics surgery department of Pak International Medical College Pakistan during the selected timeframe were screened for inclusion in this study. A specific criterion of inclusion and exclusion was designed. Patients aged 25 years and older who have undergone Total Knee Arthroplasty (TKA) and have experienced failure requiring revision surgery were included in this study. Patients for whom revision TKA was not deemed appropriate by treating orthopedic surgeon due to factors such as medical comorbidities were excluded from this study. Patients with significant orthopedic conditions affecting the lower extremities other than TKA failure, such as severe hip arthritis or spinal deformities, which could confound the assessment of functional outcomes, pregnant and lactating mothers were also excluded from this study. After screening 42 patients were selected and informed consent was signed by every patient with 2 patients lost in follow up. Revision was defined according to the Swiss National Registry: "A revision procedure was a secondary surgical procedure of a patient's knee joint whereby the complete primary implant or parts thereof were replaced by new components" [18]. The secondary patellar resurfacing due to osteoarthritis was also included in revision procedure. Only first revision was included in this study. The demographic data of patients including age, gender was recorded. Different factors leading to TKA failure were jotted down including peri-prosthetic infections, aseptic loosening, arthro-fibrosis and mal alignment. All these factors were labelled by two orthopedic consultants. The revision surgery was performed following standard protocols. The American Hospital for Special Surgery Knee Score (HSS) and patients' Visual Analog Scale (VAS) scores was used in the clinical evaluation, both preoperatively and

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at three and six months after surgery. Two researchers assessed each set of data, and the average of their findings was used. Data were entered and analyzed using SPSS (Statistical Package for the Social Sciences) version 24. The one-way ANOVA test was used to find out mean change in functional outcome and pain preoperative, 3rd and 6th month post operatively in HSS and VAS data. P-values of ≤0.05 will be considered statistically significant.

RESULTS

The result of the study has shown that mean age of the sample was 49.2 ± 5.4 years with 23 (57.5%) males and 17 (42.5%) females (BMI 24.77 ± 3.05 kg/m^2). All the patients were followed for 6 months. The patients had mild to moderate systemic disease (ASA grade II mean, range (ASA I-III). Overall meantime from primary to revision surgery 2.5 ± 1.9 year with 18 (45%) revisions occurred in the first year after surgery as shown in table 1.

Table 1: Demographic Characteristics of Study Sample

Variables	Outcomes (Mean ± SD)/N (%)
Age (Years)	49.2 ± 5.4
Body Mass Index	24.77 ± 3.05
Male	23 (57.5%)
Female	17 (42.5%)
ASA Grade	grade II
Revision Surgeries During 1 Year of Primary Knee Replacement	18 (45%)
Meantime from Primary to Revision Surgery (Years)	2.5 ± 1.9

The causes of failure in primary knee replacement varied across different factors. Aseptic loosening was observed in 5 patients (12.5%) addressing this issue with average time to revision was 1.47 ± 0.43 years. Periprosthetic fracture due to trauma was reported in only 1 patient (2.5%) time to revision, averaging at 1.66 ± 0.14 years. Patellofemoral extensor mechanism insufficiency emerged in 50% of patients (20 patients) with mean time to revision was 1.79 ± 0.31 years. Malalignment was also a notable factor contributing to prosthetic failure, accounting for 9 patients (22.5%). Arthrofibrosis and infection were identified as significant concerns, with 6 patents (15%) and 11 patients (27.5%) respectively. These patients were treated as per the recommendation of consultant orthopedic surgeon and revision surgery performed after the infection settled. Unexplained pain and wear/osteolysis were also reported, with 2 patients (5%) and 7 patients (17.5%) respectively addressing these issues. with mean time to revision of 1.96 ± 0.81 years and 2.25 ± 0.09 years respectively as shown in table 2.

Table 2: Analysis of Factor Leading to Failure of TKA

Causes of Failure	Number of Patents N (%)	Time to Revision (Years) (Mean ± SD)
Aspetic Loosening	5 (12.5)	1.47 ± 0.43
Peri Prosthetic Fracture	1 (2.5)	1.66 ± 0.14
Pattelo Femoral Extensor Mechanism Insufficiency	20 (50)	1.79 ± 0.31
Malalignment	9 (22.5)	2.82 ± 0.97
Arthrofibrosis	6 (15)	2.62 ± 0.63
Infection	11 (27.5)	1.58 ± 0.48
Un Explained Pain	2 (5)	1.96 ± 0.81
Wear/Osteolysis	7 (17.5)	2.25 ± 0.09
Other	4 (10)	1.91 ± 0.35

Following surgery, notable improvements in hip function were observed over time. At the 3-month post-operative mark, the mean HSS score increased to 73.17 ± 3.85. Continued progress in knee function was evident at the 6-month post-operative assessment (Figure 1). The mean pre-operative VAS score was determined to be 3.71 ± 0.97. At the 3-month mark, the mean VAS score decreased to 2.12 ± 0.85. At the 6-month post-operative evaluation, the VAS score was 1.49 ± 0.79. This indicates that both pain levels (VAS scores) and functional outcomes (HSS scores) showed significant improvement over time following surgery (p-value<0.05) as shown in figure 1.

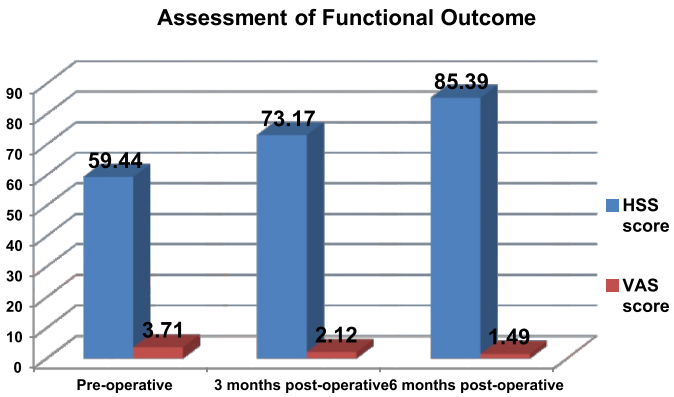

Figure 1: Assessment of Functional Outcome

DISCUSSION

This study provides insights into the common causes of orthopedic prosthesis failure and the average timeframes within which revisions were required. These causes encompass a spectrum of complications ranging from aseptic loosening and periprosthetic fracture to malalignment, infection and unexplained pain. Notably, patellofemoral extensor mechanism insufficiency emerges as the most prevalent issue. These findings correlate with a systemic review that has listed infections and aseptic loosening as the reason behind TKA failure worldwide with regional differences in failure modes [19]. Another study has also listed Infection as the main cause of failure in total knee arthroplasty (47.9%), followed by stiffness (10.3%), extensor mechanism failure (5.4%), and pain (2.9%) [20]. While a recent study has labelled the most frequent reasons for first revision in primary total knee arthroplasty were instability, patellofemoral problems, extensor mechanism insufficiency and malalignment [21]. To lower the knee operation failure rate, a multifaceted approach must be adopted. It was possible to reduce an

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unnecessary early post-operative complication occurrence rate by comprehensive preoperative assessment of the patients [22]. In addition, surgeons who have a lot of experience in TKA and who have worked with new advanced surgical approaches [23]. These discoveries furthermore stress the effectiveness of the surgery in enhancing knee capability, as indicated by the remarkable rise in HSS and VAS ratings three and six months after surgery compared to styling standards. Newer implant models and materials have contributed towards better functional outcomes [24]. When a patient undergoes revision surgery, it was a common that various structural damages were addressed such as loose ligaments, tight tissues and problems with extensor mechanism. Doctors take advantage of very careful muscle matching procedures like fixing the ligaments; so as to make the joint stable hence increasing its movement as well as giving out better results in terms of performance improvement [24]. It was important to note, however, that this single center study had a small data sample size and a short follow-up period of only 12 months. While examining causes of failure in Total Knee Arthroplasty (TKA) and assessing functional results after reoperation can give an invaluable understanding of the problem, it was worth noting the limitations of such. Further studies should conduct in order to surmount these challenges thereby improving the quality and generalizability of findings within our local setup.

CONCLUSIONS

The study analyzed a cohort of patients undergoing revision knee replacement surgery. It revealed that the factors leading to failure of primary knee replacement includes patellofemoral extensor mechanism insufficiency, infection, malalignment, wear/osteolysis, arthrofibrosis, aseptic loosening, unexplained pain and peri-prosthetic fracture emphasizing the need for targeted interventions to address these issues. While revision knee surgery was necessitated by various mechanical and biological failures, it effectively improves knee function and reduces pain, leading to better patient outcomes.

Authors Contribution

Conceptualization: FQ
Methodology: AW
Formal analysis: MA, MA
Writing, review and editing: AW, NA, NQ, WA

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

Conflicts of Interest

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Original Article

Occupational Health and Safety Practices Among Coal Mine Workers in Pakistan

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ABSTRACT

Coal mining operations lead to a wide range of health hazards that may cause serious injuries, deaths, and other health problems. The intricate relationship between health-related issues and occupational safety practices among coal mine workers in Pakistan. **Objective:** To identify occupational health issues and safety measures application among coal mine workers in Sindh, Pakistan. **Methods:** Descriptive cross-sectional study was conducted from Oct 2023- Feb 2024 by the department of community medicine and public health Sciences at the surrounding area of Lakhra coal mines, Taluka Manjhand, District Jamshoro, Pakistan. All the currently working individuals in the coal mines for the last six months, age 20 to 60 years and those who gave consent to participate in the study were included. **Results:** Out of 317 coal mine workers, total 36.6% cases had breathing difficulty, 31.9% were suffering from cough, 14.2% of the respondent had musculoskeletal issues, 59.3% had skin problems, 57.4% had eye problems, 9.1% of the cases had hearing problems, 14.0% cases were diabetics, 27.1% were hypertensive and 4.4% of the cases had cardiovascular disease. Only 3.8% of the respondent were trained on the proper use of safety measures by their organizations. **Conclusions:** Coal miners were suffering from numerous occupational health issues with predominance of respiratory illness along eye and skin related issues. No proper protective measures were practiced by the coal miners while no proper health facility, alternate oxygen and drinking water facility available for the coal mine workers.

INTRODUCTION

Occupational health hazards have been considered the main source of potential harm in terms of accidents, injuries, illness, disabilities, and deaths among workers at the workplace due to poor working conditions worldwide [1]. There are various health hazards reported such as physical, chemical, biological and psychological that may affect the workers in their related occupations [2]. According to the International Labor Organization (ILO) approximately 374 million workers suffer every year from non-fatal accidents in comparison, 2.78 million workers die due to occupational accidents and work-related disease worldwide [3]. Coal mining is one of the most hazardous professions because of its dangerous work and the high frequency of accidents. Coal mining operations lead to a wide range of health hazards that may cause serious injuries, deaths, and other health problems. Injuries sustained in the field and prolonged exposure to the coal are the two primary factors that contribute most to morbidity and mortality among coal workers [4]. Every year, thousands of coal mine workers die in accidents and suffer from many other associated factors such as dust inhalation, exposure to toxic chemicals, noise, vibration, and fire [5]. Pakistan has a high rate of coal mining occupation because the nation has abundant coal deposits and a sizable mining sector employing a big share of the labor force. The coal mining industry in the country has become more dangerous due to the lack of advanced technology, equipment safety, and safety knowledge and

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poor working environment [6]. According to the Pakistan Central Mines Labor Federation (2019), coal miners face a range of occupational health and safety hazards, including exposure to coal dust, gas explosions, and cave-ins while on average, over 200 workers lose their lives every year due to explosions related to coal mining throughout the country [7]. Coal workers are exposed to serious risk factors such as dust, vibrations, and high heat load as overloading of the upper extremities when working with heavy tools. Among these risk factors, mine dust contains a crystal form of silica that affects coal miners' health and life [8]. Chemical hazards are harmful to life and health it is the main source of infection in mining caused by dust particles attached to the nasal opening and entering into the breathing system and affect the lungs. The impact of biological hazards due to poor working conditions also causes the health problems such as snakebite, bacterial, viral and fungal disease [5, 8] Psychological hazards are related to long working hours, long-distance traveling, heavy workload, and poor working environment [9]. According to American psychological counsel, the feeling of job insecurity, poor working life, and unrealistic job expectation cause severe stress and anxiety in coal workers. This situation can develop chronic and costly diseases such as diabetes, heart disease, and other psychological disorders [9]. Keeping in view the harmful effects of coal mining and significant dangers they faced without any protective measures.

This study was designed to identify occupational health issues and safety measures application among coal mine workers in Sindh, Pakistan.

METHODS

Descriptive cross-sectional study was conducted by the department of community medicine and public health sciences, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan at the surrounding area of Lakhra coal mines, Taluka Manjhand, District Jamshoro from October 2023- February 2024. The Lakhra Coal Field is situated in Sindh, Pakistan's District Jamshoro. It is 27 km from Jamshoro to Sehwan along the Indus Highway, which runs parallel to the river's right bank. It is made up of 1309 square kilometers, of which 1206 were designated areas. The study was carried out after getting approval from the ethical review committee of LUMHS, Jamshoro, Pakistan (No. LUMHS/REC/-91) while permission from the senior manager Lakhra coal mine was also taken prior to the study. Moreover, informed consent was also taken from all the miners after explaining them the purpose of the study. All the miners currently working in the selected coal mines for the last six months, age 20 to 60 years and those who gave consent to participate in the study were included. Whereas, miners working outside the selected area, managers, supervisors, women and those not willing to participate were excluded. Non-probability purposive sampling technique was applied for the selection of participants. Whereas, sample size of 317 was obtained using open epi. Online sample size calculator by taking anticipated health hazards among coal miners of 25%, setting confidence interval at 95% confidence level and a margin of error at 5% [9]. Participants were inquired about their general information, about the occupational health issues and the availability of equipment's for their safety measures using a semi-structured written questionnaire regarding occupational health hazards and their safety measures. The questionnaire comprise of three different sections of total 30 questions. Section A includes the demographic and general information of participants, section B comprise of questions about the health related issues while the last section includes questions about the health safety practices, available protective equipment, health facilities, first-aid facilities etc. Health examination of all the participants was also performed by qualified medical doctor and findings were recorded in the pre-designed checklist. The data were entered and analyzed using SPSS version 26. All the qualitative variables were presented as frequency and percentages.

RESULTS

A total of 317 coal miners currently working in the selected coal mines were interviewed. Most 151 (47.6%) of the participants were of age 31-40 years, followed by 91(28.7%) aged 20-30 years, 60 (19.0%) 41-50 years and 15 (4.7%) of age 50 years. Table 1 was presenting the socio-demographic details of study participants. Majority, 282 (89.0%) were married while 35 (11.0%) were single. Based on the working experience, majority of participants had of >6 years whereas, most of them reported that their routine working hours were of 8-12 hours/day (Figure 1).

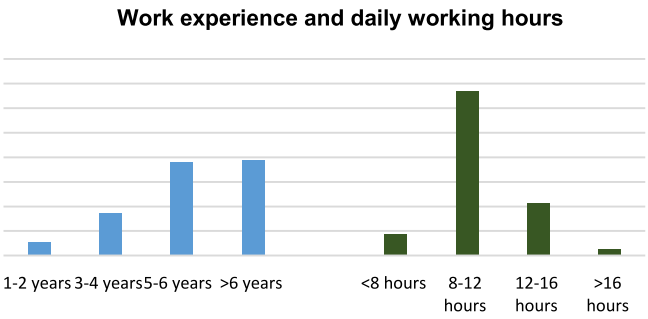

Figure 1: Working Experience and Routine Working Hours of Participants(n=317)

According to the health-related issues, majority of them were suffering from the breathing difficulty, having complaints of cough, had skin and eye related problems. Among the participants, majority of them were hypertensive(Table 1).

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Variables	Criteria		Frequency (%)
History Difficulty in Breathing	No		116 (36.6%)
	Yes		201 (63.4%)
Suffering from a Cough	No		101 (31.9%)
	Yes	Cough with Sputum	77 (24.3%)
		Dry Cough	139 (43.8%)
History of the Musculoskeletal Problem	No		202 (63.7%)
	Yes		115 (36.3%)
Any Skin Problems	No		129 (40.7%)
	Yes		188 (59.3%)
Eye Problems	No		135 (42.6%)
	Yes		182 (57.4%)
Hearing Problem	Yes		29 (9.1%)
	No		215 (67.8%)
	Sometimes		73 (23.0%)
Do you have any of the following Existing Diseases?	Cardiovascular		14 (4.4%)
	Diabetic		46 (14.5%)
	Hypertension		86 (27.1%)

According to the availability of safety measures, only very few were trained on the proper use of safety measures by their organizations, while less than one-third were taking proper safety measures during work. Majority of them reported that there was an emergency safety exit plan (Table 2).

Table 2: Availability of Safety Measures According to Respondents(n=317)

Variables	Criteria	Frequency (%)
Does your Organization Provide you with Trainings on the Proper use of Safety Measures?	No	12 (3.8%)
	Yes	283 (89.2%)
	Don't know	22 (7.0%)
Are you taking Proper Safety Measures During Work?	Yes	38 (12.0%)
	No	262 (82.6%)
	Don't know	17 (5.4%)
	Helmet with Cap Torch	241 (76.0%)
What types of Equipment's for Safety Measures do you use at work?	Helmet with Cap Torch Safety Mask and Shoes	17 (5.3%)
	Safety Mask and Eye Goggles	06 (2.0%)
	Safety Gloves Only	12 (3.8%)
	Safety Mask Only	24 (7.6%)
	Safety Mask Only	17 (5.3%)
Is there any Emergency Safety exit Plan?	No	250 (79.0%)
	Yes	67 (21.0%)
Are there any Alternate Oxygen Facility in Mines?	No	210 (66.3%)
	Yes	73 (23.0%)
	Don't know	34 (10.7%)

Surprisingly, over two-third of participants reported that there were no health facilities provided by the company, while a very small number of participants reported that company providing them first aid facility within the coal mines' premises only. Regarding medical cost for any health related issue, over half of them reported that they themselves bear the treatment costs. Over two-third of participants reported that there were no safe drinking water facilities in the mine and they were not frequently washing their hands with soaps (Table 3).

Table 3: Evaluation of Health Care Status According to Respondents(n=317)

Variables	Criteria	Frequency (%)
Is there any Health Facility Provided by the Company?	Yes	85 (26.8%)
	No	232 (73.2%)
Is there Availability of medical Staff?	Yes	85 (26.8%)
	No	232 (73.2%)
Does the Company Provide you first Aid Facility within the Coal Mines' Premises?	No	283 (89.3%)
	Yes	34 (10.7%)
Does the company provide you periodic checkup?	No	303 (95.6%)
	Yes	14 (4.4%)
Who bears the Cost of Treatment?	Coal Worker	179 (56.5%)
	Company	138 (43.5%)
What is the Monthly Cost of Treatment if Paid by Coal Workers?	>4000	26 (8.2%)
	1000-2000	113 (35.6%)
	2000-3000	167 (52.7%)
	3000-4000	11 (3.5%)
Is there a Safe Drinking Water Facility in the Mine?	No	310 (97.8%)
	Yes	7 (2.2%)
Do you Frequently Wash your Hands with Soap?	No	240 (75.7%)
	Yes	77 (24.3%)

DISCUSSION

Coal mining is a dangerous occupation that exposes workers to various occupational health hazards. Coal mine workers were at risk of developing a range of health conditions due to exposure to dust, noise, and chemicals. Prolonged exposure to coal dust can lead to a range of respiratory diseases [10]. Current study has been done to evaluate the occupational health hazards among coal mine workers and its associated factors. In this study 36.6% cases had breathing difficulty, 31.9% were suffering from cough, 14.2% of the cases had musculoskeletal issues, 59.3% cases had skin problems, 57.4% had eye problems, 9.1% of the cases had hearing problems, 14.0% cases were diabetics, 27.15 were hypertensive and 4.4% of the cases had cardiovascular disease. Consistently Panhwar S *et al.*, reported that the health problems in the coal mine workers were a result of being exposed to these gases [11]. In the line of this series Ayaaba E *et al.*, also reported that "prevalence of asthma, pneumonia, bronchitis and emphysema were respectively 47.55%, 14.29%, 9.69% and 5.10%, while coughing was the most cited respiratory symptom (35.4%)[12]. High exposure to SO2 by populations living near power plants, led to them commonly suffering from suffocation, wheezing, coughing, and reductions of lung" function. In the current study, among the participating miners, 63.4% reported to have

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breathlessness while 43.8% were with dry cough and 24.3% with productive cough. Occupational health hazards among coal mine workers were a significant concern due to the potential impact on the health and well-being of these workers. There were several justifications for the concern regarding occupational health hazards among coal mine workers. Firstly, coal mine workers were exposed to high levels of coal dust, which can lead to the development of respiratory diseases such as pneumoconiosis, silicosis, and chronic bronchitis. These conditions can have long-term health consequences and can significantly reduce a worker's quality of life. Workers in underground coal mines were at varying risk of experiencing this kind of discomfort depending on their personal characteristics and work-related circumstances. Along with these respiratory, skin and eye related issues, many (36.3%) coal mine workers in this study reported to suffering from musculoskeletal problems. These findings were consistent with other Pakistani studies by Sarikaya S *et al.*, and Sahito WS *et al.*, that also reported high prevalence of musculoskeletal problems and body pain complaints reported by their study participant coal miners [13, 14]. Jeripotula SK *et al.*, and Yong X *et al.*, also reported the high incidences of musculoskeletal injuries and related issues among the coal mine workers in their study along with their related factors [15, 16]. It has been reported and documented that among the miners, coal miners suffer from different illnesses (such as respiratory conditions, gastrointestinal issues, headaches, musculoskeletal injuries, and bodily discomfort) that raises the cost of treatment among these workers [17]. Along with these Methane and carbon monoxide were two environmental factors that poses a significant health problem among these workers that further increase the health costs associated with coal mining [18]. In the present study, workers reported the high cost of health related issues among these workers. Additionally, only 43.5% workers reported that the cost of their health issues borne by company while 10.7% said company providing them first aid facility within the coal mines' premises. Furthermore, availability and applicability of safety measures in this study was found poor and only 3.85% of participants were trained on the proper use of safety measures by their organizations. Astoundingly, over two-third of participants (78.9%) don't even know about the safety exit plan in case of any sort emergency while 66.3% reported that they don't have any alternate emergency oxygen facility in their mines. Yang L *et al.*, reported that the safety difficulties in mining activities and the influence of IoT were found and grouped into three primary factors [19]. They further reported that these elements were general safety problems, environmental considerations, and mines information technology. Lately, mechanization and automation have been introduced into coal mines, which has led to increases in safety as well as productivity and cost savings. Tactlessly, human factors such as a lack of sufficient competence, lack of experience, perception error, and risky behaviors were the major causes of coal mining injuries [20]. Moreover, a lack of a thorough emergency rescue plan was another contributing factor. Unfortunately, these has been observed among the workers in this study which may result in some serious accident and cause fatal injuries. Most of the workers in this study reported that there was no safe drinking water facility available within the mine. The lack of safe drinking water facility in the coal mines is a critical issue that needs urgent attention. It can lead to serious health problems, such as dehydration and waterborne diseases, which can affect the productivity and well-being of workers [17]. The provision of safe drinking water should be a priority for mine owners and management to ensure the health and safety of workers. Due to time constraints and limited resources, only one coal mine of the province included. Moreover, limited access to the working sites and inclusion of more workers were the main constraints of the study.

CONCLUSIONS

The study concludes that coal miners were suffering from numerous occupational health issues with predominance of respiratory illness along eye and skin related issues. No proper protective measures were practiced by the coal miners while no proper health facility, alternate oxygen and drinking water facility available for the coal mine workers. It was recommended to conduct a study including large number of mines will give more insight of the challenges. Government and other stakeholders should focus such issues and policy-makers need to organize events and seminars for improving education and access to resources for workers from low socioeconomic backgrounds, improving safety regulations and enforcement, and ensuring that employers prioritize the safety and health of their workers, regardless of their level of education or socioeconomic status. By doing so, we can help protect the health and safety of workers in hazardous industries like coal mining, and ensure that they were able to work in safe and healthy environments.

Authors Contribution

Conceptualization: AAT
Methodology: TFM
Formal analysis: KNA, TFM, RS
Writing, review and editing: AAT, MIS, TFM, MUH

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Being Mindful Affects Experiences and Treatment of Arthritis Patients: A Qualitative Study

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ABSTRACT

Arthritis, a common chronic disease, presents major difficulties to patients' functional abilities. Mindfulness therapies may help to compensate for the lack of positive health outcomes that arthritis symptoms cause in a patient's life. **Objective:** To describe the perceptions and experiences of the participants of mindfulness practices in Faisalabad, Pakistan, who have arthritis? It describes the attitudes towards mindfulness, its implementation and impact on the symptoms. **Methods:** There were 7 males and 7 females, and all were selected purposively, aged 31 to 51 years, interviewed by the researcher using semi-structured interviews. Thematic analysis revealed following themes; awareness, benefits, challenges, ways of managing, and sources of support. **Results:** Some key issues were identified as elevation in the recognition of the body and mind associations, pain control, strengthening of the emotional aspects, and some issues like time limitations and cultural attitudes. Mindfulness was identified as an important aspect that enabled participants to regain control of their conditions; however, participants stressed the need to design the mindfulness-based interventions that are culturally appropriate or responsive to the informational needs of patients. The results highlight the feasibility of using mindfulness practices for enriching the quality of life of patients. **Conclusions:** However, the experience of implementation demonstrates that there are various types of barriers, educational needs, and practices as well as cultural beliefs in this sphere. Adapting mindfulness' intervention to the particular nature and circumstances of arthritis could potentially enhance the programs' application and acceptance in both clinical and community practicing environments.

INTRODUCTION

Millions of people worldwide are afflicted with arthritis, a common chronic ailment. Complementary therapies like mindfulness have drawn attention for their potential to enhance patients' quality of life, even while medical treatments are still essential for controlling arthritic symptoms. Rheumatoid Arthritis (RA) is characterized by a steady, continuous deterioration of joints. The two primary pathogenic symptoms are pannus and synovitis. Consequently, the joint is damaged, leading to joint dysfunction. The global incidence of RA was estimated to be 0.24% [1]. Mindfulness include two elements. It centers awareness and attention on the experience of the present moment like physical sensations and emotional responses [2, 3]. Mindfulness as a complementary therapy has shown beneficial effects on disease activity, depressive symptoms, psychological distress, and overall well-being in patients with rheumatoid arthritis. However, due to the low quality of evidence from the included studies in a systematic review, further robust clinical trials are needed to confirm its effectiveness in clinical practice [4]. Mind Body Therapies (MBTs), including meditation, yoga, and mindfulness, have shown various beneficial effects on patient-reported outcomes and disease activity markers in Rheumatoid Arthritis (RA) patients. A systematic review highlights that mindfulness-based interventions particularly reduce subjective disease activity parameters

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and are especially beneficial for RA patients with recurrent depression [5]. A meta-analysis of six randomized trials (337 participants) examined mindfulness therapies for rheumatoid arthritis, finding significant improvements in pain, mood, and symptoms compared to controls. Larger trials are needed for conclusive validation [6]. Another study (63 participants) assessed a Mindfulness-Based Stress Reduction (MBSR) program's impact on rheumatoid arthritis. While initial results at two months were not significant, improvements in psychological well-being were evident six months post-MBSR, suggesting potential benefits for patients' mental health [7]. Empirical data suggests Mindfulness-Based Interventions (MBIs) enhance psychological well-being by improving emotional and cognitive responsiveness, which is crucial for chronic illnesses like Rheumatoid Arthritis (RA) where emotional dysregulation and symptom burden are prominent [8-10]. A meta-analysis of five trials involving 399 RA patients found MBIs inconsistently impacted clinical outcomes like disease activity but consistently improved psychological measures such as self-efficacy, distress, and depressive symptoms [11]. While promising, more research is needed due to limited trial availability.

This study aimed to address the knowledge gap regarding arthritis patients' perspectives on mindfulness practices in Faisalabad, Pakistan. Arthritis significantly impacts quality of life, yet little research has explored how Pakistani patients might benefit from alternative therapies like mindfulness. Through qualitative interviews and thematic analysis, this study seeks to understand how arthritis patients perceive and engage with mindfulness, identifying benefits, barriers, coping strategies, and support needs. It aims to develop culturally sensitive interventions to enhance arthritis management and improve well-being by incorporating diverse patient viewpoints into comprehensive healthcare strategies. The Research Questions were: What are the experiences and perceptions of arthritis patients in Faisalabad, Pakistan, regarding mindfulness practices, what are the perceived benefits of mindfulness practices for managing arthritis symptoms among patients in Faisalabad, what are the barriers to adopting and practicing mindfulness among arthritis patients in Faisalabad, how do arthritis patients in Faisalabad cope with arthritis-related challenges through mindfulness practices ad what support and resources are available and needed for arthritis patients in Faisalabad to engage effectively with mindfulness practices?

METHODS

Using purposive sampling, patients with arthritis were selected from Faisalabad hospitals. Participants may only be eligible if they were at least eighteen years old, had a diagnosis of arthritis and agreed to take part in interview. Semi-structured interviews were conducted with 14 participants. Interviews were conducted in Urdu, audio-recorded, and transcribed verbatim for analysis. Ethical approval was sought from Research and Ethical Review Committee University Medical and Dental College Faisalabad with Ref.no. UMDC/RERC/2023/12. Data collection was done from May 8 to July 15, 2023. To find repeating themes and patterns in the interview data, thematic analysis was used. Two researchers coded the transcripts independently, and after some discussion, a consensus was established. A detailed organization of topics and subthemes was employed to fully capture the opinions of the participants.

RESULTS

The 14 arthritis patients in the study had an average age of 41 years, with 10 men and 4 females. The sample included patients with osteoarthritis, juvenile idiopathic arthritis, and rheumatoid arthritis. The participants' different educational and socioeconomic backgrounds reflected the wide range of demographics seen in Faisalabad. Restricted Knowledge: Although most of the people had heard of mindfulness, their understanding of its key principles and its possible benefits was unclear. Cultural Perceptions: The participants' ideas about mindfulness were molded by their cultural values and religious beliefs; a few of them were against or skeptical about it. Individual Experiences: They shared their own experiences and anecdotes, and thus participants stressed the importance of mindfulness in their daily lives.

Participant 1: I have heard about mindfulness, but I really don't know what it means. Some people say it's about focusing attention, but I don't know how it helps with my joint pain.

Participant 7: My cousin told me about mindfulness. They said it means being present in the moment and letting go of worries. But I don't believe it's for me. Stress Reduction: Most of the participants who took part in mindfulness activities said that they felt less tense and had better emotional health. Pain Management: Through the use of mindfulness practices, it was found that many people have reduced pain intensity and acquired better pain coping skills. Improved Quality of Life: Mindfulness was believed to be a catalyst in the improvements in mood, energy, and sleep quality as well as the general quality of life.

Participant 4: Mindfulness has changed my life. I used to be very stressed, but now I can better manage my pain and enjoy the small joys.

Participant 13: When I practice mindfulness, it feels like a burden has been lifted. It brings peace to my heart and helps me forget the pain. Time Restraints: The hectic schedules and the household chores were the reasons for the participants not to be able to practice the mindfulness.

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Physical Limitations: The physical difficulties connected with the practice of mindfulness because of arthritis symptoms, such as pain and stiff joints, were its main reason for the satisfaction and disengagement. Lack of direction: To get started and continually practice mindfulness, participants emphasized the requirement for organized guidance and help from healthcare professionals. Participant 5: I don't have much time for mindfulness, but being occupied with work and family duties, it's impossible for me to save time for myself.

Participant 10: Because of the pain in my joints, sitting for long periods is difficult, so focusing is hard for me. Sometimes I feel worried that I can't do it like others.

Customized Practices: Participants used chair yoga and light stretching exercises as a means of modifying the mindfulness approaches to fit their physical abilities. Integration into Daily Life: As stress-relief for the arthritis-related symptoms and daily challenges, mindfulness exercises were added to the everyday routine of the participants.

Participant 8: I have seen a yoga class for people with arthritis. The instructor arranges poses that are easy on the joints. It has been very helpful.

Participant 2: I have started practicing mindfulness while cooking or cleaning. It helps me focus on these tasks and forget the pain. Healthcare experts: Study participants highlighted the importance of healthcare specialists being the one to give advice and guidance on mindfulness, for instance, rheumatologists and physiotherapists. Family Support: The participants were highly motivated to practice mindfulness and overcome the obstacles by the encouragement from the friends and family. My doctor recommended a mindfulness app that guides me through meditation exercises. It has improved my life. Participant 11: My husband sometimes practices mindfulness with me. It feels good to have his support, and we motivate each other to stay focused.

DISCUSSION

The main purpose of the study was to analyze the views and the encounters of the patients with arthritis living in Faisalabad on the mindfulness practices. The various opinions of the participants were shown through thematic analysis. Some of the people were aware of the mindfulness ideas, while others were not that much into them because of the cultural prejudices or the poor comprehension. The participants' stories and experiences proved that the Faisalabad arthritis patients' level of awareness and acceptance of mindfulness activities was diverse. The participants stressed on the various advantages of mindfulness in the treatment of the symptoms linked with arthritis. The conversation of stress reduction was started since many of the participants said that practicing mindfulness had made them feel less stressed and better emotionally. The participants' life quality was improved in general along with their mood, energy and sleep quality which was a result of the better coping mechanisms and a decrease in the pain intensity. The results of this study prove the possible benefits of mindfulness in improving the different kinds of wellbeing of the arthritis people. The study that investigated the online mindfulness and gratitude intervention on arthritis self-management revealed that the patients' health status improved in pain anxiety, interference of pain, pain intensity, fear to move, and self-efficiency in handling pain. This pilot study provides support for gratitude and mindfulness interventions for physical health conditions and shows the feasibility of online delivery of such health interventions [12]. In a research of physical activity and exercise for PsA, the levels of sleep quality and individual concern in anxiety and symptoms of depression were higher among the participants using an MBI for PsA. Meditation as well was indicated to be related directly with sleep efficiency and their functioning during the daytime and the capacity to act more mindfully [13]. In a realistically designed small pilot trial, MBSR was provided for RA patients under good inflammation control but with nasty perceived symptoms. The results showed that the intervention had positive effects on anxiety, depression, sleep and function up to 12 months after the treatment, while pain and disease activity indices were not affected. There is a need for a power standing studies, with more significant samples, in order to ascertain the impacts of MBSR on RA related pain and PGA [14]. Thence, majority of the people found it difficult to accept and implement the practice of mindfulness although, they were aware of its benefits. Having a mindfulness practice on a regular basis was hard because of time limitations that were caused by the busy schedules and the household chores. The restrictions put forth by the pain and stiffness of arthritis were the obstacles that also caused challenges. The participants stressed the requirement of formal teaching and healthcare experts to refute the myths and to make the mindfulness practice better. This shows that the value of overcoming these obstacles and the promotion of mindfulness as a treatment of arthritis should not be ignored. Our participants managed the challenges with arthritis while practicing the particular exercises according to their physical capabilities during the mindfulness training therapy. The way those activities were advised was very special because they were personalized and included attention through mindfulness methods that guided us to find a suitable choice that fits individual likes and dislikes. A randomized controlled trial compared the efficacy of online Mindfulness-Based Stress Reduction (MBSR) and Cognitive-Behavioral Therapy (CBT)

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for rheumatoid arthritis, finding that a history of recurrent depression moderated treatment outcomes, particularly in pain interference and psychological well-being [15]. A clinical trial comparing CBT and MBSR for rheumatoid arthritis found both interventions significantly improved sleep quality, chronic fatigue, and executive function, but not disease activity, compared to the control group [16]. A study in same city demonstrated that quality of life significantly mediated the relationship between perceived stress and sleep quality among RA patients, indicating that interventions to reduce stress and enhance quality of life could improve sleep and overall well-being [17]. Peer support groups as well as medical personnel receive great recognition by the participants for their role in enhancing mindfulness activity. Research has found that without the talking, philosophical discussions, and planned events, people are less likely to get where they need to in the mindfulness journey. The participants, including physiotherapists and rheumatologists, played a major role as the dominant engine in the popularization of mindfulness program and public acknowledgement. Apart from the counseling or guidance being provided by the trained professionals, friends and family members are your biggest advocates who support and help individuals overcome challenges and achieving peace of mind. These existing support group and resources can be leveraged for better and wider mindfulness-based treatments of arthritis in patients of Faisalabad. In a study where the researcher attempted to establish the roles of the pro-inflammatory cytokines, trait mindfulness and psychological well-being among RA patients, the study indicated that there was a strong connection between those RA patients with high trait mindfulness and enhanced PWB besides noting that prescriptive mindfulness had negative correlation with depressive symptomatology. Higher IL-6 was associated with higher depression, pointing to the possible efficiency of mindfulness approaches for decreasing depressive signs and levels of proinflammatory cytokines in RA patients [18]. One research has discovered that integrating MBSR with Intensive education reduced the patients' symptoms, anxieties, depressive rates, coping ability, quality of life and cortisol levels if they are diagnosed with both diabetes and arthritis. Also, the rate of patient satisfaction and awareness was greater than those groups who received only intensive education [19]. A review demonstrates that psychological interventions like CBT, emotional disclosure, group therapy, mindfulness, patient education, and relaxation significantly benefit RA management. The analyzed meta-analyses reveal moderate to large overall positive impact and therefore it can be concluded that they should be incorporated into the routine treatment. However, further large sample size, high quality RCTs are necessary to substantiate these findings [20]. Healthcare professionals need to realize the specific requirements and possible cultural backgrounds that influence the arthritis patients when they teach various mindfulness techniques. Patients of arthritis in Faisalabad require specialized treatments that brings cultural impact and at the same time assistfulness for the therapy to be embraced and sustained. Not only the implementation of mindfulness-based therapy that makes it more effective and also accessible but also the partnership with the peer support groups and community resources is also helpful.

CONCLUSIONS

Current study offers in-depth insights on the mindfulness methods used by Pakistani arthritis patients in Faisalabad. The study sheds insight on the complex viewpoints, perceived advantages, obstacles, coping mechanisms, and support requirements associated with mindfulness among arthritis patients by answering the research topics. These results highlight the significance of tailored and culturally aware methods for fostering mindfulness in the treatment of arthritis. Healthcare professionals may improve the incorporation of mindfulness into holistic arthritis care by resolving obstacles and utilizing support networks, which will ultimately improve patients' quality of life.

Authors Contribution

Conceptualization: MM, ZKJ, KM, MAK, ALA
Methodology: MM, ZKJ, KM, MAK, KP
Formal analysis: MM, ZKJ, KM, ALA
Writing, review and editing: MM, ZKJ, KM, MAK, KP

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Experience of Endoscopic Ultrasound Guided Fine Needle Aspiration and Fine Needle Biopsy: Data from Tertiary Care Hospital in Pakistan

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ABSTRACT

Endoscopic ultrasound guided fine needle aspiration and biopsy (EUS-FNA/FNB) are minimally invasive and yet very effective techniques for tissue acquisition and diagnosis of sub-epithelial or other lesions in close premises of gastrointestinal tract. **Objective:** To evaluate the diagnostic accuracy and safety of the EUS-FNA FNA/FNB in various lesions. **Methods:** This was a single center study of consecutive 189 patients who presented to Gastroenterology department of Lahore General Hospital, Lahore for EUS FNA/FNB during October 2019 to March 2023. **Results:** 189 patients undergoing EUS-FNA/FNB, 60% were males, 40% females. Mean age was 48.84±15.96 years. EUS-FNA and FNB was done in 28 (14.8%) and 161 (85.2%) patients respectively. Median number of passes was 3 (IQR: 1-4). Most of the lesions were of pancreatic origin (n=110, 58.2%) pancreatic adenocarcinoma was found in 69.3 % solid pancreatic lesions. Other lesions were abdominal/mediastinal lymphadenopathy (n=37, 19.5%), gastric (n=26, 13.8%) and liver (n=10, 5.3%). Malignant lesions were found in 105 (55.6%) cases, benign diseases (n=34, 18%) and normal tissue (n=12, 6.3%).The overall diagnostic yield was 151/179(79.9%) with comparable yield of EUS-FNA and FNB, 21/28(75%) and 130/161 (80.7%) respectively (p=0.06).Complications rate was 2.1%. **Conclusions:** EUS FNA/FNB is effective and safe technique for evaluation of suspicious lesions in or around the gastrointestinal tract especially pancreatic lesions and further studies are needed to establish the best technique to improve tissue acquisition.

INTRODUCTION

Endoscopic Ultrasound (EUS) is a newer highly efficient, cost effective diagnostic modality that gives high-resolution, real-time snapshot of the gastrointestinal tract and adjacent structures. It is widely used to assess a wide spectrum of benign and malignant gut diseases. In past it has played an important role as an adjunct to traditional surgical therapies [1]. Recently EUS guided sampling has been widely used for the diagnostic management of thoracic and abdominal structures specially lymph nodes and solid structures and is being preferred over invasive modalities such as mediastinoscopy and laparotomy [2]. Among the two widely used diagnostic management sampling tools are Fine Needle Aspiration (FNA) and Fine Needle Biopsy (FNB) [3]. Despite improvement in imaging modalities like Computed Tomography (CT) scan, Positron Emission Tomography (PET) and use of tumor markers, diagnosis of pancreatic lesion, other sub epithelial lesions of gastrointestinal lesions or nodal masses remained problematic before the evolution of EUS as diagnostic tool [4]. There are number of lesions where these techniques

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have been used. These include esophageal, gastric, hepatic, pancreatic and lymph nodes of mediastinum and abdomen. It was reported in a study that EUS FNB resulted in a change of clinical management in about every tenth patient of pancreatic cysts; however, the associated adverse event risk was more and careful patient selection is mandatory [5]. EUS FNA/FNB provides histopathological confirmation of diseases. These are safe with comparable diagnostic accuracy in pancreatic and non-pancreatic lesions. FNB improved the histopathological quality of specimens with little blood contamination. In diagnosing pancreatic lesions, FNB had more sensitivity and diagnostic accuracy than FNA. The diagnostic accuracy of EUS-FNA in solid pancreatic lesion is from 78% to 95% with sensitivity ranging from 64% to 95% and specificity ranging from 75% to 100%. However, diagnostic accuracy lower in mediastinal lesions and gastrointestinal stromal tumors [6]. Diagnostic accuracy is affected by factors like location of lesion, scope position, type and size of EUS needle, use of additional methods like suction. In a study it has been concluded that keeping in view these factors, EUS-FNA/FNB are accurate diagnostic procedure for the evaluation of intra-abdominal masses [7]. With the improvement of FNA/FNB needles and methodologies; studies have confirmed the improvement of diagnostic accuracy. In other studies FNB was found with superior diagnostic accuracy without compromising safety when compared to FNA [8]. The worldwide survey of EUS-FNA and FNB practice patterns showed wide variations in practice patterns. There is a need of randomized studies to establish the best approach for optimizing the FNA/FNB procedures [9]. As both techniques are considered accurate and safe for tissue sampling of intramural and extramural gastrointestinal lesions but data from our country are lacking [10].

Therefore, the objective of this study was to evaluate the diagnostic accuracy of EUS-FNA/FNB in our settings.

METHODS

It was a descriptive cross sectional study conducted at Department of Gastroenterology and Hepatology, Lahore General Hospital Lahore from October 2019 to March 2023 after taking institutional review board approval vide letter No. AMC/PGMI/LGH/Article/Research No/190/19. After informed consent, all the patients above 18 years with mass lesion of pancreas, sub-epithelial lesions of stomach, abdominal or mediastinal lymph nodes on Magnetic Resonance Imaging (MRI), CT scan or trans abdominal ultrasound of size > 1cm who underwent endoscopic ultrasound guided fine needle aspiration or biopsy were included in the study by non-probability consecutive sampling technique. The major exclusions were pregnant females, patients having Hb < 8 g/dl, patients with uncorrectable coagulopathy or anticoagulant drugs use within 14 days of EUS-FNA, patients with cardio-respiratory dysfunction or any other co-morbid illness that could not tolerate anesthesia and who were unable to give informed consent. Patient demographics (gender, age, location of lesion), procedure details (number of passes, tumor characteristics), complications (bleeding, pneumothorax, perforation, pancreatitis), impression of endoscopist/ EUS diagnosis and histological diagnosis recorded through a predesigned proforma. EUS-FNA/FNB was performed by two Endo- sonographers who have more than 4 years of EUS experience. Procedures were performed at endoscopy suite of the Lahore General Hospital Lahore under propofol induced sedation. There was no on-site cytopathologist present. The number of passes and needle actuations were not standardized and was at the discretion of the Endo-sonographer after assessment on adequate specimen made by visual assessment of the material expressed from the needle. Further, cytological or histopathological analysis was done by the same histopathologist at the Department of Pathology, Lahore General Hospital Lahore. All patients satisfying the inclusion criteria were included in the study after informed consent. The protocol of study was approved by institutional review board. Patient demographics (gender, age, location of lesion), procedure details (number of needle passes, tumor characteristics), complications (bleeding, pneumothorax, perforation, pancreatitis) and final diagnosis recorded through a predesigned proforma. EUS-FNA/FNB was performed by two Endo sonographers who have more than 4 years of EUS experience. Procedures were performed at endoscopy suite of the Lahore General Hospital, Lahore under propofol induced sedation. On-site cytopathologist (ROSE) was not there. Procedures were done with EU-ME2 processor and GUC-UCT 180 curvilinear EUS gastrovideoscope. Rapid onsite evaluation, meaning by availability of onsite cytopathologist in the room, was not available. Fanning technique was used in all cases to improve EUS tissue acquisition. The number of needles passes and needle throws, type of additional measures like type and amount of suction when needed, slow pull technique was at the discretion of the Endo- sonographer after assessment on adequate specimen made by visual assessment of the material expressed from the needle and subsequent examination under microscope by a gastroenterologist to access tissue adequacy. Further, cytological or histopathological analysis was done by the same histopathologist at the Department of Pathology, Lahore General Hospital Lahore. The data were entered and analyzed using SPSS version 23.0. Descriptive statistics calculated for all the variables. Qualitative variables including gender and positive cases presented as frequency and percentage. Quantitative variables like age presented as mean and standard deviation.

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RESULTS

The mean age was 48.84 ± 15.96 years (Range 16-81years). There were 113 (59.8%) males and 76 (40.2%) females. EUS-FNA and FNB was done in 28 (14.8%) and 161 (85.2%) patients respectively. Median number of passes was 3 (IQR: 1-4). Most of the lesions were of pancreatic origin 110 (58.2%) followed by abdominal and mediastinal lymphadenopathy 37 (19.5%), gastric 26 (13.8%), liver 10 (5.3%) ampulla (n=4) and esophageal (n=2) as shown in table 1.

Table 1: Site, Eus Diagnosis and Histopathology/Cytology of the Lesions

Site	Types	Category	n
Pancreas	Solid Pancreatic Mass	Adenocarcinoma of Pancreas	68
		Focal Pancreatitis	6
		Autoimmune Pancreatitis	4
		Neuroendocrine Tumor	3
		Normal Tissue	2
		Epitheloid Neoplas	1
		Inconclusive	14
	Cystic Lesion	Serous Cystadenoma	3
		Intrapapillary Mucinous Neoplasm (IPMN)	3
		Mucinous Cystic Neoplasm (MCN)	2
		Solid Pseudopapillary Neoplasm	1
		Inconclusive	3
Abdominal Lymphadenopathy	Benign Looking LN	Benign Tissue	8
		Chronic Granulomatous Inflammation	3
		Adenocarcinoma	1
		Inconclusive	2
	Malignant Looking LN	Inconclusive	3
		Malignant Neoplasm	1
		Reactive Tissue	1
Mediastinal Lymphadenopathy	Benign Looking LN	Benign Tissue	2
		Chronic Granulomatous Inflammation	3
		Normal Tissue	5
	TB/Lymphoma	Chronic Granulomatous Inflammation	1
		Inconclusive	4
Esophagus	CA Esophagus	CA Esophagus	1
Esophageal SEL	Esophageal Sub Epithelial Lesion (SEL)	Leiomyoma	1
Gastric	Gastric Sub Epithelial Lesions (SEL)	Gastrointestinal Stromal Tumor (GIST)	21
		Neuroendocrine Tumor	1
		Inconclusive	1
	Linitis Plastica	Adenocarcinoma	3
Ampulla	Ampullary Tumor	Inconclusive	4
Liver	Autoimmune Hepatitis	Autoimmune Hepatitis	1
	Primary Sclerosing Cholangitis	Inconclusive	1
	SOL Liver	Inconclusive	4
		Malignant Neoplasm	4

Malignant lesions were found in 105 (55.6%) cases followed by inconclusive results 38 (20.1%), benign diseases 34 (18%) and normal tissue 12 (6.3%). The overall diagnostic yield was 151/179 (79.9%) with comparable yield of EUS-FNA and FNB, 21/28 (75%) and 130/161 (80.7%) respectively (p=0.06).

Table 2: Categories of Lesions Based On Histological/Cytological Characteristics

Procedure	Histological/Cytological Characteristics				Diagnostic Yield	p-Value
Cases	Normal	Inconclusive	Benign	Malignant		
FNA	6	7	6	9	75%	0.06
FNB	6	31	28	96	80.7%	
Total	12	38	34	105	79.9%	

Complications rate was 2.3%. P-value was 0.06

DISCUSSION

Experience from this single center study confirms the utility of EUS- FNA/FNB to characterize and diagnose different hepatopancreatico-biliary, sub-epithelial and nodal lesions with good diagnostic yield ~ 80 %, similar diagnostic accuracy was found in previous studies [11, 12]. EUS has been shown to be the most efficacious for detecting and establishing a diagnosis for smaller lung cancer lesions [13]. The present study found that overall diagnostic accuracy was better with EUS-FNB, 130/161 (80.7%) as with compared with EUS-FNA, 21/28(75%) but was not statically significant (p=0.06). EUS-FNB has been shown to outperform EUS-FNAC with respect to diagnostic accuracy (89.8% vs. 79.1%; P value = 0.013) and tissue adequacy (95.9% vs. 86.1%; p value < 0.001) [14]. Fewer passes are required with EUS-FNB technique and there is no need for rapid on site evaluation (ROSE), so has great practical implications [15]. Most common lesions in present study were pancreatic in origin (58.2%) Most of there were solid lesions and pancreatic adenocarcinoma was the diagnosis in 69.3% cases. Other diagnosis was focal pancreatitis [16]. Similarly distinguishing pancreatic adenocarcinoma from focal pancreatitis has practical implications for treatment and prognosis. In cystic lesions of pancreas serous cystadenoma and Intrapapillary Mucinous Neoplasm (IPMN), Mucinous Cystic Neoplasm (MCN) were most common diagnosis and one cystic lesion in a young lady with was diagnosed as Solid pseudo-papillary neoplasm. Similar result were shown by Jabłońska B *et al.*, were IPMN, MCN and Serous cystadenoma were commonest pancreatic cystic neoplasms in patients presenting with pancreatic cystic lesions [17]. Most of the patients with nodal biopsy 16/34 (47.1) had reactive/normal tissue, tuberculosis found in 7/34 (20.5%) cases. Tuberculosis is endemic in our area so should be considered in any patient with nodal enlargement. Junare PR *et al.*, from India on EUS-FNA/ FNB found tuberculosis in 62.5% patients with mediastinal lymphadenopathy, a number much higher than we found [18]. In a study on esophageal lesions esophageal

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carcinoma and Leiomyoma were found. In Gastric Sub Epithelial Lesions (SELs) GIST was commonest diagnosis, found in 21/23 (91.3%) cases followed by Neuroendocrine Tumor (NET). While evaluating SELs, Leiomyoma is most common diagnosis in esophagus and GIST in stomach [19]. In another study on liver focal lesions, all were malignant, mostly metastatic, with high inconclusive results in 5/10 (50%) cases which is higher than reported previously [20]. In a study on pancreatitis 184 patients it was found that the recent acute pancreatitis with high echo component within the tumor were independently associated with false-negative EUS-TA results. Meanwhile, using Fine-Needle Biopsy (FNB) needles, more needle passes, large tumor size, and high CA-19-9 level were independently associated with true-positive EUS-TA outcomes. Three needle passes are needed to achieve optimal EUS-TA outcomes. Tumor location in the body/tail passes ≥3 and using the FNB needle was independently related to sample adequacy [20]. In another study on lymph nodes sampling, the diagnostic accuracy of FNB was found more as compared to FNA [20, 21]. In a meta-analysis the databases of PubMed, Cochrane and Google Scholar were used, including studies published between 2011–2021 comparing the diagnostic yield (diagnostic accuracy or probability of positivity, sensitivity, specificity, predictive value) of EUS-FNA and EUS-FNB for the diagnosis of pancreatic cancer. Among these, five studies found no statistically significant difference between the EUS-FNA and EUS-FNB, whereas the other four did. The meta-analysis found EUS-FNB accuracy superior to EUS-FNA for the diagnosis of pancreatic cancer [21]. A further prospective study with a larger number of patients is required to see more concise results.

CONCLUSIONS

It was concluded that EUS-FNA/FNB has emerged a powerful modality for investigating various lesions in or around the gastrointestinal tract especially pancreatic lesions and is able to diagnose neoplastic lesions with good sensitivity/ specificity and with excellent safety.

Authors Contribution

Conceptualization: HIM
Methodology: FS, SR, GUH, SJ, FJ, SR, AD, GUNT
Formal analysis: FS, SR, GUH, SJ, FJ, SR, AD, GUNT
Writing, review and editing: HIM, FS, SR, GUH, SJ, FJ, SR, AD, GUNT

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

Conflicts of Interest

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Original Article

Determining the Stage of Kaposi Sarcoma Through Histopathological Analysis: Identifying The Most Effective Finding

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ABSTRACT

Kaposi Sarcoma (KS) is a complex disease presenting as vascular tumors affecting the skin, mucous membranes, lymph nodes, and internal organs. It shows variable clinical presentations and forms. **Objective:** To identify the most effective histopathological indicators for staging Kaposi Sarcoma. **Methods:** This cross-sectional study was conducted at Bithai Medical and Dental Center, Mirpur Khas, from December 2022 to December 2023. A total of 119 biopsy specimens were analyzed for spindle cell density, arrangement, atypia, vascular space formation (size and morphology), inflammatory cells (lymphocytes, plasma cells), hemosiderin extent and distribution, and mitotic activity. Data analysis was performed using SPSS version 24.0. **Results:** The study included 38 males (31.93%) and 81 females (68.07%). The nodular stage was most prevalent (72 cases, 60.5%), followed by the patchy stage (29 cases, 24.37%) and plaque stage (18 cases, 15.12%). Significant histopathological findings included spindle cell proliferation in 62 cases (52.11%), vascular space formation in 39 cases (32.77%), inflammatory infiltrate in 31 cases (26.05%), hemosiderin deposits in 43 cases (36.13%), and mitotic activity in 35 cases (29.41%). **Conclusions:** Spindle cell proliferation and vascular space formation are the most reliable indicators for staging KS. Inflammatory infiltrate composition, hemosiderin deposits, and mitotic activity showed less consistency across different specimens.

INTRODUCTION

Kaposi Sarcoma (KS) is an angio-proliferative disorder associated with human herpesvirus 8 (HHV-8). Initially described by Moritz Kaposi in 1872, it was once considered an uncommon malignancy primarily affecting elderly men of Mediterranean or Eastern European descent [1]. However, the epidemiological landscape of KS has dramatically changed, especially with the advent of the HIV/AIDS pandemic. Among people with HIV (PWH), KS rates are elevated 521-fold compared to the general population [2]. From 2000 to 2015, KS incidence declined from 109 per 100,000 person-years to 47 per 100,000 person-years, with an annual percentage change of –6%. Rates decreased across all demographic and HIV transmission groups, with 1,904 PWH (0.20%) diagnosed with KS by the end of 2015. In the general population, the incidence of classic KS is approximately 1 case per 10 million inhabitants per year. The prevalence of Kaposi sarcoma herpesvirus is higher among Black individuals, people living with HIV, and those with a history of syphilis [3]. KS presents in four main epidemiological forms. Classic KS typically occurs in older men of Mediterranean, Eastern European, or Middle Eastern descent, progressing

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slowly and primarily affecting the lower extremities [4]. Endemic KS is found in sub-Saharan Africa, affecting children and adults independent of HIV infection and can be more aggressive than the classic form. Iatrogenic KS is associated with immunosuppressive therapy, particularly in organ transplant recipients, with potential regression upon reducing immunosuppression [5]. AIDS-related KS is highly aggressive and common in individuals with HIV infection, being one of the AIDS-defining illnesses, though its incidence has decreased with widespread antiretroviral therapy (ART) [6].

HHV-8 infection plays a crucial role in KS pathogenesis. Hemangioendothelioma cells infected by HHV-8 proliferate due to various viral oncogenes such as the viral G-protein coupled receptor (vGPCR) and latency-associated nuclear antigen (LANA) [7]. These genes contribute to cell survival and division, while HHV-8 infection increases the production of pro-inflammatory cytokines like interleukin-6 (IL-6) and vascular endothelial growth factor (VEGF), leading to angiogenesis and tumor growth. The virus's ability to evade immune monitoring facilitates chronic infections and cancer growth in immunosuppressed individuals. KS manifests in different forms and stages, with presentations ranging from purple patches, plaques, and nodules to more severe symptoms affecting the oral cavity, gastrointestinal tract, and internal organs, causing significant morbidity and necessitating systemic treatment [8]. Diagnosis of KS primarily relies on histopathological biopsy samples, supported by clinical findings and imaging studies. Characteristic histopathological findings include spindle cell proliferation, slit-like vascular spaces, inflammatory infiltrates, and hemosiderin deposits. Immunohistochemical staining for HHV-8 latent nuclear antigen-1 (LNA-1) confirms the virus's presence [9]. Imaging studies such as CT or PET scans assess the extent and visceral involvement. In AIDS-related KS, HIV tests and CD4+ T cell counts provide insight into immune compromise. Treatment varies by stage, involvement, and patient status, ranging from surgical excision and radiation therapy for localized lesions to systemic treatments like liposomal anthracyclines and antiretroviral therapy for more extensive disease. Immunotherapy agents like interferon-alpha have been used, particularly for classic KS [10]. Despite advances in understanding KS histopathology, gaps remain, notably the lack of universally accepted criteria for histopathological staging [11]. Most studies rely on qualitative descriptions of histopathological features, and quantitative methods for assessing spindle cell density, vascular space formation, and mitotic activity are underutilized [12]. Such approaches could offer more objective and reproducible criteria for staging KS [13]. Moreover, limited research correlates histopathological findings with clinical outcomes, such as therapy response and survival rates.

The primary objective of this study was to identify the most effective histopathological findings for accurately determining the stage of Kaposi Sarcoma (KS). By systematically analyzing the histopathological features associated with the patch, plaque, and nodular stages of KS, this study aims to characterize key histopathological features and evaluate diagnostic accuracy. This research seeks to identify the most indicative and consistent markers for staging KS, thereby providing a robust basis for clinical diagnosis and treatment planning.

METHODS

This cross-sectional study was conducted at Bithai Medical and Dental Center, Mirpur Khas, from December 2022 to December 2023, after receiving approval from the Ethics Review Committee, Bithai Medical and Dental Center, Mirpur Khas (Reference Number: BDMC/R&D/ERC/2022-01). Patient demographics, clinical history, and preoperative diagnostic results were documented along with other pertinent clinical data. Specific inclusion and exclusion criteria were designed. Sample size was calculated through open EPI software. Biopsy samples from patients diagnosed with Kaposi Sarcoma, confirmed through histopathology, were included in this study. Inadequate or poor-quality biopsy samples and samples from patients with concurrent malignancies or conditions that might confound histopathological analysis were excluded. Informed consent was obtained from all patients/participants. Patient registration numbers, dates, and unique identifying numbers were appropriately labeled on each specimen container. Hematoxylin and eosin (H&E) staining was used to assess general tissue morphology, while immunohistochemical (IHC) staining for HHV-8 latent nuclear antigen-1 (LNA-1) confirmed the presence of HHV-8 infection. A comprehensive macroscopic analysis of the biopsy samples was performed, noting dimensions, weight, color, and any obvious anomalies. The specimen's orientation and specific areas of interest identified during physical inspection were documented and sampled. The fixed tissue was processed through clearing, paraffin embedding, and dehydration. A microtome was used to cut thin sections, typically 4-5 micrometers in size, which were then mounted on glass slides. Hematoxylin and eosin (H and E) staining was carried out routinely for light microscopic examination at different magnifications. The biopsy tissue's cellularity, architecture, and cytological characteristics were assessed by a resident histopathologic and two consultant histopathologists. Each specimen was thoroughly examined for the density, arrangement, and atypia of spindle cells, the vascular space formation by assessing the presence, size, and morphology of vascular spaces. The type and density of

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inflammatory cells (lymphocytes, plasma cells, etc.), extent and distribution of hemosiderin, and mitotic activity were also documented to assess the staging and identification of the most effective findings. Data analysis was conducted using the Statistical Package for Social Sciences (SPSS) version 24. For quantitative variables, the calculations included mean and standard deviation; for qualitative variables, frequencies and percentages were calculated. A p-value of less than or equal to 0.05 was considered significant.

RESULTS

The study involved a total of 119 patients distributed across various age groups. In the youngest cohort, ages 11-20, there was 1 patient (0.84%), who was female. The 21-30 age group had 23 patients (19.32%), with a male-to-female ratio of 8 to 15. The largest group was the 31-40 age bracket, encompassing 43 patients (36.13%), comprising 13 males and 30 females. In the 41-50 age range, there were 26 patients (21.85%), with 8 males and 18 females. The 51-60 group included 19 patients (15.97%), split into 6 males and 13 females. Lastly, the 61-70 age group had 7 patients (5.89%), with 3 males and 4 females. Overall, the patient population consisted of 38 males (31.93%) and 81 females (68.07%), illustrating a higher prevalence of the condition in females across all age groups (Table 1).

Table 1: Age and Gender Distribution of Kaposi Sarcoma in The Study Sample

Age Groups (Years)	Number of Patients	Males	Females
11-20	01 (0.84%)	00	01
21-30	23 (19.32%)	08	15
31-40	43(36.13%)	13	30
41-50	26(21.85%)	08	18
51-60	19 (15.97%)	06	13
61-70	07 (5.89%)	03	04
Total	119	38 (31.93%)	81 (68.07%)

The study analyzed 119 cases of Kaposi Sarcoma, distributed across different pathological stages and genders. The nodular stage was the most prevalent, accounting for 72 cases (60.5%). Among these, 22 were males and 50 were females. The patchy stage was observed in 29 cases (24.37%), with a gender distribution of 9 males and 20 females. The plaque stage comprised the remaining 18 cases (15.12%), including 7 males and 11 females. This data highlights that females are more frequently affected across all stages of Kaposi Sarcoma, with the nodular stage being the most common form observed in the patient cohort. Total cases were 119 in which males were 38 and females were 81 (Table 2).

Table 2: Stages of Kaposi Sarcoma

Variables	Total Cases N (%)	Male (n)	Female (n)
Pathological Staging			
Nodular stage	72 (60.5%)	22	50
Patchy stage	29 (24.37%)	9	20
Plaque stage	18 (15.12%)	7	11

The histopathological analysis of 119 Kaposi Sarcoma cases revealed significant findings in various parameters. Spindle cell proliferation was observed in 62 cases (52.11%), with a p-value of 0.04, indicating statistical significance. Vascular space formation was present in 39 cases (32.77%), with a p-value of 0.02. Inflammatory infiltrate was found in 31 cases (26.05%), also with a p-value of 0.02. Hemosiderin deposits were identified in 43 cases (36.13%), showing a highly significant p-value of less than 0.01. Lastly, mitotic activity was noted in 35 cases (29.41%), with a p-value of 0.04. These findings underscore the importance of these histopathological features in the assessment and staging of Kaposi Sarcoma, with each parameter contributing significantly to the diagnosis (Table 3).

Table 3: Histopathological Findings of Kaposi Sarcoma

Histopathological Findings	Results N (%)	P-Value
Spindle Cell Proliferation	62 (52.11%)	0.04
Vascular space formation	39 (32.77%)	0.02
Inflammatory Infiltrate	31 (26.05%)	0.02
Hemosiderin Deposits	43 (36.13%)	<0.01
Mitotic Activity	35 (29.41%)	0.04

In figure 1, the histopathological features of Kaposi Sarcoma are depicted as follows: A) Perivascular infiltrate primarily consisting of plasma cells, B) Spindled cells with slit-like vascular channels containing hemosiderin, C) Vascular spaces lined by lesional cells, and D) Spindled cells.

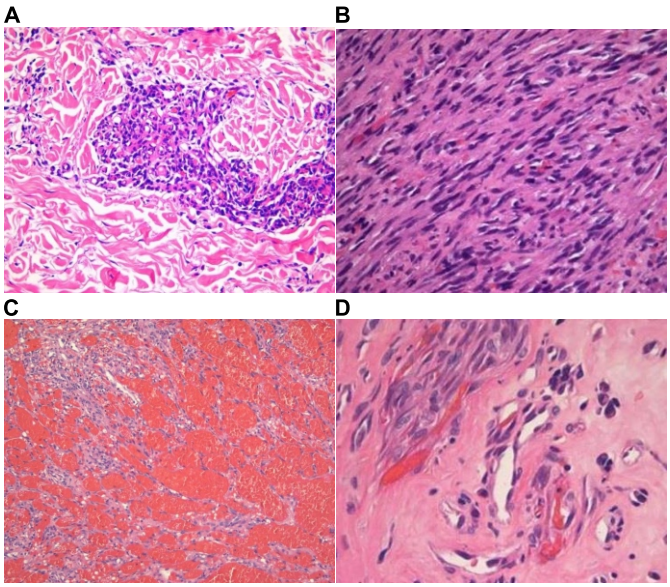

Figure 1: A: Perivascular Infiltrate Comprised Mainly Of Plasma Cells, **B:** Spindled Cells, With Slit-Like Vascular Channels Containing Hemosiderin, **C:** Vascular Spaces Lined By Lesional Cells, **D:** Spindled Cells

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DISCUSSION

Kaposi Sarcoma (KS) is a multifaceted disease primarily associated with Human Herpesvirus 8 (HHV-8), also known as Kaposi Sarcoma-associated herpesvirus (KSHV). It manifests as vascular tumors affecting the skin, mucous membranes, lymph nodes, and internal organs. KS presents in various forms, including classic, endemic, iatrogenic, and AIDS-related variants [14]. This study has shown that the most common stage of KS observed is the nodular stage, found in 60.5% of cases, followed by the patch and plaque stages, found in 24.3% and 15.12% of cases, respectively. These findings align with previous research by Gervas R et al., who reported the nodular stage in 74.5% of cases, followed by patchy (19.4%) and plaque (6.1%) stages, albeit in a different sequence [15]. The histopathological analysis provided crucial insights into diagnosing and classifying KS. Spindle cell proliferation was observed in 62 cases (52.11%), with a statistically significant p-value of 0.04. Spindle cells are a hallmark of KS, representing the transformed endothelial cells that proliferate in response to HHV-8 infection. The presence of spindle cells is essential for diagnosing KS, as these cells form the bulk of the tumor mass in advanced stages. Vascular space formation was noted in 39 cases (32.77%), with a p-value of 0.03. These spaces, formed by endothelial cells, appear as slit-like structures in plaque and nodular stages of KS [4]. Inflammatory infiltrates were observed in 31 cases (26.05%), with a p-value of 0.02. These infiltrates, composed of lymphocytes, plasma cells, and macrophages, play a role in the progression of KS lesions, especially in the early stages [16]. Hemosiderin deposits were identified in 43 cases (36.13%), indicative of chronic bleeding and erythrocyte extravasation, frequently coinciding with extensive vascular proliferation and hemorrhage in the plaque and nodular phases. Mitotic activity was observed in 35 cases (29.41%), with a p-value of 0.04. Higher mitotic rates suggest increased proliferation, characteristic of more advanced and aggressive disease stages [17]. These findings have significant implications for clinical practice and research. Establishing a unified histological staging system for KS could reduce diagnostic variability and ensure uniformity across medical settings [18]. Identifying critical histological markers of disease progression allows for better prognostication and tailored interventions based on disease severity [19]. These results can enhance the education and training of pathologists, improving their ability to identify and stage KS accurately. Incorporating these findings into medical school curricula and continuing medical education programs can enhance diagnostic accuracy and consistency. Additionally, the study's insights can inform health policies, particularly in regions with high KS prevalence, such as areas heavily affected by HIV/AIDS. By understanding the most indicative histopathological features, healthcare providers can implement more effective management strategies for KS [20]. The cross-sectional nature of the study does not capture the dynamic changes during KS progression. Longitudinal studies tracking histopathological features over time would provide a more comprehensive understanding of disease evolution.

CONCLUSIONS

The histopathological examination revealed that spindle cell proliferation and vascular space formation are the most consistent and reliable indicators for staging KS. These features demonstrate progressive changes from the patch stage to the nodular stage, reflecting the increasing aggressiveness and complexity of the disease. Additionally, inflammatory infiltrate composition, hemosiderin deposits, and mitotic activity were found to provide supplementary information for KS staging, albeit with less consistency.

Authors Contribution

Conceptualization: MA
Methodology: MA, QAS
Formal analysis: MA, JK
Writing, review and editing: MA, HA, SA, AJ, JK, QAS

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparative Analysis of Trans Vaginal Ultrasound and Bishop Score For Successful Prediction of Induction of Labor in Term Primigravidas

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ABSTRACT

Successful prediction of labor induction outcomes in the term primigravidas has significant implications for maternal and neonatal health. **Objective:** To compare trans vaginal ultrasound (TVS) and bishop score for successful prediction of induction of labor in term primigravidas. **Methods:** This cross sectional comparative study was carried out at Department of Gynecology and Obstetrics and Department of Radiology of Shahida Islam Medial Complex, Lodhran, Pakistan using non-probability purposive sampling technique. The duration of study was six months from October 2023 to March 2024. Booked primigravidas in-between 18 to 40 years at 37-40 gestational week having singleton pregnancy were included Each female underwent Bishop scoring and TVS ultrasound **Results:** From total 151 pregnant females mean age was 28.63 ± 8.12 years, mean gestational age was 40.24 ± 0.77 weeks, mean bishop score and mean cervical length measured by TVS was 6.95 ± 2.21 and 27.2 ± 3.98 mm respectively. 117 (77.48 %) females had positive Bishop Score, 106 (70.2 %) positive Cervical Length (>27 mm) and 90 (59.6 %) induction of labor. Diagnostic accuracy of Bishop Score was 65.9 % while for TVS ultrasound was 80.2 %. Significant difference of p<0.001 was reported in-between cervical length >27 mm on TVS and successful induction of labor. TVS showed higher sensitivity 89.7%, specificity 62.3%, positive predictive value 77% and negative predictive value 82.1% as compared to Bishop Score. **Conclusions:** The results of this study concluded that the assessment of cervical length on TVUS was more accurate than Bishop Score in predicting successful induction of labor in term primigravidas.

INTRODUCTION

Labor induction is one of the frequent obstetrical interventions aimed at initiating uterine contractions to achieve vaginal delivery in cases where continuation of pregnancy poses risks to maternal or fetal health [1]. Labor induction rates have been steadily increasing globally, reflecting changes in obstetric practices, maternal demographics, and medical indications [2]. Indications for labor induction include post-term pregnancy, preeclampsia, fetal growth restriction, gestational diabetes, and maternal medical conditions such as hypertension or renal disease [3]. Successful labor induction relies on the readiness of the cervix, characterized by cervical ripeness and effacement, to respond to oxytocin or prostaglandin administration [4]. Effectively predicting labor induction successfully is crucial for optimizing obstetric outcomes and minimizing the need for cesarean delivery [5]. In primigravida at term, several techniques are employed to assess readiness of cervix for induction, including Trans-Vaginal Ultrasound (TVUS) and the Bishop score [6]. TVUS offers a non-invasive method for assessing cervical length, position, and morphology, providing valuable information on cervical ripeness and predicts likelihood of successful induction of labor [7]. TVUS measures cervical length from the external

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os to the internal os and evaluates cervical consistency, dilatation, and effacement. A shorter cervical length and increased cervical dilatation and effacement on TVUS are associated with a higher likelihood of labor's spontaneous onset with successful induction [8]. The Bishop score is a widely used clinical score to assess readiness of cervix for labor induction, comprising five components: cervical dilatation, effacement, consistency, position, and fetal station [9]. Each component is assigned a score ranging from 0 to 3 or 0 to 2, with higher scores indicating favorable cervical conditions for induction. The total Bishop score provides an overall assessment of cervical readiness, with scores ≥ 5 considered favorable for successful labor induction [10]. Successful prediction of labor induction outcomes in term primigravidas has significant implications for maternal and neonatal health, healthcare resource utilization, and patient satisfaction [11]. While both TVUS and the Bishop score are established methods for assessing cervical readiness, limited research has directly compared their predictive accuracy and clinical utility, particularly in term primigravidas [12]. Understanding the comparative performance of these two approaches can inform evidence-based decision-making in clinical practice and optimize the management of labor induction in this population [13]. By elucidating the comparative performance of TVUS and the Bishop score, this research can inform evidence-based obstetric practice, optimize resource allocation, and improve maternal-fetal outcomes in this high-risk population [14]. Additionally, identifying the most reliable predictor of successful labor induction may facilitate personalized approaches to obstetric care and enhance patient counseling and decision-making regarding labor management strategies [15].

This study hypothesized that Trans Vaginal Ultrasound (TVS) is more accurate than the Bishop Score in predicting the successful induction of labor in term primigravidas. By conducting a comparison of TVUS and the Bishop score, this research seeks to identify the most reliable predictor of successful labor induction and guide individualized patient care.

METHODS

A comparative cross sectional study was carried out at Department of Gynecology and Obstetrics and Department of Radiology of Shahida Islam Medical Complex, Lodhran, Pakistan using non-probability purposive sampling. The study was carried after obtaining Institutional review board No. SIMC/H.R./7726/23. Study duration was six months from October 2023 to March 2024. Using open epi online software for sample size calculation, keeping 74 % as the expected frequency of successful induction of labor as reported in a study, the sample size came out to be 151 at 95 % confidence level [16]. Booked primigravidas in-between 18 to 40 years of age at around 37-40 gestational week (from LMP) having singleton pregnancy (cephalic) were included in the study. Booked primigravidas were chosen to reduce variability caused by previous childbirths and ensuring homogenous population. The age of 18 to 40 years was chosen as this is the reproductive child age group years and gestational age of 37 to 40 weeks was chosen to ensure focus on full-term pregnancies standardizing the gestational timeframe, ensuring that all participants are at a comparable stage of pregnancy, which is critical for assessing the effectiveness of induction methods. Limiting the study to singleton pregnancies eliminates the increased risks and different management protocols associated with multiple gestations, allowing for a more straightforward comparison between TVS and Bishop Score. In females with multiple pregnancies as reported by ultrasonography (USG), females with premature rupture of membrane or premature prolonged rupture of membrane (PROM or PPROM) on clinical examination, high risk pregnancy such as gestational diabetes (blood glucose >200 mg/dl), pregnancy induced hypertension (PIH) with blood pressure >140/90 mmHg, pre-eclampsia or eclampsia were excluded from the study due to additional monitoring and interventions that could skew the results. Excluding multiple pregnancies ensures the study focuses on standard induction protocols without the additional complexities and risks associated with multiple gestations. PROM or PPROM can significantly alter the approach to labor induction and the natural progression of labor, confounding the study results. Informed consent was sought from every female prior to inclusion. Complete medical and surgical history including demographics, general physical and clinical examination was included in the study. During clinical examination, each pregnant female underwent bishop scoring and vaginal examination and were labeled as negative or positive according to operational definition. Thereafter, trans-vaginal ultrasound (TVS) was performed by the researcher themselves using a high-resolution transvaginal ultrasound machine (LOGIQ S6, General Electrical, Japan) equipped with a 5-9 MHz transducer probe. The ultrasound machine was equipped with advanced obstetric software for precise measurements of cervical length and detection of cervical funneling. A high-frequency transvaginal transducer probe was used to provide detailed imaging of the cervix. This probe allows for close proximity imaging, resulting in high-resolution images critical for accurate measurements. Examination was conducted with the pregnant female in dorsal lithotomy position having empty bladder. Sagittal plane through cervix was determined when external os, cervical canal and internal os were visible and length of cervix was calculated measuring distance in-between internal and external os, thereafter being labeled positive or negative. Cervical length was defined as distance in-between internal and external os while induction of labor was defined as administration of misoprostol drug per vaginum in each pregnant female for

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inducing labor at 40 weeks gestation. Using TVS ultrasound, a cervical length of >27 mm was considered as positive. Successful induction of labor on TVS was termed when vaginal delivery was carried out within 24 hours as TVS predicted (at >27 mm length). A Bishop score of >5 was considered as positive while <5 as negative. For induction of labor, all pregnant females were administered 50 mcg of Misoprostol as per protocol of the hospital and waited. If induction did not pursue, dose was repeated at six hours. To monitor fetal heart rate, Cardiotocography (CTG) was used. All the information was recorded with confidentiality. For analysis of data, SPSS version 23.0 was used. Quantitative variables were presented as, mean and standard deviation (maternal and gestational age, cervical length and bishop scores). For categorical variables such as successfl labor induction, specificity, sensitivity, Positive and Negative Predictive Value (PPV and NPV) and diagnostic accuracy of TVS and bishop scoring, frequency and percentage were reported. Chi square test was applied between accuracy of TVS and bishop scoring, keeping p value <0.05 of statistical significance.

RESULTS

Total 151 pregnant females were enrolled with mean age of 28.63 ± 8.12 years. Mean gestational age was 40.24 ± 0.77 weeks at time of presentation. The mean bishop score and cervical length by TVS was 6.95 ± 2.21 and 27.2 ± 3.98 mm respectively. Total of 90 females achieved success, from which 75 (83.3 %) were positive for >5 Bishop Score. Amongst 62 females without successful induction, positive Bishop Score was observed in 43 (69.3 %) females. A significant difference of <0.03 was observed between Bishop Score and successful induction of labor. This suggests that a higher Bishop Score is associated with a higher likelihood of successful labor induction, although the association is moderate. In 90 females with successful induction of labor, 81 (90 %) had >27 mm of cervical length and in 62 females without successful induction of labor, 25 (40.3 %) had cervical length of >27 mm on TVS. Significant difference of p<0.001 was reported in-between cervical length >27 mm on TVS and successful induction of labor as shown in table 1. This indicates that a cervical length greater than 27 mm is strongly associated with successful labor induction. The data shows that both the Bishop Score and cervical length measured by TVS are useful predictors of successful labor induction in term primigravidas. However, cervical length appears to be a stronger and more reliable predictor compared to the Bishop Score.

Table 1: Comparison of Bishop Score and Cervical Length on TVS Success Rate for Induction of Labor (n=151)

Variables		Successful Induction of Labor N (%)		p-Value
		Yes	No	
Bishop Score >5	Yes	75 (83.3 %)	43 (69.3 %)	0.03
	No	15 (16.6 %)	19 (30.6 %)	
Cervical Length >27 mm on TVS	Yes	81 (90 %)	25 (40.3 %)	<0.001
	No	09 (10 %)	37 (59.7 %)	

Predictive values of both Bishop Score and Cervical Length >27 mm on TVS in terms of sensitivity, specificity, PPV, NPV and diagnostic accuracy were recorded in table 2. Cervical length measurement via TVS demonstrates higher sensitivity, specificity, PPV, NPV, and diagnostic accuracy compared to the Bishop Score. This suggests that cervical length > 27 mm on TVS is a more reliable and accurate predictor of successful labor induction in term primigravidas.

Table 2: Comparison of Predictive Values in Terms of Bishop Score versus Cervical Length on TVS (n=151)

Variables	Sensitivity (%)	Specificity (%)	Positive Predictive Value %	Negative Predictive Value %	Diagnostic Accuracy %
Bishop Score >5	86.2%	41%6	67.1%	59%	65.9%
Cervical Length >27 mm on TVS	89.7%	2.3%	77%	82.1%	80.2%

There were 117 (77.48 %) females having positive Bishop Score while 106 (70.2 %) had positive Cervical Length and 90 (59.6 %) had induction of labor as shown in figure 1.

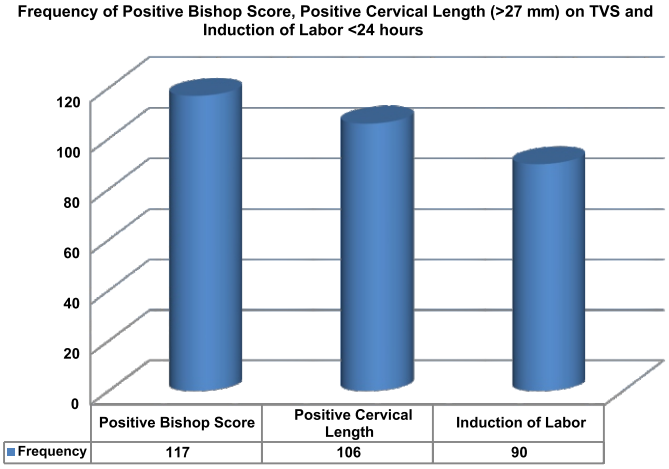

Figure 1: Graphical representation of Positive Bishop Score, Positive Cervical Length (>27 mm) on TVS and Induction of Labor <24 hours (n=151)

DISCUSSION

The results of this study showed that although both TVUS and Bishop Score were successful in prediction of labor induction, TVUS was observed to be a far better predictor. In terms of sensitivity (89.7 % vs 86.2 %), specificity (62.3 % vs 41 %), PPV (77 % vs 67.1 %) and NPV (82.1 vs 59 %) as well as diagnostic accuracy (80.2 % vs 65.9 %), TVUS was reported to be better suited in prediction of labor induction successfully in term primigravidas. TVS and the Bishop score are commonly used methods for predicting the labor induction in primigravidas at term successfully [17]. The Bishop score, which evaluates cervical consistency, dilation, position, effacement and presenting part's station, has been widely used as a standard method for

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assessing cervical ripeness. However, its subjectivity and high intra and inter observer variability have caused searching for a more objectively sound method of assessment [18, 19]. Several studies have assessed predictive values of cervical measurements measured via TVS. In accordance with our research, a pilot study found that trans-vaginal ultrasound of cervix prior to labor induction was better a predicting effective induction as compared to Bishop score [20]. Another research similar to ours reported that women that were scheduled for labor induction reported assessment through digital examination of cervix and trans-vaginal ultra-sonographic of cervix more accurate in predicting cervical inducibility than the Bishop score [21]. Likewise a more recent study of 131 women found that trans-vaginal ultrasonography of length of cervix was much accurate and objective compared to Bishop Score in prediction of likelihood of successful labor induction. The study found that specificity and sensitivity, positive and negative predictive values were much more based on length of cervix 27 mm when compared with bishop score (> 5) [22]. Another comparative study, similar to our research, cervical TVS and Bishop score in predicting effective labor induction found that trans-vaginal ultrasonography, with its ability to objectively measure cervical parameters, could possibly be able to give better way for prediction [23]. The research concluded that cervical TVS score, which comprises of 5; cervical length and position, distance from presenting part to external os and funneling at internal os performed better compared with the Bishop score in prediction [24]. In addition to cervical length, other parameters such as distance from the presenting part to the external os, funnel length and width at internal os and position of cervix have been found to be important predictors of successful induction [25]. A research showed cervical length, presence of funneling, parity and Bishop Score were significantly termed as independently predicting of labor induction successfully [26]. The study population was restricted to low-risk, term primigravidas with singleton, cephalic pregnancies, which may limit the generalizability of the results to other obstetric populations, such as multiparous women, those with high-risk pregnancies, or those with non-cephalic presentations. Additionally, the cost-effectiveness and feasibility of implementing TVS in routine clinical practice need to be evaluated. Finally, long-term maternal and neonatal outcomes should be studied to understand the broader implications of using TVS for labor induction prediction.

CONCLUSIONS

In conclusion, there was moderate association between higher Bishop Score and likelihood of successful induction of labor. However TVS cervical score, which includes objective measurements of cervical parameters, has been found to be a more accurate and objective method of predicting successful labor induction in primigravidas at term compared to the Bishop score. The positive and negative predictive values of cervical length, diagnostic accuracy, sensitivity and specificity on TVS were found to be superior as compared to Bishop Scoring. Nonetheless, further researches are required for confirming such findings and to determine optimal cut-off values for predicting successful induction.

Authors Contribution

Conceptualization: WA

Methodology: NM

Formal analysis: SB

Writing, review and editing: WA, NM, FU, SB, ZUA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Evaluation of Laparoscopic Appendectomy in Response to Anatomical Variation of Appendix

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Laparoscopic Appendectomy, Anatomical Variations, Appendix, Surgical Outcomes

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ABSTRACT

Laparoscopic appendectomy also known as minimally invasive surgery has revolutionized the field of surgery by offering patients less invasive alternatives to traditional open procedure. However, anatomical variations in the location of appendix can prove challenging for laparoscopic surgeons. **Objective:** To evaluate the effectiveness and challenges of laparoscopic appendectomy in patients with anatomical variations in the location of the appendix. **Methods:** It was a cross-sectional study conducted at Jinnah international hospital Abbottabad KPK Pakistan from January 2023 to December 2023. After screening through the selected criteria 91 patients were included in this study. Data were entered and analyzed using SPSS version 24.0. P-values of ≤0.05 will be considered statistically significant. **Results:** The mean age of the study population was 49.2 ± 5.4years. Among the 91 patients analyzed, the anterior position was observed in 54 individuals, pelvic position observed in 10 patients, the retrocecal position observed in 19 patients, and the subhepatic position observed in 8 patients. Among patients with a retrocecal appendiceal position 19 (13.6%) experienced appendiceal rupture, while 2.9% had appendiceal bleeding. A notable proportion (11.11%) required conversion to open surgery. Among patients with a subhepatic appendiceal position 8 (17.1%) experienced appendiceal rupture, while 1.9% had appendiceal bleeding. A considerable proportion (12.5%) required conversion to open surgery. **Conclusions:** In conclusion, laparoscopic appendectomy, while advantageous over open surgery in many aspects, presents specific challenges when dealing with anatomical variations of the appendix, particularly in the retrocecal and subhepatic positions. The study found that these variations are associated with higher rates of intraoperative complications and conversion to open surgery.

INTRODUCTION

Laparoscopic surgery, sometimes referred to as minimally invasive surgery, has transformed the field of surgery for patients by offering them less intrusive options that are used instead of conventional open procedures. By using a laparoscope, a small video camera, inserted through a small incision in the patient's skin, that capture a high-quality magnified image of organs within the abdominal cavity enabling them to make precise cuts or other necessary medical manipulations using a screen [1]. Laparoscopic appendectomy is ranked among top emergency surgical procedures globally. Traditionally, appendectomy was performed using an open surgical approach, which involves a larger incision in the abdomen [2]. Laparoscopic appendectomy has grown in popularity since early 2000s due to its significant advantages including smaller incisions than the open method, better cosmetic outcomes, shorter hospital stay durations and lower risks of wound infections [3]. Typically, the appendix is found in the right lower quadrant (RLQ) of the abdomen. It is typically located about one third of the distance between the anterior superior iliac spine (ASIS) and the umbilicus which is also known as McBurney's point [4]. It is the place

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where three bands of longitudinal muscles called taeniae coli converge at the cecum, which is the approximate location. The appendix differs in size and position; some appendices are about 20 cm long, being one of the longest ever recorded [5]. 33% are in retrocecal position but others like pelvic appendix are seen among 28.5% patients as well as ileal which is also present in 14.5% [6, 7]. Appendices are usually fixed in 32% of normal cases and 22.6% of pathological appendices but this position is linked to fixity and complications [8]. Atypical presentations of appendicitis due to anatomical variations can make it difficult to diagnose the ailment. Apparent but mild right lower quadrant pain and tenderness can manifest in retrocecal appendicitis and may easily be confused with renal colic or diverticulitis among other conditions. Moreover, if the appendix is located within the pelvis, typical signs may only arise from the lower parts hence creating confusion when trying to distinguish it from gynecologic or urological problems [9]. A thorough knowledge of their locations is necessary for efficient surgical interventions especially because the anatomical variations in the caecum and appendix can pose diagnostic and surgical challenges [10]. When laparoscopy is used for appendectomy, anatomical variations in the appendix make it a challenge but an understanding of these variations is important in positioning the ports safely and for optimal performance [11]. Studies have shown that laparoscopic appendectomy is safe and suitable for various anatomical positions of the inflamed appendix, with a conversion rate of 4.7% due to other pathologies [12]. The existing literature has scarce information on the effect of anatomical variations to surgical outcomes and complications after doing laparoscopic appendectomy. Moreover, there is little information on best surgical practices in cases of anatomical variations of the appendix during laparoscopy [13]. Long-term follow-up data on patients that have undergone laparoscopic appendectomy for appendicitis with anatomical variations are scarce [14]. Filling these voids in literature will add value by aiding in understanding the difficulties and considerations in lap appendectomy due to anatomical variations of the appendix hence leading to better treatment and operative results.

This research aimed to determine how anatomical variations of the appendix (e.g., retrocecal, pelvic, and subcecal positions) influence surgical parameters such as operative time, intraoperative complications, frequency of conversion to open surgery, hospital stay length, and postoperative complications. The study seeks to provide evidence-based guidelines for managing appendicitis in various anatomical settings, focusing on preoperative imaging, surgical planning, intraoperative techniques, and postoperative care to improve treatment outcomes in complex cases.

METHODS

A cross-sectional study was performed at Jinnah International Hospital Abbottabad, KPK, Pakistan from January 2023 till December 2023 after the approval of Institutional review board (IRB), Jinnah International Hospital, Abbottabad (JIHA/QMS/7611). All patients admitted to surgical ward of Jinnah International Hospital Abbottabad KPK Pakistan within the chosen period were screened for inclusion in this research. Patients of all ages with clinical signs of acute appendicitis (abdominal pain, tenderness, systemic inflammation) who underwent laparoscopic appendectomy were included. Excluded were patients with non-appendicitis diagnoses (e.g., appendiceal tumor, inflammatory bowel disease), incomplete records, missing preoperative imaging, contraindications to laparoscopic surgery (e.g., severe cardiopulmonary disease, coagulopathy, hemodynamic instability), prior abdominal surgery, or complications requiring immediate open surgery. A total of 132 patients were admitted for laparoscopic appendectomy in surgery department and after screening through the selected criteria 91 patients were included in this study. The sample size was calculated by using population proportion 26.3%. The confidence interval of 95% and error margin of 6.5%. The selected sample was provided detailed information about the steps and procedure involved in this study and informed consent was taken. Patients were divided into four groups according to the appendiceal positions (anterior, retrocecal, pelvic and sub-hepatic). All the selected participants were evaluated for demographic variables such as age and gender, clinical variables including BMI, duration of symptoms, vomiting, diarrhea, urinary symptoms, fever, and abdominal pain. Anatomical positions of the appendix (anterior, pelvic, retrocecal, subhepatic) was considered. Intraoperative variables include appendiceal rupture, appendiceal bleeding, conversion to open surgery, and operative time. Postoperative variables were assessed for the duration of analgesia therapy, hospital stay, oral refeeding time, and postoperative complications like bowel obstruction. Descriptive statistics summarized age, operative time, anatomical positions, and complications. Chi-square tests compared intraoperative complications, conversion to open surgery, and postoperative complications among different anatomical positions. One-way ANOVA analyzed differences in operative time and hospital stay length, with Tukey's test for post-hoc comparisons. P-values ≤0.05 were statistically significant, and confidence intervals provided estimate precision. Data were entered and analyzed using SPSS (Statistical Package for the Social Sciences) version 24.0. It was presented as mean, standard deviation, and percentages. P-values of ≤0.05 will be considered statistically significant.

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RESULTS

The result of the study has shown that the mean age of the study population was 49.2 ± 5.4years. In terms of gender distribution, 55 patients (60.44%) were male, while 36 patients (39.56%) were female. The BMI of the study cohort was 28.3 ± 5.6kg/m. Among the included patients, 34 individuals (37.36%) had a documented history of diabetes, while 31 patients (34.07%) had hypertension. Among the 91 patients analyzed, the anterior position was observed in 54 individuals, pelvic position observed in 10 patients, the retrocecal position observed in 19 patients, and the subhepatic position observed in 8 patients (Table 1).

Table 1: Demographic Characteristics of Study Sample (n=91)

Variables	(Mean ± SD) / N (%)
Age (Years)	49.2 ± 5.4
Male	55 (60.44 %)
Female	36 (39.56 %)
BMI	28.3 ± 5.6

This study has examined the symptoms and signs presented by patients with different appendiceal positions. Among patients with the anterior position (n=54), the mean duration of symptoms was 1.4 days. Vomiting was reported in 57% of cases, followed by diarrhea in 15.2% of cases. Urinary symptoms were less common, occurring in 7.6% of patients. Fever, defined as a temperature of ≥38ºC, was observed in 37.6% of patients with an anterior appendiceal position. Abdominal pain was predominantly localized to the right iliac fossa in 81.9% of cases, with a smaller proportion reporting widespread (14.0%) or other locations (4.1%) (P=0.29). In patients with a pelvic appendiceal position (n=10), the mean duration of symptoms was slightly longer at 1.7 days. Vomiting occurred in 67% of cases, while diarrhea was reported in 19.2% of cases. Urinary symptoms were less frequent, occurring in 4.7% of patients The anatomical variations of the appendix observed in the study were as follows: anterior (n=54), pelvic (n=10), retrocecal (n=19), and subhepatic (n=8) (Table 2).

Table 2: Comparison of Clinical Signs and Symptoms

Symptoms and Signs	Anterior (Mean ± SD) /N (%)	Pelvic (Mean± SD) /N (%)	Retrocecal (Mean ± SD) /N (%)	Sub hepatic (Mean ± SD) /N (%)	P-Value
Duration of Symptoms (Days)	1.4 ± 0.01	1.7 ± 0.034	1.2 ± 0.031	1.2 ± 0.04	0.29
Vomiting	57%	67%	59%	72%	0.14
Diarrhea	15.2%	19.2%	9.3%	8.4%	0.07
Urinary symptoms	7.6%	4.7%	3.9%	1.1%	0.01
Fever (≥38ºC)	37.6%	49%	29.6%	52.3%	0.06
Abdominal Pain					
Right iliac fossa	81.9%	71.4%	88.8%	81.4%	0.22
Widespread	14.0%	22.2%	7.4%	14.8%	
Other locations	4.1%	6.4%	3.8%	3.8%	

The intraoperative and postoperative findings among patients with different appendiceal positions were as follows. Among patients with an anterior appendiceal position (n=54), intraoperative findings revealed that 7% experienced appendiceal rupture, while 2.1% had appendiceal bleeding. A small proportion (1.9%) required conversion to open surgery. The mean operative time for laparoscopic appendectomy in this group was 55.7 minutes. Postoperatively, patients received analgesia therapy for an average of 3.4 days, with a hospital stay averaging 2.7 days. The duration of oral refeeding was relatively short, with an average of 1.3 days. Additionally, 2.1% of patients experienced postoperative bowel obstruction. Statistical analysis revealed significant differences between groups in terms of intraoperative appendiceal rupture (P = 0.02), appendiceal bleeding (P = 0.03), conversion to open surgery (P = 0.005), operative time (P = 0.006), analgesia therapy duration (P = 0.001), and oral refeeding duration (P = 0.009). In patients with a pelvic appendiceal position (n=10), intraoperative findings showed a slightly higher incidence of appendiceal rupture (11%) and appendiceal bleeding (3%), with no conversions to open surgery. The mean operative time for laparoscopic appendectomy in this group was 56.9 minutes. Postoperatively, patients received analgesia therapy for an average of 5.3 days, with a hospital stay averaging 3.5 days. The duration of oral refeeding was slightly longer, with an average of 1.5 days. Postoperative bowel obstruction was observed in 7.7% of patients. Statistical analysis revealed significant differences between groups in terms of operative time (P = 0.006), analgesia therapy duration (P = 0.001), and oral refeeding duration (P = 0.009). Among patients with a retrocecal appendiceal position (n=19), 13.6% experienced appendiceal rupture, while 2.9% had appendiceal bleeding. A notable proportion (11.11%) required conversion to open surgery. The mean operative time for laparoscopic appendectomy in this group was 64.8 minutes. Postoperatively, patients received analgesia therapy for an average of 2.8 days, with a hospital stay averaging 2.8 days. The duration of oral refeeding was relatively short, with an average of 1.1 days. No cases of postoperative bowel obstruction were reported. Statistical analysis revealed significant differences between groups in terms of intraoperative appendiceal rupture (P = 0.02), conversion to open surgery (P = 0.005), operative time (P = 0.006), and oral refeeding duration (P = 0.009). Among patients with a subhepatic appendiceal position (n=8), 17.1% experienced appendiceal rupture, while 1.9% had appendiceal bleeding. A considerable proportion (12.5%) required conversion to open surgery. The mean operative time for laparoscopic appendectomy in this group was 79.2 minutes. Postoperatively, patients received analgesia therapy for an average of 2.1 days, with a hospital stay averaging 3.1 days. The anatomical variations of the appendix observed in the study were as follows: anterior (n=54), pelvic (n=10), retrocecal (n=19), and subhepatic (n=8) (Table 3).

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Table 3: Intra Operative and Post-Operative Findings of the Study

Symptoms and Signs	Anterior (Mean ± SD) /N (%)	Pelvic (Mean± SD) /N (%)	Retrocecal (Mean ± SD) /N (%)	Sub hepatic (Mean ± SD) /N (%)	P-Value
Intra Operative Findings					
Appendiceal Rupture	7%	11%	13.6%	17.1%	0.02
Appendiceal Bleeding	2.1%	3%	2.9%	1.9%	0.03
Conversion to Open Surgery	1.9%	0	11.11%	12.5%	0.005
Mean Operative Time (Minutes)	55.7 ± 5.14	56.9 ± 4.32	64.8 ± 7.31	79.2 ± 6.32	0.006
Post-Operative Findings					
Analgesia Therapy (Days)	3.4 ± 0.14	5.3 ± 0.84	2.8 ± 0.15	2.1 ± 0.05	0.001
Hospital Stay (Days)	2.7 ± 0.07	3.5 ± 0.09	2.8 ± 0.074	3.1 ± 0.031	0.05
Oral Refeeding (Days)	1.3 ± 0.02	1.5 ± 0.1	1.1 ± 0.01	1.5± 0.047	0.009
Bowel Obstruction	2.1%	7.7%	0	0	0.083

DISCUSSION

Laparoscopic appendectomy has become the preferred approach for many cases of appendicitis due to its minimally invasive nature and associated benefits such as reduced postoperative pain and faster recovery times. However, anatomical variations in the position of the appendix, particularly in pelvic and retrocecal locations, can present unique challenges during laparoscopic surgery. In cases where the appendix is located in the pelvic region, visualization and access may be hindered by surrounding pelvic structures such as the bladder, uterus, and rectum which has been reported by literature as well [15]. It can be hard for the surgeon to handle tools and successfully expose the operating region because there is just not enough room in this part of abdomen. In addition, this area is very small because it is crowded with organs like blood vessels, nerves and intestinal organs. It likely that some harm will occur accidentally when dissecting/mobilizing appendicitis. This contributed to prolonged operation time, increased complexity and an increased chance of intraoperative complications like appendiceal rupture [16]. Similarly, a retrocecal appendix also presents problems for its direct view and during laparoscopic surgery access. The surgeon could hardly see a retrocecal appendix based in the retroperitoneal region and it could limit his laparoscopic motions. Great care must be taken when dissecting any structure inside the retroperitoneal space to prevent the ileocecal vessels and ureter from getting damaged [17]. Furthermore, the angle of approach in retrocecal area is not favorable for the dissection of appendix leading to possible difficulties in getting enough exposure and dissecting it well. To overcome with these issues, surgeons that perform laparoscopic appendectomy on pelvic or retrocecal appendix must carefully handle the anatomical intricacies in the pelvis and retroperitoneal [18]. By positioning the patient cautiously, choosing the best place for ports and disassembling the appendix with careful direct visualization, can increase the reliability of useful safety profile of laparoscopic appendectomy. Furthermore, the laparoscopic ultrasonography can be use for localization and imaging the appendix when usual landmarks are invisible [19]. The need for additional research on how anatomical differences affect outcomes of laparoscopic appendectomy requires more extensive studies using larger and diverse patient pools from future prospective research [20].

CONCLUSIONS

In conclusion, laparoscopic appendectomy has many advantages compared to open surgery but challenges brought about by anatomical variation involving pelvic-retrocecal position of appendices ought to be recognized and addressed. Surgeons can navigate these challenges and improve results for patients who undergo laparoscopic appendectomy by understanding anatomical complications and using proper surgical methods.

Authors Contribution

Conceptualization: AI
Methodology: FJ, ANA, AH, I
Formal analysis: MZ
Writing, review and editing: FJ, ANA

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparison Between Gow-Gates Mandibular Nerve Block Versus Inferior Alveolar Nerve Block in Extraction of Mandibular Third Molars

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ABSTRACT

Because of the intricacy of the process and the possibility of severe patient suffering, a successful extraction of mandibular third molars, or wisdom teeth, depends on an effective anesthetic. **Objective:** To compare the efficacy of Gow-Gates Mandibular Nerve Block (GGNB) versus Inferior Alveolar Nerve Block (IANB) in the extraction of mandibular third molars. **Methods:** This comparative cross-sectional study involved patients aged 20 to 45 years, of both genders, with impacted mandibular third molars. Using non-probability consecutive sampling, 160 patients were allocated to two groups: Group A (IANB) and Group B (GGNB), each with 80 patients. Outcomes such as pain, onset of anesthesia, and post-operation recovery time were measured. Efficacy between the groups was compared using Chi-square and independent t-tests. **Results:** The mean age was 30.29 ± 6.96 years. The mean pain in IANB (1.43 ± 1.19) was lower than in Gow-Gate (1.59 ± 2.02) statistically ($p = 0.041$). For anesthetizing the buccal, inferior alveolar nerve, and lingual nerve shows that only the buccal nerve the GGNB (100%) was more effective than IANB (81.5%) statistically ($p<0.001$). The onset of anesthesia was quicker in GGNB than in IANB for all three nerves ($p<0.001$). Post-operative recovery time between IANB and GGNB techniques was not statistically different ($p=0.227$). **Conclusions:** The research concluded that IANB resulted in significantly lower pain compared to GGNB. GGNB demonstrated greater effectiveness in anesthetizing the buccal nerve compared to IANB. The onset of anesthesia was statistically quicker in GGNB than in IANB for all three nerves.

INTRODUCTION

In oral surgery, local anesthesia is essential for pain management by inhibiting nerve action potentials. Lidocaine 2% with a vasoconstrictor like adrenaline is commonly used to enhance effects and reduce toxicity. Effective anesthesia is influenced by the operator's technique and patient-specific factors [1, 2]. Achieving effective pulpal anesthesia in adult mandibular cases is challenging due to the high density of cortical alveolar bone, which impedes anesthetic penetration [3]. The success of the inferior alveolar nerve block (IANB) depends on various factors, including patient anxiety, injection issues, anatomical variations, infections, intravascular injection risks, dense bone structure, bifid mandibular nerve, accessory mental foramen, expired solutions, and injection technique errors [4, 5]. Mandibular local anesthesia primarily employs three techniques: IANB, Gow-Gates, and Vazirani-Akinosi. IANB, the most commonly used, involves injecting near the inferior alveolar nerve, providing comprehensive anesthesia to the lower teeth and surrounding tissues on one side of the jaw [6, 7].

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While effective, the IANB does not affect other branches like the lingual, buccal, and mylohyoid nerves, requiring supplementary injections. Anatomical variations and accessory nerve supply can affect success rates, which range from 65 to 79 percent [8]. Gow-Gates Mandibular Block technique involves a single intraoral injection at the lateral aspect of the mandibular condyle, targeting the mandibular nerve's main division at the foramen ovale. It achieves comprehensive anesthesia of the entire mandibular nerve, a significant branch of the trigeminal nerve [9, 10]. The GGMB technique has a higher success rate and lower incidence of positive aspiration (2% vs. 10-15%) compared to the Inferior Alveolar Nerve Block (IANB), effectively addressing accessory sensory innervation issues [11, 12]. This research explores the influence of anesthesia techniques, particularly by comparing the inferior alveolar nerve block and Gow-Gates nerve block. The focus is on assessing pain levels and success rates during the extraction of impacted teeth, aiming to identify alternatives that can provide effective anesthesia, particularly in situations where the conventional inferior alveolar nerve block might be less successful. Proficiency in both techniques enhances the probability of attaining pain-free dental procedures for all patients, underscoring the significance of broadening anesthesia approaches in oral surgery.

This study aimed to compare the effectiveness of the Gow-Gates mandibular nerve block with the inferior alveolar nerve block in the extraction of mandibular third molars.

METHODS

This comparative cross-sectional study was conducted at the Department of Oral and Maxillofacial Surgery, Institute of Dentistry, Liaquat University of Medical and Health Sciences, located in Jamshoro/Hyderabad from November 1, 2021 to April 30, 2022 after obtaining ethical approval (LUMHS/REC/-117) by using a non-probability consecutive sampling technique. The calculated sample size for the study was determined to be 160 participants. The sample was calculated in openepi to be 104 (52 per group) at 80%, 95% confidence level using the success of the Conventional IANB group (88.9%) and the GGNB group (64.4%) [13]. The total sample size was then divided into two groups: Group A comprised 80 participants undergoing conventional IANB, while Group B included 80 participants undergoing GGNB. Participants of both genders were included in the study, provided they fell within the age range of 20 to 45 years and exhibited impacted mandibular third molars. Exclusion criteria comprised pregnant patients, individuals with trismus and pericoronitis, those with oral submucous fibrosis, acute oral cavity infections, medically compromised conditions, and individuals engaged in alcohol consumption, smoking, or tobacco chewing. In this research conducted at the oral and maxillofacial surgery department, eligible patients who expressed a willingness to participate were enrolled after providing informed written consent. Demographic and clinical details, such as age, gender, pain, and medical history, were documented. The study undertook a comparative assessment of two groups: Group A, which received the traditional IANB, and Group B, which underwent mandibular nerve block using the GGNB technique. A specific local anesthesia solution (2% lignocaine with 1:100000 epinephrine) was administered with precise needles and techniques. The onset time was recorded, and for IANB, 1.5 ml of the solution was administered over 60-90 seconds, including an additional deposit for lingual and long buccal nerve anesthesia. In the GGNB, 1.8 ml of the solution was administered over the same time frame. Following injection, patients were instructed to maintain an open mouth posture for one minute. Demographics like age and gender were recorded. Pain was evaluated using a Visual Analog Scale (VAS) from 0 (no pain) to 10 (worst pain). The onset of anesthesia was the time from block injection to effect. Anesthesia was considered unsuccessful if patients didn't experience lip and tongue numbness or reported pain 10 minutes after administration. Onset times for the Inferior Alveolar, Buccal, and Lingual nerves were categorized. Recovery time was recorded from anesthesia onset to its subsiding [12]. The data were analyzed using SPSS version 22.0. Frequencies and percentages were computed for categorical variables. Mean and standard deviation were calculated for continuous variables such as age and pain score. A Chi-square test assessed the association between post-operative efficacy for GGNB and IANB groups. An independent t-test compared pain between the two groups. $p \leq 0.05$ was considered significant.

RESULTS

The mean age was 30.29 ± 6.96 years with a range from 20 to 45 years. The distribution of gender ($p = 0.74$), age groups ($p = 0.87$), and occupation ($p = 0.199$) among the participants in both groups (IANB and GGNB) were not statistically different (Table 1).

Table 1: Age, Gender and Occupation Distribution of the Participants in Both Groups (n=160)

Variables	Characteristics	IANB (n=80)	GGNB (n=80)	p-Value*
Age Groups (Years)	20-30	51 (63.7)	53 (66.2)	0.74
	31-45	29 (36.3)	27 (33.8)	
Gender	Male	32 (40.0)	33 (41.2)	0.872
	Female	48 (60.0)	47 (58.8)	
Occupation	House Girl	2 (2.5)	3 (3.8)	0.199
	House wife	25 (31.2)	23 (28.7)	
	Student	16 (20.0)	8 (10.0)	
	Indoor Job	22 (27.5)	20 (25.0)	
	Outdoor Job	15 (18.8)	26 (32.5)	

*Chi-square test, IANB; inferior alveolar nerve block, GGNB; Gow-Gate nerve block

The pain scores differed significantly between the groups ($p = 0.041$). The mean pain score for IANB was 1.43 ± 1.19, while for GGNB, it was 1.59 ± 2.02 (Table 2).

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Table 2: Comparison of Pain Score Between IANB and GGNB (n=160)

Pain Score	IANB (n=80)	GGNB (n=80)	p-Value*
Range	0-7	0-10	0.041
Mean	1.43 ± 1.19	1.59 ± 2.02	

*Independent T Test, IANB; Inferior Alveolar Nerve Block, GGNB; Gow-Gate Nerve Block

For the Inferior Alveolar Nerve, 77 participants (96.3%) in the IANB group and 79 participants (98.8%) in the GG group experienced successful anesthetization, while 3 participants (3.7%) in the IANB group and 1 participant (1.2%) in the GGNB group were not anesthetized. The difference in anesthetization rates was not statistically significant (p = 0.311). For Buccal Nerve, 65 participants (81.2%) in the IANB group and all 80 participants (100.0%) in the GGNB group were successfully anesthetized, whereas 15 participants (18.8%) in the IANB group were not anesthetized, with none in the GGNB group. This discrepancy in anesthetization rates was highly significant (p < 0.001). For the Lingual Nerve, 71 participants (88.8%) in the IANB group and 77 participants (96.2%) in the GGNB group were anesthetized, while 9 participants (11.2%) in the IANB group and 3 participants (3.8%) in the GGNB group were not (Table 3)

Table 3: Comparison of Efficacy of IANB and GGNB Technique in Anesthetizing Buccal, Inferior Alveolar Nerve and Lingual Nerve

Nerve	Anesthetize	IANB (n=80)	GGNB (n=80)	p-Value*
Inferior Alveolar Nerve	Yes	77 (96.3)	79 (98.8)	0.311
	No	3 (3.7)	1 (1.2)	
Buccal Nerve	Yes	65 (81.2)	80 (100.0)	<0.001
	No	15 (18.8)	0 (0.0)	
Lingual nerve	Yes	71 (88.8)	77 (96.2)	0.072
	No	9 (11.2)	3 (3.8)	

*Chi-Square Test, IANB; Inferior Alveolar Nerve Block, GGNB; Gow-Gate Nerve Block

A thorough examination of the time of onset for the IANB and GGNB techniques is presented, detailing both frequency and percentage distributions. For the Inferior Alveolar Nerve, IANB demonstrated onset times of 1.2% within < 5 minutes, 49.4% within 5-10 minutes, and another 49.4% exceeding 10 minutes. In contrast, GGNB showed 35.4%, 53.2%, and 11.4% for the respective categories. These differences in onset times between the two techniques were highly significant (p < 0.001). For the Buccal Nerve, IANB showcased distinct onset times: 0.0% within < 5 minutes, 32.3% within 5-10 minutes, and 67.7% exceeding 10 minutes, while GG exhibited 58.8%, 41.2%, and 0.0% for the corresponding intervals. The dissimilarities in onset times were once again highly significant (p < 0.001). Similarly, the Lingual Nerve, IANB, and GGNB displayed variations in onset times across the three categories, and these differences were highly significant (p < 0.001) (Table 4).

Table 4: Comparison of Time of Onset of IANB and GGNB Technique in Anesthetizing Buccal, Inferior Alveolar Nerve and Lingual Nerve

Variable	Time of Onset (Minutes)	IANB (n=80)	GGNB (n=80)	p-Value*
IANB	< 5	1 (1.2)38	28 (35.4)	<0.001
	5-10	(49.4)	42 (53.2)	
	> 10	38 (49.4)	9 (11.4)	
Buccal	< 5	0 (0.0)	47 (58.8)	<0.001
	5-10	21 (32.3)	33 (41.2)	
	> 10	44 (67.7)	0 (0.0)	
Lingual Nerve	< 5	0 (0.0)	17 (22.1)	<0.001
	5-10	30 (42.3)	45 (58.4)	
	> 10	41 (57.7)	15 (19.5)	

*Chi-Square Test, IANB; Inferior Alveolar Nerve Block, GGNB; Gow-Gate Nerve Block

A comprehensive comparison of post-operative recovery times between the IANB and GGNB techniques, involving a total of 160 participants. The frequency and percentage distributions of recovery times are detailed for both groups. For recovery times less than 30 minutes, 6 (7.5) of participants in the IANB group and 2 (2.5) in the GGNB group were observed, with no statistically significant difference (p = 0.227). In the 30-45 minutes 1 (1.2) category, of participants in the IANB group and 3 (3.7) in the GGNB group were noted. Additionally, for the 45-60 minutes category, 3 (3.8) of IANB participants and 8 (10.0) of GGNB participants fell within this range. In the 60-90 minutes category, 13 (16.2) of IANB participants and 15 (18.8) of GGNB participants were observed. For recovery times exceeding 90 minutes, a substantial proportion was found, with 57 (71.3) in the IANB group and 52 (65.0) in the GGNB group. The statistical analysis, conducted through the chi-square test, did not reveal a significant difference in post-operative recovery times between the IANB and GGNB techniques (Table 5).

Table 5: Comparison of Postoperative Recovery Time Between IANB and GGNB Techniques (n=160)

Recovery Time (minutes)	IANB (n=80)	GGNB (n=80)	p-Value*
< 30	6 (7.5)	2 (2.5)	0.227
30-45	1 (1.2)	3 (3.7)	
45-60	3 (3.8)	8 (10.0)	
60-90	13 (16.2)	15 (18.8)	
> 90	57 (71.3)	52 (65.0)	

DISCUSSION

Our findings showed that pain was significantly lower with IANB compared to GGNB. Gow-Gates was more effective in anesthetizing the buccal nerve, and its onset of anesthesia was statistically quicker for all three nerves: inferior alveolar, lingual nerve, and buccal nerve. In this study, male patients with impacted mandibular third molar were 32 (40.0%) and 33 (41.2%) and female patients were 48 (60.0%) and 47 (58.8%) in Group A (Conventional IANB) and Group B

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(GGNB) respectively. A study by Maqsood *et al.*, reports that 33.3% and 23.2% of male patients and 70.8% and 76.8% of female patients in Conventional IANB and GGNB respectively [14]. Whereas a study by Usama *et al.*, reports that 55.5% and 60.0% of male patients and 44.4% and 40.0% of female patients in Conventional IANB and GGNB groups respectively [15]. All of these studies indicate that impacted mandibular third molars affect both male and female patients with no sexual dimorphism. In this study, the mean age of patients with impacted mandibular third molars was 30.29 ± 6.96 (20-45) years in Group A (Conventional inferior alveolar nerve block) and 28.84 ± 5.25 (20-42) years in Group B (Gow-Gates mandibular nerve block). The majority of patients, 63.7% in group A and 66.2% in group B, fell into the age group of 20-30 years. In group A, 36.3% were in the age group of 31-45 years, while in group B, 33.8% were in the same age range. Maqsood *et al.*, reported mean ages of 34.16 ± 10.77 years and 33.70 ± 10.20 years in the Conventional IANB group and Gow-Gates mandibular nerve block group, respectively [14]. Usama *et al.*, documented mean ages of 41.11 ± 9.23 years and 43.31 ± 8.56 years in the Conventional IANB group and Gow-Gates mandibular nerve block group, respectively [15]. Jamalpour and Tamilkhani reported an overall mean age of 25.6 years for groups [16], Conventional IANB and GGNB. In this study, the effectiveness of anesthesia was evaluated for both the conventional IANB technique (group A) and the GGNB technique (group B). The results revealed that successful anesthesia rates were notably high for both groups, with 96.3% of patients in group A and 98.8% in group B achieving successful anesthesia of the inferior alveolar nerve. For the buccal nerve, success rates were 81.2% in group A and 100.0% in group B, and for the lingual nerve, success rates were 88.8% in group A and 96.2% in group B. The onset of anesthesia and found that it was significantly faster in GGNB compared to conventional IANB for all three nerves: inferior alveolar nerve ($p < 0.001$), buccal nerve ($p < 0.001$), and lingual nerve ($p < 0.001$). This suggests that the GGNB offers a quicker onset of anesthesia, enhancing its efficiency in achieving effective local anesthesia during oral surgery procedures. According to Maqsood *et al.*, successful anesthesia rates for the Conventional IANB group were 91.3% for the inferior alveolar nerve, 100.0% for the buccal nerve, and 94.2% for the lingual nerve and in the GGNB group, the rates were 92.3%, 84.1%, and 91.3% for the respective nerves [14]. It was reported an overall success rate of 59.1% with a single injection in the Conventional IANB group and a higher success rate of 77.3% in the GGNB group [16]. An overall success rate of 90.6% in the Conventional IANB group, and a slightly higher success rate of 96.9% in the GGNB group [17]. Usama *et al.*, documented an overall success rate of anesthesia, revealing a significant difference ($P = 0.006$) between the Conventional IANB group (88.9%) and the GGNB group (64.4%) [15]. The study by Aggarwal *et al.*, showed the impact of VAS score on both the techniques and concluded a success rate of 88% in the GGNB technique and only 61.5% success rate in the IANB technique [18]. When comparing the effectiveness of GGNB and IANB for the extraction of mandibular molars or premolars, Ghoddusi *et al.*, found that GGNB was more successful in 88.89% of instances whereas IANB was effective in 64.44% of cases [19]. In his research, Sabari *et al.*, similarly concluded that GGNB is better than IANB for mandibular anesthesia after surgical removal of an impacted mandibular third molar [20]. The study was associated with limitations like a single center, small sample, and non-randomized. Future studies using large sample sizes and randomized nature can better address the research question.

CONCLUSIONS

Pain experienced with IANB was significantly lower than with GG. Additionally, Gow-Gate showed a statistically quicker onset of anesthesia. There was no significant difference in post-operative recovery time between the two techniques.

Authors Contribution

Conceptualization: SUR, KAC
Methodology: SUR, AAK
Formal analysis: FJ, AB
Writing-review and editing: WM,

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Intraoperative Complications of Posterior (Forceps) Capsulorhexis in Pediatric Cataract Surgery through Anterior Approach

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ABSTRACT

Pediatric cataract surgery often involves a posterior capsulorhexis with forceps to prevent posterior capsule opacification, but it is associated with intraoperative complications such as vitreous loss, anterior hyaloid damage, and zonular dehiscence, which require meticulous surgical skill to manage effectively. **Objective:** To determine Intraoperative complications encountered during posterior (forceps) capsulorhexis in pediatric cataract surgery through anterior approach. **Methods:** This prospective cohort study was comprised up on 50 peadiatric patients having congenital cataract with age up to 12 years who presented at the study setting included in the. Data were analyzed using SPSS 26.0. **Results:** The study had 52% population as male while 48% were female, with 58% were right eyes 42% were left eyes. Anterior chamber was collapsed in 14 eyes (28%) after initial paracentesis incision while 36 eyes (72%) maintained original position. Forward bulge of posterior capsule was present in 36% of eyes while in 64% forward bulge was absent. Vitreous thrust was found in 38% cases while in 62% there was no vitreous thrust. Clearance of anterior vitreous face was done in 42 eyes (84%). **Conclusions:** We found that performing posterior capsulorhexis in pediatric cataract surgery through anterior approach is a safe procedure and encountered posterior capsular bulging and vitreous thrust as the most common complications.

INTRODUCTION

Cataract, characterized by the opacification of the crystalline lens, leads to significant visual disturbances. In pediatric patients, this condition can severely impact education, quality of life, personality development, and career opportunities, thereby increasing the socioeconomic burden on families and communities [1]. Childhood blindness due to cataract is one of the major devastating avoidable causes of blindness in both developed and under-develop countries [2]. Cataract is one of significant cause of childhood blindness in all countries [3]. Pediatric cataract is a significant preventable cause of visual impairment in children, particularly in developing countries, where it negatively impacts national growth. Each year, an estimated 500,000 children worldwide become blind, with 75% of childhood blindness in these regions being preventable or treatable. [4]. Timely detection and appropriate management by skilled ophthalmic surgeons enhance the visual outcomes of pediatric cataract surgery, which is vital for optimal visual development and preventing amblyopia [5, 6]. In developing nations, cataract is responsible for 12% to 39% of childhood blindness, with India at the lower end and Jamaica at the higher end of this range [4]. In contrast, the incidence of congenital cataract in the UK has been calculated at 2.49 to 3.46 per 10,000 [7]. Reasons for increased incidence of congenital cataracts in developing countries are miscellaneous, like over population, inter family marriages, early age conception, malnutrition, lack of medical facility and lack of awareness. Congenital cataracts are commonly diagnosed at birth. If a cataract goes undetected in an infant, permanent visual loss may ensue [8]. Managing congenital cataract differs from adult

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cataract in several ways, including ocular anatomy, cataract morphology, and the occurrence of Posterior Capsular Opacification (PCO) after surgery, the necessity for amblyopia therapy, and the selection of Intraocular Lenses (IOLs). Additionally, the management of the anterior and posterior capsules often requires anterior vitrectomy to prevent PCO. Studies have reported PCO rates ranging from 50% [9, 10] to nearly 100% [11, 12] if the posterior capsule is left intact. Leaving the posterior capsule intact after pediatric cataract surgery leads to an unacceptably high rate of Posterior Capsular Opacification (PCO)[13]. The anterior vitreous serves as a scaffold for the migration of lens epithelial cells, resulting in PCO or visual axis opacification. Therefore, primary posterior capsulotomy and anterior vitrectomy are recommended for all children under 8 years old [14]. There are different methods of posterior capsulotomy and anterior vitrectomy: Anterior limbal or posterior pars plana approach. Anterior approach is most preferred approach, easy and has less complication. Anterior (limbal approach) includes manual posterior capsulorhexis and Vitrectorhexis. We conducted this study to assess these complications in peadiatric population, as understanding them is crucial for refining surgical techniques, improving patient outcomes, and minimizing the risk of long-term vision issues in children.

To determine intraoperative complications encountered during posterior (forceps) capsulorhexis in pediatric cataract surgery through anterior approach.

METHODS

This prospective cohort study was conducted in the Pediatric Ophthalmology Unit at Institute of Ophthalmology of Liaquat University of Medical and Health Sciences, Jamshoro, from 1st July 2022 to 31st December 2022. The study included 50 pediatric patients, up to 12 years old, with congenital cataracts. Only the first operated eye of each patient was considered. Pediatric cataract extraction with posterior capsulorhexis was performed, with Intraocular Lenses (IOLs) implanted in all patients. For patients under 3 years who received IOL implantation, the IOL power was calculated using biometric measurements adjusted for anticipated eye growth. Sample size was calculated via WHO Open EPI software by taking prevalence of congenital cataract in one eye as 3.3%, with confidence interval of 95% and 5% margin of error [7]. Patients with microcornea, corneal dystrophies, microphthalmos, traumatic cataract, subluxated or dislocated lens, congenital glaucoma, uveitis, previous ocular surgery, persistent fetal vasculature and retinal detachment, were excluded from this study. Approval from Research Ethics Committee of Institute of Ophthalmology, Liaquat University of me Medical and Health Sciences, was taken prior to stating research. (No. LUMHS/R.E.C./I.O.L:-33). After taking informed consent, patients were enrolled for research. Detailed history was taken from parents. Complete ocular, systemic examination and workup was done. Posterior capsular management after cataract removal was done by capsular forceps through anterior approach. Intraoperative complications for each patient were recorded in the study proforma. All surgeries performed by single surgeon and detailed surgical notes were included in discharge card. Data were analyzed using SPSS 26.0. Quantitative variables were described in mean with SD. Qualitative variables were expressed in frequencies and percentages.

RESULTS

The study had 52% population as male while 48% were female, with 58% were right eyes 42% were left eyes. 24 patients (48%) were of up to 3 years of age, 9 patients (18%) were between 3 to 6 years, and 17 patients (34%) were over 6 years old. 29 eyes (58%) were right eyes and 21 eyes (42%) were left eyes (Table 1).

Table 1: Descriptive Statistics

Variables	Frequency (%)
Gender Distribution	
Male	26 (52%)
Female	24 (48%)
Age Distribution	
Up to 3 Years	24 (48%)
3 to 6 Years	09 (18%)
More than 6 Years	17 (34%)
Laterality of Eye	
Right	29 (58%)
Left	21 (42%)

Anterior chamber was collapsed in 14 eyes (28%) after initial paracentesis incision while 36 eyes (72%) maintained original position. Forward bulge of posterior capsule was present in 36% of eyes while in 64% forward bulge was absent. Vitreous thrust was found in 38% cases while in 62% there was no vitreous thrust. Clearance of anterior vitreous face was done in 42 eyes (84%), in 08 eyes (16%) some of vitreous could not be cleared due to non-visibility of vitreous gel. Centration of intraocular lens in relation to the centre of pupil was done in 46 eyes (92%), in 04 eyes (08%) intraocular lens could not be centered. 60% of anterior capsulorhexis cases were completed conveniently, while 40% encountered difficulties. Posterior capsulorhexis, on the other hand, demonstrated a higher rate of convenience, with 74% of cases completed without major issues, whereas 26% were deemed inconvenient due to procedural complexities.

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Table 2: Intraoperative Complications of Capsulorhexis in Pediatric Cataract Surgery

Variables	N (%)
Collapsed Anterior Chamber after Paracentesis	14 (28%)
Forward Bulge of Posterior Capsule	18 (36%)
Vitreous Thrust in to Anterior Chamber	19 (38%)
Anterior Vitreous Face Clearance	42 (84%)
Centration of Intraocular Lens	6 (92%)
Collapsing of Capsular Bag	17 (34%)
Convenience of Approach through Anterior Capsulorhexis	30 (60%)
Convenience of Posterior Capsulorhexis	37 (74%)

DISCUSSION

The management of pediatric cataracts presents unique challenges distinct from adult cases. Successful surgery in children necessitates a skilled pediatric surgeon, competent anesthetist, and experienced nursing staff collaborating as a cohesive team. Utilizing state-of-the-art instruments and advanced techniques is crucial for achieving optimal visual outcomes in pediatric eye surgery, as elaborated by Self JE *et al.*, [15]. The demographic distribution in our study showed a slight male predominance (52%) compared to females (48%), consistent with some previous studies of McClatchey SK *et al.*, and Park Y *et al.*, in pediatric cataract surgery demographics [16, 17]. Age distribution highlighted a significant proportion of patients under 3 years (48%) similar to the findings reported by Lagreze WA *et al.*, emphasizing the early onset of pediatric cataracts and the need for specialized surgical techniques and careful post-operative management in this age group [18]. Regarding intraoperative findings, our study identified specific challenges likes collapsing of anterior chamber after paracentesis, collapsing of capsular bag and vitreous thrust in to anterior chamber, which are commonly encountered in pediatric cataract surgery as reported by the study of Kim TY *et al.* The collapse of the anterior chamber after initial paracentesis incision was observed in 28% of cases, suggesting variability in intraocular pressure dynamics during surgery. The presence of a forward bulge of the posterior capsule in 36% of eyes underscores the technical difficulty in achieving optimal capsular management in these young patients, which was also reported by Mandal S *et al.*, in their study [19]. Vitreous thrust was noted in 38% of cases in comparison to the 71.42% of the cases, reported in the study of Katpar NA *et al.*, highlighting the safety of this approach [20]. Centration of the intraocular lens relative to the center of the pupil was achieved in 92% of eyes, indicating successful surgical technique in the majority of cases. However, challenges in centration were noted in 8% of cases as opposed to the anterior capsulotomy technique which has high proportion of the cases with difficulties in centration of lens, as was also reported by Sharma B *et al.*, [21]. Clearance of the anterior vitreous face was achieved in 84% of eyes, with difficulties in visibility leading to incomplete clearance in 16% of cases. This highlights the importance of intraoperative visualization techniques and surgeon experience in managing vitreous clearance effectively [22]. Visually significant posterior capsular opacification causes deprivation amblyopia, so our goal in pediatric cataract surgery to clear visual axis by removing lens opacity, creating a posterior capsular opening (rhexis) and anterior vitrectomy to prevent Visual Axis Opacification (VAO) and decrease the risk of deprivation amblyopia. Hosal BM and Biglan AW elaborated that primary posterior capsulorhexis and limited anterior vitrectomy is necessary to decrease the need of second surgery or YAG laser capsulotomy, as YAG laser capsulotomy in pediatric population is difficult to remove thickened capsule / membrane, intra ocular lens pitting is common, release of pigments further hamper the vision, so the primary posterior capsulorhexis and anterior vitrectomy is very important and mandatory step in pediatric cataract surgery to clear visual axis [23]. Recent literature highlights the intraoperative challenges and complications associated with performing posterior capsulorhexis using forceps in pediatric cataract surgery through an anterior approach. Compared to the use of a vitrectomy cutter, forceps capsulorhexis presents significant difficulties, particularly during anterior vitrectomy. However, it offers notable advantages over methods such as vitrectomy cutter or electrocautery. The stronger margins of the capsule achieved with forceps are better able to withstand pressure during intraocular lens implantation and help contain vitreous prolapse, thereby preventing the extension of the capsulorhexis. It is worth noting that the younger the child undergoing cataract surgery, the more challenging the procedure becomes, increasing the risk of a "run-away capsulorhexis" [24, 25]. The single-center design of our study and a small sample size of 50 pediatric patients, potentially has restricted the applicability of findings to larger, more diverse populations. Exclusion criteria for specific eye conditions have also further narrowed the representation of pediatric cataract cases typically seen in clinical settings, which are counted as major limitations of the study.

CONCLUSIONS

We found that performing posterior capsulorhexis in pediatric cataract surgery through anterior approach is a safe procedure and encountered posterior capsular bulging and vitreous thrust as the most common complications.

Authors Contribution

Conceptualization: AJ
Methodology: NAS, MLM, AJ
Formal analysis: NAS, MLM, AJ

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Writing, review and editing: NAS, MLM, AJ

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Conflicts of Interest

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Original Article

Outcome of Left Anterior Descending Coronary Artery Ostial Lesions Treated with Drug-Eluting Stents

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ABSTRACT

Patients with severe Left Main Stem (LMS) stenosis have very high risk of major cardiovascular events because of the extent of myocardium suffering ischemia. Coronary artery disease of left main stem is not very common but key cause of characteristic coronary artery disease. Such stenosis is usually treated with CABG which is the gold standard treatment. **Objective:** To determine the outcome of left anterior descending coronary artery ostial lesions stenting with drug-eluting stents. **Methods:** The descriptive case series was conducted at a teaching hospital in Lahore, from 01-08-2019 to 29-07-2020. After informed consent 113 patients were included in study; both genders and diagnosed cases of LAD ostial disease, keeping in view inclusion and exclusion criteria. Then patients were admitted in cardiology wards after recording demographic data. Next day, the patients underwent angioplasty under local anesthesia. After procedural success patients were followed-up there for 3 days to assess if there was repeat myocardial infarction or mortality within hospital stay. All information obtained was recorded on a standard performa. Quantitative and qualitative data were analyzed and outcome of the procedure was recorded. **Results:** In our study 104(92.04%) patients were male and 9(7.96%) patients were females. The Drug-Eluting Stents (DES) procedural success was found in 93.81% patients, post stenting MI observed in 6.4% patients and the mortality occurred in 2.7% patients. **Conclusions:** The left anterior descending coronary artery ostial lesions stenting with DES is effective and feasible procedure with good outcome.

INTRODUCTION

Bifurcation lesions of coronary arteries treatment with Percutaneous Coronary Intervention (PCI) is practically challenging and related to excessive frequency of complications like stent thrombosis or restenosis [1].The patients with severe Left Main Stem (LMS) and ostial LAD stenosis have high risk of main cardiovascular events, because of the extent of ischemic myocardium. The prognosis of patients with heart disease is related to the extent of myocardium at risk. LAD coronary artery often supplies a high percentage of the left ventricular myocardium, compared to circumflex or right coronary artery. Bifurcation lesions of LAD or left main coronary artery alone pose higher risk and mortality compared to triple vessel disease. Though CABG is considered gold standard in treating ostial lesions various methods are now evolving like double stent technique, use of bioresorbable vascular scaffold and drug eluting stents that cause much reduction in risk of restenosis [2]. According to one study, ostial lesions of left main stem and LAD comprise approximately 20 % of cases requiring Percutaneous Coronary Intervention (PCI) [3]. CABG is the gold standard for treating complicated LMS stenosis, particularly when it

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is coupled with multi vessel cardiac disease [4]. Percutaneous Coronary Interventions (PCI) have been shown in numerous studies to be safe and effective alternative to CABG in patients selected carefully by the Heart Group, with same death rates [5]. The results of LMS PCI have been improved constantly, to the newer PCI procedures and use of novel generation Drug-Eluting Stents (DES) [5]. Ostial LAD coronary artery lesion has been regarded as a lesion subset improper for stenting. DES acquired approval from regulatory authority of Europe and America in 2002-2003. After that a lot of clinical trials have been carried out showing efficacy of DES in reducing stent restenosis when compared to bare metal stents [6]. In one research 12-month incidence of Target Lesion Revascularization (TLR) was higher for DES but in the range of that already reported for metallic DES (between 4% and 8%), and significantly lower than that previously reported with the use of bare metal stents (in the range of 30%) [7, 8]. According to a study 118 patients with in stent restenosis were treated with drug eluting stents. After median follow up of 5.5 year Device-Oriented Composite Endpoint (DOCE) was observed 17 % at 1 year, 27 % at 2 year and 40 % at 5 years [9]. In literature, very little work has been performed regarding the outcome of DES stenting in ostial LAD artery and the available data showed controversial evidence. In a Chinese study conducted in 2023 risk of stent restenosis was shown to be 7-18 % if done without dual antiplatelet therapy or drug eluting stents [10]. However, there is no local evidence available in this regard.

Objective of this study was to determine the outcome of LAD coronary artery ostial lesions stenting with DES.

METHODS

This descriptive case series was conducted from 01-10-2019 to 30-10-2020 in the department of cardiology, Mayo Hospital, Lahore after taking consent from the Institutional review board of the hospital (Reference No CPSP/REU/CRD-2017-066-1581). Written consent was obtained from the patients after informing. Calculated sample size was 113 with 5% level of significance, 6% margin of error and taking expected percentage of repeat MI i.e-12.0% in patients who underwent ostial LAD stenting with DES. Patients of both genders, ages ranging from 35-70 years, known cases of ostial LAD disease as per operational definition were included in the study and admitted to undergo angioplasty by using DES stent. Patients who had previous history of MI, stenting, CABG, or valvular heart disease as well as the patients with co morbidity of renal disease (creatinine >1.4mg/dl or on dialysis) were excluded from the study. Demographic data (name, age, gender, BMI, duration of LAD disease, history of hypertension and smoking) was noted. Patients were admitted in Cardiology ward and next day, each patient underwent angioplasty by a single cardiologist's team with assistance of the researcher. The procedure was performed under local anesthesia. Procedural success was labeled (as per operational definition) if no myocardial infarction or death occurred during the procedure neither any need of emergency CABG arose. After the procedure, patients were shifted to cardiology wards and were followed-up there for 3 days. Patients were evaluated if there was repeat myocardial infarction and assessed after 03 days. Mortality was labeled if it occurred within the 3 day hospital stay. All information obtained was recorded on a standard performa. SPSS version 21.0 was used to analyze data. Quantitative elements as age, duration of LAD diseases, and BMI were presented in the form of mean and Standard Deviation (SD). Qualitative data components like smoking, hypertension, procedural success, repeat myocardial infarction, mortality were calculated as frequency and percentage. Data were stratified for age, gender, hypertension (BP>160/90) diabetes mellitus (BSR>200mg/dl), smoking >5pack years, BMI and duration of LAD disease. Post-stratification, stratified groups were compared for outcome by using chi-square test. P-value≤0.05 was considered as significant.

RESULTS

In table 1, 13 patients were enrolled. Average age of the patients was between 55.72 ± 7.92. There were 104 (92.04%) males and 9 (7.96%) females. The mean BMI of the patients was 25.078 ± 3.73 kg/m^2 as shown in table 1. History of smoking observed in 74 (65.5%) respondents and hypertension was found in 64 (56.6%) respondents as shown in table 1.

Table 1: Descriptive Statistics of Age, Gender and BMI

Variables	Frequency (%)/Mean ± SD
Age	55.72 ± 7.92
Gender	
Male	104 (92.04%)
Female	9 (7.96%)
BMI (Kg/m^2)	25.07 ± 3.73
Smoking	
Yes	74 (65.5%)
No	39 (34.5%)
Hypertension	
Yes	64 (56.6%)
No	49 (43.4%)

The mean duration of LAD disease was 6.24 ± 2.31 years. The procedural success was found in 106 (93.81%) patients. Post stenting MI observed in 7(6.4%) patients and the mortality occurred in 3 (2.7%) patients as depicted in table 2.

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Table 2: Summary Statistics of Duration of LAD (Years), Frequency of Procedural Success, Post Stenting MI and Mortality

Duration of LAD Disease (Years)		Frequency (%)
Procedural Success	Yes	106 (93.81%)
	No	7 (6.19%)
Post Stenting MI	Yes	7 (6.2%)
	No	106 (93.8%)
Mortality (within 03 days)	Yes	3 (2.7%)
	No	110 (97.3%)
Mean ± SD		6.24 ± 2.31

There was insignificant difference in the procedural success of different groups of age, gender and BMI respectively i.e. p-value >0.05, table 3.

Table 3: Comparison of Procedural Success between Different Groups According to Age, Gender and BMI

Variables	Category	Procedural Success N (%)		p-Value
		Yes	No	
Age	<55	56 (91.8%)	5 (8.2%)	0.45
	>55	50 (96.2%)	2 (3.8%)	
Gender	Male	97 (93.3%)	7 (6.7%)	1.00
	Female	9 (100%)	0	
BMI	<25	52 (92.9%)	4 (7.1%)	0.716
	>25	54 (94.7%)	3 (5.3%)	
Smoking	Yes	71 (95.9%)	3 (4.1%)	0.232
	No	35 (89.7%)	4 (10.3%)	
Hypertension	Yes	58 (90.6%)	6 (9.4%)	0.137
	No	48 (98%)	1 (2.0%)	
Duration of LAD Disease	<6	57 (89.1%)	7 (10.9%)	0.0018
	>6	49 (100%)	0	

Table 4 showed insignificant difference in the procedural success of different groups according to smoking and hypertension. However significant difference was seen in the procedural success of different groups according to duration of LAD disease i.e. p-value=0.0018. The results showed statistically insignificant difference according to post stenting MI in different groups according to age, gender, BMI, smoking, hypertension and duration of LAD disease i.e. p-value was greater than 0.05.

Table 4: Comparison of Post Stenting MI in different Groups According to Age, Gender, BMI, Smoking, Hypertension and Duration of LAD Disease

Variables	Category	Post Stenting MI N (%)		p-Value
		Yes	No	
Age	<55	1 (1.7%)	58 (98.3%)	0.048
	>55	6 (11.8%)	45 (88.2%)	
Gender	Male	7 (6.9%)	94 (93.1%)	1.00
	Female	0	9 (100%)	
BMI	<25	2 (3.7%)	52 (96.3%)	0.438
	>25	5 (8.9%)	51 (91.1%)	
Smoking	Yes	3 (4.2%)	69 (95.8%)	0.232
	No	4 (10.5%)	34 (89.5%)	
Hypertension	Yes	4 (6.6%)	57 (93.4%)	1.32
	No	3 (6.1%)	46 (93.9%)	
Duration of LAD Disease	<6	5 (8.2%)	56 (91.8%)	0.458
	>6	2 (4.1%)	47 (95.9%)	

According to this study there is statistically insignificant difference found in the occurrence of mortality between different groups of age, gender, BMI, smoking, hypertension and duration of LAD i.e. p-value>0.05, table 5.

Table 5: Comparison of mortality in Different Groups According to Age, Gender, BMI, Smoking, Hypertension and Duration of LAD Disease

Variables	Category	Mortality N (%)		p-Value
		Yes	No	
Age	<55	0	59 (100%)	0.096
	>55	3 (5.9%)	48 (94.1%)	
Gender	Male	3 (3.0%)	98 (97%)	1.20
	Female	0	9 (100%)	
BMI	<25	0	54 (100%)	0.243
	>25	3 (5.4%)	53 (94.6%)	
Smoking	Yes	1 (2.6%)	37 (97.4%)	1.51
	No	3 (4.9%)	58 (95.1%)	
Hypertension	Yes	3 (4.9%)	58 (95.1%)	0.252
	No	0	49 (100%)	
Duration of LAD	<6	2 (3.3%)	59 (96.7%)	1.00
	>6	1 (2.0%)	48 (98%)	

DISCUSSION

This present study was performed at department of Cardiology, Mayo Hospital Lahore to determine the outcome of ostial left anterior descending coronary artery lesions stenting with DES. Even though recent increasing and striking mechanical advances, isolated ostial Left Anterior Descending (LAD) lesions represent a challenge for interventional cardiologists. There is relatively lack of standardization and agreement across studies in treating lesions at bifurcations [11]. Various researches have demonstrated that drug eluting stents are more fruitful as opposed to bare metal stents in reducing the necessity for revascularization procedures [12]. Lesions in ostium solely pose difficulties in attaining appropriate positioning of stent in contrast to lesions that are not at ostium due to excessive prevalence of calcification, tumultuous blood flow and inflexibility [13, 14]. In a study published in journal of cardiovascular intervention ostial stenting was done with DES in 95 patients and 67 patients underwent crossover stenting. It concluded that Target Lesion Revascularization (TLR) was high in ostial stenting (12%) as compared with crossover stenting (3.5%) over the 2-year follow-up period. But incidence of complications and sudden cardiac death was higher with crossover stenting [15]. Dąbrowski EJ *et al.*, carried out a meta-analysis that compared CABG, DES and medical treatment and it revealed that PCI with DES was seen with better survival. They then conducted a non-inferiority based randomized

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trials that compared PCI with CABG in bifurcation lesion of coronary arteries. Three year and five year follow up revealed that PCI with DES was not inferior to CABG in terms of composite endpoints [16]. Institute of National Heart, Lung, and Blood Dynamic Registry carried out a research which compared outcomes of patients receiving bare metal stents and another group receiving drug eluting stents for lesions of ostium. This research concluded that use of drug eluting stents is not associated with any increased risk for complications like myocardial infarction, need for revascularization or death [17]. DES implantation in LM is a viable procedure, according to many registries and a current sub-group analysis from a randomized study, treatment plan that is both safe and effective. When compared to CABG, it produces similar outcomes, with the difference being significantly high frequency of target vessel intervention at follow-up following stenting [18, 19]. The DES use in ostial lesions, on the other hand, resulted in unfavorable results than in non-ostial lesions, and prior data suggested that the relatively higher rate of restenosis (14.7%) could be linked to insufficient lesion coverage [20]. A meta-analysis was carried out in 2020-21 regarding the outcome of left main stem stenting with drug eluting stents and it concluded that Single stent strategy was associated with a significantly lower risk of Target Lesion Revascularization (TLR) and Major Adverse Cardiovascular Events (MACE) compared to 2-stent strategy [21]. Another study published in interventional cardiology journal compared outcomes of stenting with drug coated balloon and double stenting design and it also concluded that use of drug coated balloon in side branch is safe and effective[22]. In our study the procedural success of DES was found in 106 (93.81%) patients, the post stenting MI observed in 7 (6.4%) patients and the mortality occurred in 3(2.7%) patients.

CONCLUSIONS

This study concluded that stenting of ostial lesions of left anterior descending coronary artery with DESs is effective and feasible procedure with good outcome.

Authors Contribution

Conceptualization: MAA

Methodology: RMHK, AM, AUR

Formal analysis: SBK

Writing, review and editing: SBK, IS

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Role of Inflammatory and Prognostic Markers and Its Outcome Among Patients with Pre and Post-Operative Colorectal Carcinoma

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ABSTRACT

Colorectal carcinoma is a significant health concern, often presenting with symptoms like bleeding per rectum, mucous discharge, tenesmus, altered bowel habits, and weight loss. This study examines the influence of inflammatory and prognostic markers on the outcomes of patients undergoing per and post-operative treatment for colorectal carcinoma. **Objective:** To evaluate the role of inflammatory and prognostic markers on the outcomes of patients with per and post-operative colorectal carcinoma. **Methods:** This cross-sectional study included 112 patients aged 20-60 years, of either gender, with symptoms such as bleeding per rectum, mucous discharge, tenesmus, altered bowel habits, and weight loss for ≥1 month, diagnosed with colorectal cancer regardless of stage and grade. **Results:** The mean age of the patients was 45.16 ± 10.52 years, with 51.8% males and 48.2% females. Common symptoms included abdominal pain, per rectal bleeding, and weight loss, with 89.3% presenting with anemia. Tumors were located in the colon (84.8%) and rectum (28.6%). Pre-operative markers showed elevated WBC in 59.8%, CRP in 87.5%, decreased serum albumin in 77.7%, raised ESR in 61.6%, ferritin in 65.2%, and LDH in 60.7%. Post-operative markers indicated elevated WBC in 92.9%, CRP in 94.6%, decreased serum albumin in 82.1%, raised ESR in 68.8%, ferritin in 69.6%, and LDH in 73.2%. Complications included wound infection, pneumonia, sepsis, and prolonged hospital stays, with a mortality rate of 3.6%. **Conclusions:** Serum inflammatory markers significantly influence prognoses and predict adverse outcomes in patients undergoing surgical treatment for colorectal carcinoma.

INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy in men and the second in women worldwide [1]. Despite advancements in screening programs and treatment modalities reducing mortality rates in developed countries, approximately 20% of CRC patients present with synchronous metastasis at primary diagnosis, and more than half eventually succumb to the disease. The incidence of CRC in individuals under 50 years of age is notably increasing, highlighting the need for ongoing research and improved treatment strategies [2]. Patients with CRC often exhibit symptoms such as rectal bleeding, altered bowel habits, tenesmus, fatigue, and mucus discharge [3]. Diagnosis is confirmed through clinical evaluations, including digital rectal examination, proctoscopy, and colonoscopy with histopathological biopsy [4]. Staging of CRC involves methods such as ERUS, CT scans, MRI with localizing coils, and PET/CT [5]. There is emerging evidence that inflammation plays a critical role in the development and progression of CRC. Conditions like inflammatory bowel disease, characterized by localized inflammation, are linked to a higher risk of CRC. However, the role of systemic inflammation in colon carcinogenesis is less clear [6]. Systemic inflammation is known to promote cancer through the production of pro-inflammatory cytokines and reactive oxygen species, which activate tumor-promoting transcription factors [7]. In CRC, systemic inflammation often leads to increased production of proteins like CRP by the liver and manifests as fever, anemia, fatigue, and loss of appetite, eventually resulting in cachexia. Key inflammation markers, such as

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elevated CRP and decreased serum albumin, are recognized as significant in predicting outcomes in CRC [8]. Despite the established association of inflammatory markers with cancer progression and patient outcomes, data on their prognostic significance and related survival outcomes in specific populations, including the Pakistani population, remain limited. This study aims to address this gap by determining the significance of blood-based inflammatory biomarkers in prognostication and prediction of outcomes and survival among CRC patients in Sindh, Pakistan.

METHODS

The cross sectional study was conducted in the Department of Surgery, surgical unit-II, Liaquat University Hospital, Hyderabad/Jamshoro. It was carried out over six months following the approval of the synopsis, from January 2022 to June 2022. The non-probability consecutive sampling method was chosen due to the specific inclusion criteria and the need to enroll all eligible patients within the study period, ensuring a comprehensive assessment of the target population within the constraints of the study's timeframe and resources. Inflammatory and prognostic markers were measured using standardized laboratory procedures, with specific assays for each marker, ensuring accuracy and reliability in the obtained results. The sample size was determined to be 112 patients, calculated using the prevalence of raised inflammatory markers as 24.8%, with a margin of error of 8%, using the formula for sample size calculation [9]:

$$n = \frac{Z^2 \times P \times (1-P)}{d^2}.$$

where: n is the sample size, Z value (1.96 for 95% confidence level), P is the prevalence (24.8% or 0.248), d is the margin of error (8% or 0.08). Patients included in the study were between 20 to 60 years old, of either gender, with a history of bleeding per rectum or mucous discharge, tenesmus, altered bowel habits, and weight loss for at least one month, and diagnosed with colorectal cancer through histopathological reports, regardless of stage and grade. Excluded from the study were elderly patients with ASA-3 and 4, known cases of other GI malignancies, cirrhosis, malabsorption syndrome, those already on corticosteroids, immunosuppressive therapy, albumin or antibiotic therapy, patients with chronic renal failure, nephrotic syndrome, pregnant and lactating women, vitally unstable patients due to intestinal obstruction or perforation, and those already on iron supplements and recurrent blood transfusions. Data were collected from patients admitted to the surgery ward after obtaining informed consent. A brief clinical history was taken, and relevant physical examinations were performed. Baseline investigations and specific investigations (colonoscopy and biopsy, CT scan of the chest, abdomen and pelvis, and transrectal ultrasound) were advised, and the history of associated co-morbidities was recorded. Diagnosed cases of colorectal cancer were further explored for inflammatory markers (white blood cell count, serum albumin, erythrocyte sedimentation rate, serum C-reactive protein, fibrinogen, and cytokines including interleukin-6 and tumor necrosis factor) and prognostic markers (serum LDH and ferritin). These were measured pre-operatively and post-operatively on the third day, and CEA levels were measured after one month by taking a 2-cc venous blood sample in a 5 cc disposable syringe and sending it to the laboratory for analysis. All maneuvers, including history taking, physical examination, sampling, and data collection, were conducted by the principal researcher. Data were collected using a pre-designed proforma, and the financial burden of the study was borne by the researcher. Biopsy specimens and biochemical analyses were performed by a senior pathologist with over five years of experience. Patients were kept in the ward for 5-7 days according to their status and the quantity of drainage, and were observed for in-hospital outcomes. The collected data were analyzed using SPSS version 21.0. The frequency and percentage of inflammatory markers, gender distribution, associated co-morbidities, and effect modifiers were computed. The mean and standard deviation were calculated for quantitative variables such as age, duration, WBC count, ESR, serum albumin, ferritin, LDH, and CRP levels. The study was conducted following ethical guidelines, and approval was obtained from the Research Ethics Committee, Liaquat University of Medical and Health Sciences, Jamshoro (LUMHS/REC/-203).

RESULTS

A total of 112 cases were studied with a mean age of 45.16±10.52 years (range: 25-67 years). The gender distribution was 51.8% males and 48.2% females. Most patients were urban residents (53.6%), while 36.4% were rural residents. The majority of patients presented with abdominal pain, per rectal bleeding, and weight loss (Table 1). According to comorbidities, 67.9% of the patients had hypertension, 44.6% were diabetics, 49.1% were smokers, 29.5% were obese, 24.1% had dyslipidemia, and 89.3% had anemia (Table 1).

Table 1: Socio-Demographic and Clinical Characteristics of Patients (n=112)

Variables	Frequency (%)
Age (Mean ± SD)	45.16 ± 10.52
Gender	
Male	58 (51.8)
Female	54 (48.2)
Residence	
Urban	60 (53.6)
Rural	52 (46.4)

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Presenting Complaints	
Abdominal Pain	112 (100.0)
Per Rectal Bleeding	112 (100.0)
Weight Loss	112 (100.0)
Comorbidities	
Hypertension	76 (67.9)
Diabetes	50 (44.6)
Smokers	55 (49.1)
Obesity	33 (29.5)
Dyslipidemia	27 (24.1)
Anemia	100 (89.3)

Tumor grading revealed that 58.0% had a tumor grade of T2N1M0, 37.5% had T2N0M0, 2.7% had T1N0M0, and 1.8% had T3N1M0 (Table 2). Surgical procedures included right hemicolectomy (23.2%), left hemicolectomy (11.6%), sigmoidectomy (11.6%), transverse colectomy (11.6%), high anterior resection (11.6%), low anterior resection (15.2%), abdomino-perineal resection (1.8%), and extended hemicolectomy (13.4%). Tumor locations were predominantly in the colon (71.4%) and rectum (28.6%). Surgical intent was curative in 84.8% of cases and palliative in 15.2% (Table 2).

Table 2: Tumor Characteristics and Surgical Procedures (n=112)

Variables	Frequency (%)
Tumor Grade	
T2N0M0	42 (37.5)
T2N1M0	65 (58.0)
T1N0M0	3 (2.7)
T3N1M0	2 (1.8)
Surgical Procedures	
Right Hemicolectomy	26 (23.2)
Left Hemicolectomy	13 (11.6)
Sigmoidectomy	13 (11.6)
Transverse Colectomy	13 (11.6)
High Anterior Resection	13 (11.6)
Low Anterior Resection	17 (15.2)
Abdomino-perineal Resection	2 (1.8)
Extended Hemicolectomy	15 (13.4)
Tumor Location	
Colon	80 (71.4)
Rectum	32 (28.6)
Surgical Intent	
Curative	95 (84.8)
Palliative	17 (15.2)

Pre-operative inflammatory markers indicated raised WBC in 59.8% of cases, raised CRP in 87.5%, decreased serum albumin in 77.7%, raised ESR in 61.6%, raised ferritin in 65.2%, and raised LDH in 60.7%. Post-operatively, these markers showed a significant increase with raised WBC in 92.9% ($p < 0.001$), raised CRP in 94.6% ($p = 0.03$), decreased serum albumin in 82.1% ($p = 0.36$), raised ESR in 68.8% ($p = 0.24$), raised ferritin in 69.6% ($p = 0.48$), and raised LDH in 73.2% ($p = 0.04$) (Table 3).

Table 3: Pre-Operative and Post-Operative Inflammatory Markers (n=112)

Inflammatory Marker	Pre-Operative N (%)	Post-Operative N (%)	P-Value
Raised WBC	67 (59.8)	104 (92.9)	<0.001
Raised CRP	98 (87.5)	106 (94.6)	0.03
Decreased Albumin	87 (77.7)	92 (82.1)	0.36
Raised ESR	69 (61.6)	77 (68.8)	0.24
Raised Ferritin	73 (65.2)	78 (69.6)	0.48
Raised LDH	68 (60.7)	82 (73.2)	0.04

The hospital outcomes showed that 30.4% of patients had a normal recovery, while 18.8% experienced postoperative wound infections. Reoperation was required in 7.1% of cases, and 12.5% had sepsis, wound infection, and prolonged hospital stay. Mortality was 3.6% (Table 4).

Table 4: Hospital Outcomes and Mortality (n=112)

Hospital Outcomes	N (%)	P-Value
Normal	34 (30.4)	-
Reoperation	8 (7.1)	0.23
Pneumonia and Prolonged Stay	4 (3.6)	0.46
Pneumonia, Shock and Prolonged Stay	2 (1.8)	0.62
Pneumonia, Wound Infection and Prolonged Stay	8 (7.1)	0.23
Pneumonia	4 (3.6)	0.46
Sepsis, Wound Infection and Prolonged Stay	14 (12.5)	0.07
Sepsis and Prolonged Stay	4 (3.6)	0.46
Wound Infection and Prolonged Stay	11 (9.8)	0.13
Shock and Prolonged Stay	2 (1.8)	0.62
Postoperative Wound Infections	21 (18.8)	0.11
Mortality	4 (3.6)	-

DISCUSSION

This study investigated the socio-demographic characteristics, tumor grading, surgical procedures, inflammatory markers, and hospital outcomes of 112 patients with colorectal cancer at Liaquat University Hospital, Hyderabad/Jamshoro. The mean age of the patients was 45.16±10.52 years, with a slight predominance of males (51.8%). Elderly people with a high burden of coexisting disorders may be less likely to pay attention to cancer symptoms, may put off treating them, or may have other medical issues masking the warning signals of cancer (masked symptomatology not visible to patients or physicians). When it comes to the elderly, colon disruption is frequently thought to come with getting older [10-12]. The reason for this age related alteration in gut morphology night be due to the mitochondrial changes, oxidative stress, DNA damage and microbial damage in the intestinal ephithelium [10,12]. Most patients resided in urban areas (53.6%). The primary presenting complaints were abdominal pain, per rectal bleeding, and weight loss (Table 1). The prevalence of hypertension (67.9%), diabetes (44.6%), smoking (49.1%), obesity (29.5%), dyslipidemia

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(24.1%), and anemia (89.3%) among the patients is consistent with comorbidity patterns observed in other studies on colorectal cancer. These comorbidities can complicate treatment and affect prognosis, emphasizing the need for comprehensive management strategies [13]. For instance, the study by Yancik R et al., in 1998 highlights that comorbid conditions like hypertension and heart problems significantly increase early mortality risks in colon carcinoma patients [14,15]. Our findings similarly underscore the high prevalence of comorbid conditions, which necessitates careful consideration during treatment planning. Several studies report the presence of these comorbidities among CRC patients [16-20]. Tumor grading in our study showed that the majority of patients had T2N1M0 (58.0%) or T2N0M0 (37.5%) tumors, which is comparable to other studies reporting early-stage colorectal cancer as the most common diagnosis at initial presentation [21]. Surgical interventions were diverse, with right hemicolectomy being the most frequent procedure (23.2%), followed by left hemicolectomy, sigmoidectomy, and transverse colectomy (each 11.6%). The distribution of surgical procedures reflects standard practice in colorectal cancer management and is supported by existing literature. The study by Vissers PA et al., in 2016 suggests that lifestyle factors and BMI significantly affect health-related quality of life (HRQoL) in colorectal cancer patients [22]. Obesity is reported to be a common risk factor and affects prognosis in colorectal cancer. Obese patients displayed more comorbidities, more pain after cancer surgery, worse coping, and more depression and perceived less social support than nonobese patients [23]. This finding is relevant to our study, as we observed a high prevalence of obesity (29.5%) and smoking (49.1%), which are critical lifestyle factors influencing patient outcomes. The study by Abualkhair WH et al., in 2020 further supports our findings by demonstrating a significant increase in colorectal cancer incidence from ages 49 to 50, correlating with the onset of average-risk screening [24]. This steep increase indicates a high prevalence of undetected preclinical cases, suggesting that earlier screening could benefit those under 50. Our patient demographics reflect a need for heightened awareness and potential earlier screening interventions to detect colorectal cancer at more treatable stages. The study found significant pre-operative and post-operative elevations in inflammatory markers, such as WBC, CRP, ESR, ferritin, and LDH. Raised WBC (59.8% pre-operative, 92.9% post-operative, $p < 0.001$) and CRP (87.5% pre-operative, 94.6% post-operative, $p = 0.03$) were particularly notable. These markers are associated with systemic inflammation and have been linked to poorer prognosis in colorectal cancer patients. Elevated inflammatory markers may indicate a more aggressive disease course and a higher likelihood of complications, reinforcing the importance of monitoring these parameters during patient management. The study by Yancik et al., in 1998 also emphasizes that comorbidity and inflammation increase the complexity of cancer management and affect survival duration, which is consistent with our findings [14, 22]. Longitudinal studies with extended follow-up periods are necessary to evaluate the long-term prognostic significance of raised inflammatory markers in colorectal cancer. Additionally, investigating the potential therapeutic benefits of targeting inflammation in colorectal cancer could provide valuable insights into improving patient outcomes. Studies should also consider including detailed assessments of lifestyle factors and their interactions with comorbidities and inflammatory markers to develop more comprehensive treatment strategies.

CONCLUSIONS

The study demonstrates that serum inflammatory markers, both pre-operative and post-operative, play a significant role in influencing the prognosis and outcomes of patients with colorectal carcinoma. Elevated levels of markers such as WBC, CRP, ESR, ferritin, and LDH, along with decreased serum albumin, were associated with adverse surgical outcomes including wound infections, pneumonia, sepsis, and prolonged hospital stays. The mortality rate was noted to be 3.6%. These findings underscore the importance of monitoring inflammatory and prognostic markers in managing colorectal carcinoma to predict and potentially mitigate complications, ultimately improving patient outcomes.

Authors Contribution

Conceptualization: AIM

Methodology: SR, HK, N., SHI

Formal analysis: AIM

Writing, review and editing: AIM, AMB,

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Assessment of Knowledge and Practices of Influenza and Pneumococcal Vaccination Among Type 1 and Type 2 Diabetes Patients in Bewal International Hospital

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ABSTRACT

Patients with diabetes have high risk of developing pneumococcal and influenza infections and are advised to take immunization for prevention against the disease. **Objective:** To determine the level of awareness and immunization behaviors for influenza and pneumonia among patients with type 1 and type 2 diabetes received treatment at Bewal International Hospital, Gujar Khan. **Methods:** This cross-sectional study was performed at the diabetic clinic of Bewal International Hospital, Gujar Khan, from June 2023 to August 2023. A total of 200 patients with diabetes were included in the study. Socio-demographic details were noted on a pre-structured questionnaire. Questions about knowledge and practices of vaccination particularly influenza and pneumococcal were asked and responses were noted. **Results:** The mean age of the patients was 47.0 ± 1.18 years. 193 (96.5%) had poor knowledge regarding influenza and pneumococcal infections and their vaccines. An alarming 99% of the people did not have any clue about any vaccination against pneumococcal and influenza infection in patients with diabetes. Similarly, only 1.0% of patients had good practices regarding these vaccinations. **Conclusions:** The knowledge and practice of influenza and pneumococcal vaccination in patients with diabetes is drastically low in the study population. The health care providers should educate the patients and the government should take concrete steps towards education and improvement of the socioeconomic condition of people along with cost-effectiveness and availability of vaccines for every individual.

INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic condition characterized by increased plasma glucose levels as a result of β-cells malfunction and insulin resistance [1]. It is a grave public health concern, prevailing as an epidemic with an approximate global prevalence of 6.1% [2]. As a chronic disease, DM is associated with a reduction in immunity, making affected individuals more prone to other diseases. Due to immunodeficiency, patients with diabetes have a higher prevalence as well as severity of infectious diseases typically respiratory tract infections. The outcomes of these diseases also tend to be poor in patients with diabetes [3]. The prevalence of pneumococcal infections are substantially higher in individuals with diabetes [4]. The rate of complications of pneumococcal and influenza disease is higher in these patients as compared to the patients without diabetes [5]. Most international organizations suggest seasonal pneumococcal and influenza vaccination to patients with diabetes in order to reduce hospitalization and complication rates [6,7]. Two types of pneumococcal vaccines including pneumococcal conjugate vaccines and polysaccharide vaccines are available and recommended

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for patients with diabetes [8,9]. Similarly, annual vaccination of trivalent inactivated influenza and live attenuated influenza vaccines are also recommended for patients with diabetes [10]. Despite these guidelines, there is unsatisfactory adherence to vaccination in the general population particularly due to lack of awareness. Increasing the knowledge and awareness among these patients related to pneumococcal and influenza vaccination is the most efficacious way to minimize the complications of such infections [11]. There is a poor level of knowledge, awareness, and practice regarding influenza vaccination among patients with diabetes all over the globe, according to several studies that have been conducted [12,13]. According to Sözen M *et al.*, the primary obstacle that prevents patients with diabetes from obtaining the influenza vaccination is a lack of understanding about the relevance of the vaccine regarding influenza [7]. There is a paucity of studies on this subject in Pakistan, even though several studies have been carried out to evaluate the knowledge and habits of patients with diabetes about immunization. As a result, the purpose of this research was to investigate the level of awareness and immunization habits about influenza among patients with type 1 and type 2 diabetes who were receiving treatment at Bewal International Hospital Gujar Khan, Punjab, Pakistan.

METHODS

This cross-sectional study was performed at the diabetic clinic of Bewal International Hospital, Gujar Khan, Punjab, Pakistan, from June 2023 to August 2023. A sample size of 200 patients was estimated using 95% confidence level, 5% margin of error and 15.3% rate of pneumococcal disease in adults with chronic medical conditions [14]. The study was approved by the hospital Ethical Committee i.e. Ref No: /01/01/2023/S2 ERB. Consecutive sampling technique was used to collect data. Patients of either gender with age ≥18 years having type I or type II diabetes diagnosed at least one year before were included. Type II Diabetes was considered if the patient was currently on hypoglycemic drugs or previous history of taking hypoglycemic drugs, and had random blood glucose ≥ 200 mg/dL, a fasting blood glucose ≥ 126 mg/dL, or 2-hour blood glucose of 200mg/dL on 75g oral glucose tolerance test [15]. Type I diabetes was considered if the patient had a positive islet cell autoantibody test in addition to the other diagnostic findings of diabetes. Patients <18 years without confirmed clinical diagnosis of diabetes mellitus, having cognitive impairment or psychological problems (on history) and critically ill patients were excluded. Following the receipt of clearance from the ethical committee and the provision of informed consent from patients, a total of two hundred diabetes patients who fulfilled the inclusion criteria contributed to the research project. Clinical history was taken in form of the duration of the disease and diabetic control. Diabetic control was assessed using glycated hemoglobin. In the present study, the structured survey questionnaire was used as a tool for data collection. The tool was designed after reviewingdifferent studies [16-17]. The Cronbach's α coefficient was found to be 0.817 for the total questionnaire. While, it was 0.796 for knowledge and 0.756 for practices section of the questionnaire. For the accuracy of data, most of the questions in the questionnaire were close-ended. Initially, a self-administration method was attempted, but this approach led to many unanswered questions due to language barriers. Consequently, direct interviews lasting 15-20 minutes were conducted instead. During these interviews, the participants did not have trouble understanding the questions. The questionnaire had three sections. The first part included the socio-demographic data comprised of questions about the respondents personal details such age, gender, area of residence, educational status, and monthly income. The second part of the questionnaire was about the knowledge of influenza and pneumococcal infection and vaccination. Nine main close-ended questions related to knowledge were included. Responses were scored, percentages were calculated and divided into two categories. The total score ranged from 0 to 9. In terms of knowledge about pneumococcal and influenza vaccination, respondents were graded based on their correct answers: a score of 65% or higher was considered good, while a score below 65% was taken as poor, as reported in a similar study [17]. The third part of the questionnaire was about the practices of the respondents regarding vaccination. Practices were also assessed through direct interviews and structured questions within the survey were used to eastimate it. Four main close-ended questions related to practices were included. Each correct answer was given a score of one and wrong answer a score of zero. Responses were scored, percentages were calculated and divided into two categories. The total score ranged from 0 to 4. For practices, the study classified respondents with any two positive responses as good, representing 50%. Conversely, two negative responses were categorized as poor on the basis of the answers in the Practices section, as reported in a comparable study [17]. All data were entered and analyzed using SPSS version 24.0. Quantitative data such as age were presented using mean and standard deviation. Qualitative data such as age groups, gender, residence, education status, financial status in terms of monthly income, and responses about knowledge and practices regarding pneumococcal and influenza vaccination in patients with diabetes were presented using frequencies and percentages.

RESULTS

A total of 200 patients with diabetes were included in the study. Socio-demographic parameters are shown in table 1.

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The mean age of the patients was 47.0 ± 1.18 years. There were 54.5% males and 45.5% females in the study. The majority was living in Gujar Khan 63.0%. 40.5% patients received no formal education and only 3.5% patients were post-graduate. Monthly income ranged between 10,000 to 20,000 PKR in majority (43.0%) of the patients. The M majority of the patients (37.5%) had diabetes for less than 5 years. 54.5% patients had good diabetic control.

Table 1: Clinical and Socio-Demographic Parameters of Patients with Diabetes (n=200)

Variables	Mean ± S.D
Mean Age* (Years)	47.0 ± 1.18
Age Groups (years) N (%)	
18 - 30	12 (6.0%)
31 - 40	20 (10.0%)
41 - 50	40 (20.0%)
51 - 60	65 (32.5%)
>60	63 (31.5%)
Gender N (%)	
Male	109 (54.5%)
Female	91 (45.5%)
Residence N (%)	
Gujar Khan	126 (63.0%)
Other Areas of Punjab	74 (37.0%)
Education Status N (%)	
No formal education	81 (40.5%)
Islamic education	10 (5.0%)
Primary	49 (24.5%)
Intermediate	40 (20.0%)
Graduation	13 (6.5%)
Post-graduation	7 (3.5%)
Monthly income (PKR) N (%)	
<10,000	34 (17.0%)
10,000 - 20,000	86 (43.0%)
20,001 - 30,000	36 (18.0%)
30,001 - 40,000	24 (12.0%)
>40,000	20 (10.0%)
Duration of disease (years) N (%)	
<5	75 (37.5%)
5 - <10	56 (28.0%)
10 - <15	29 (14.5%)
15 - <20	18 (9.0%)
≥20	22 (11.0%)
Diabetic control N (%)	
Good (HbA1c ≤ 6.5%)	109 (54.5%)
Poor (HbA1c >6.5%)	91 (45.5%)

n=number of patients; %=percentage of patients; * = mean ± standard deviation; PKR = Pakistani rupee; HbA1c = Glycated hemoglobin

Table 2 explains the knowledge of patients with diabetes regarding pneumococcal and influenza infection and vaccination. Only 3.0% patients knew that influenza and pneumococcal infections are caused by a virus or a bacteria. 5.0% patients knew that these infections can spread from person to person while only 2.0% patients knew that they can be prevented. 7.0% of patients knew that patients with diabetes are at higher risk of infection, and 5.5% reported that symptoms are worse in patients with diabetes. Only 1.0% of patients reported that they had ever heard about vaccination against influenza and pneumococcal infections, while 1.0% believed that it can prevent the disease. 4 (2.0%) patients reported that vaccine can protect from infections for 1 year.

Table 2: Knowledge of patients with diabetes regarding pneumococcal and influenza infection and vaccination

Questions		n (%)
What do you know about influenza and pneumococcal infection?	It is caused by a virus or a bacteria	6 (3.0%)
	It can spread from person to person	10 (5.0%)
	It can be prevented	4 (2.0%)
	Patients with diabetes are at a higher risk of infection	14 (7.0%)
	Symptoms are worse in patients with diabetes	11 (5.5%)
Have you ever heard of that a vaccine could prevent influenza and pneumococcal infection?	Yes	2 (1.0%)
	No	198 (99.0%)
Does the vaccine prevent this infection?	Yes	2 (1.0%)
	No	198 (99.0%)
How is the vaccine administered?	Injection	10 (5.0%)
	Oral drops	102 (51.0%)
	Nasal drops	88 (44.0%)
Does the vaccine have side effects?	Yes	109 (54.5%)
	No	91 (45.5%)
How long vaccine can protect you?	1 year	4 (2.0%)
	2 year	7 (3.5%)
	Lifelong	189 (94.5%)
Does vaccine prevent serious complications associated with the influenza and pneumococcal infection in patients with diabetes?	Yes	14 (7.0%)
	No	186 (93.0%)
When is the appropriate time to take vaccine?	Before the start of winters	9 (4.5%)
	During winters	81 (40.5%)
	Immediately after winters end	110 (55.0%)
Is it true you can never get infection as long as you are vaccinated?	Yes	126 (63.0%)
	No	74 (37.0%)

n = number of patients; % = percentage of patients

Table 3 demostrates the differentiation of the patients based on their knowledge scores. The scoring of the participants' knowledge documented that 96.5% of patients had poor knowledge regarding influenza and pneumococcal infections and their vaccination.

Table 3: Patients' knowledge score

SCORE	Good knowledge (Score ≥ 65%) n (%)	Poor knowledge (Score < 65%) n (%)
Influenza and Pneumococcal Vaccination Knowledge	7 (3.5%)	193 (96.5%)

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n = number of patients; % = percentage of patients

Table 4 explains the practices of patients with diabetes regarding pneumococcal and influenza infection and vaccination. Only 1.0% of patients had received the vaccination before, among whom 0.5% patients received it every year. Among these 1.0% of patients, vaccine was recommended by their doctor. Reasons of not receiving vaccination included lack of knowledge about the vaccine in 96.5% of patients, followed by the vaccine being expensive (1.0%), having alternate protection (1.0%), and perceived side effects of the vaccine (0.5%).

Table 4: Practices of patients with diabetes regarding pneumococcal and influenza infection and vaccination

Questions		n (%)
Have you ever received influenza or pneumococcal vaccine before?	Yes	2 (1.0%)
	No	198 (99.0%)
How regularly do you take this vaccine?	Every year	1 (0.5%)
	Received only once	1 (0.5%)
	Never received	198 (99.0%)
What influenced you to take the vaccine?	Recommended by doctor	2 (1.0%)
	Been told by a fellow patient	0 (0.0%)
	Vaccine is available free of cost	0 (0.0%)
	Advised by pharmacist	0 (0.0%)
	Media campaign	0 (0.0%)
What are the reasons for not taking vaccine?	Don't know about vaccine	193 (96.5%)
	I have alternative protection	2 (1.0%)
	side effects	1 (0.5%)
	Not effective	0 (0.0%)
	Not necessary	0 (0.0%)
	Expensive	2 (1.0%)
	Fear of injection	0 (0.0%)

n = number of patients; % = percentage of patients

Table 5 demostrates the differentiation of the patients based on their practices scores. Only 1.0% patients reported to have good practices regarding vaccination based on the cut-off value of 66.3%.

Table 5: Patients' practices score

Practices	n (%)
Good practices (≥50%)	2 (1.0%)
Poor practices (<50%)	198 (99.0%)

n = number of patients; % = percentage of patients

DISCUSSION

Diabetes is an epidemic condition worldwide and is associated with an alarming decrease in immunity causing patients to become more prone to infections, typically respiratory tract infections [17,18]. Although vaccines are available to protect against these diseases and to reduce the hospitalization and complication rates in patients with diabetes, this practice is not common in developing countries like Pakistan [19]. Therefore, the purpose of this research was to investigate the level of awareness and immunization habits about influenza among patients with type 1 and type 2 diabetes who were receiving treatment at Bewal International Hospital, Gujar Khan. The findings of this research showed that there is a lack of knowledge regarding pneumococcal and influenza vaccination in patients with diabetes. Only 1% of patients knew such vaccinations in patients with diabetes. A study by Alsaad SM *et al.*, showed that Saudi patients had a good knowledge of the flu (70.9%), vaccine (64.3%) and affirmative attitudes towards vaccination (65.7%) [20]. Al-Qerem W *et al.*, reported that 70.6% never had the influenza vaccine, and only 23.7% planned to take it in the coming season [12]. A study conducted in Lahore, Pakistan revealed that 52% had awareness regarding increased susceptibility to pneumonia and influenza among patients with diabetes. However, only 12 % had received the vaccines against it during the last five years [19]. These results contradict the findings of the current study. An Indian study reported that influenza and pneumococcal vaccination was administered in only 2% and 0.7%, respectively. After counseling, 52% of individuals agreed to get the vaccination owing to its safety and efficacy but only 17.4% got it [21]. In a study performed in Saudi Arabia, it was documented that 47.8% of the patients with type II diabetes took the flu vaccine while only 2.8% received the pneumococcal vaccine. There was a lack of awareness regarding the pneumococcal vaccine [22]. Another South Indian study reported that only 4.8% and 4.1% of the patients with diabetes had Knowledge about influenza and pneumococcal infections, respectively. While the majority (98.7%) had no awareness regarding the availability of the vaccines [23]. These findings are comparable to the current study. However, this study also has some limitations. Firstly, the geographical limitation as it was carried out in Gujar Khan with the majority of the population residing in Gujar Khan, so the results cannot be generalized. Secondly, it did not consider the availability of the vaccinations which might have impacted the frequency of awareness in patients with diabetes. Based on the results, the study suggests that healthcare providers should play a pivotal role in creating awareness as well as motivating them to take the vaccine.

CONCLUSIONS

The knowledge and practice of influenza and pneumococcal vaccination in patients with diabetes is drastically low in the study settings. The foremost barrier is the lack of knowledge followed by socioeconomic conditions and perceived decreased benefits of vaccines. The health care providers should educate the patients and the government should take solid steps towards education and improvement of the socioeconomic condition of people along with cost-effectiveness and availability of vaccines for every individual.

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Authors Contribution

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Formal analysis: MS, HAK, MI, MKUH, MZ, SN
Writing, review and editing: MS, HAK, MI, MKUH

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Association of Adiponectin and Oxidized HDL with ABO Blood Groups in Fatty Liver Patients

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ABSTRACT

Non-Alcoholic Fatty Liver Disease (NAFLD) is a group of liver diseases that are not brought on by alcohol usage and are defined by an excessive buildup of fat in the liver cells. **Objective**: To identify the relationship between the Body Mass Index (BMI) and liver function markers in the study group, as well as Oxidized High-Density Lipoprotein (oxHDL) levels. **Methods:** This study was conducted at the University of Lahore, for the duration of six months from January 2022 to June 2022. For determining the role of adiponectin and oxHDL, (n=200) patients and divided into two group, healthy group (n=100) and disease group (n=100) participants. Biochemical identification, liver function test, lipid profile test and ELISA was done for analyzing the association with NAFLD. SPSS software was used for statistical analysis. **Results:** In this study different parameters were used that's values of parameters mean of cases according to blood group system were varied than normal range, such as adiponectin level, BMI, oxLDL, oxHDL, ALT, AST, ALP, Cholesterol level, d-LDL, Calculated LDL, sdLDL, V-LDL, Triglyceride level, Apolipoprotein-B level was significantly higher and AST/ALT Ratio values, albumin, HDL were slightly less than normal values. O Blood groups was reported very low risk of fatty liver patients due to high adiponectin. **Conclusions:** From analysis it was concluded, that adiponectin and oxHDL associated with high risk of non-alcoholic fatty liver disorder.

INTRODUCTION

Fatty liver well-defined such as increase of 5% to 10% fat in liver cells. NAFLD include non-alcoholic steatohepatitis, 5% liver fat with inflammation and hepatocellular hyperplasia with or without fibrosis [1]. Several risk factors are elaborated to rise the high risk of NAFLD, high-calorie diets, rise saturated fat level, usage of refined sugar, abnormal metabolism, type 2 diabetes, hypertension, hyperlipidemia, Obesity (overweight) and insulin resistance are the key contributor of develop and growth of NAFLD [2, 3]. The race of NAFLD is frequently higher in Middle East that have 32%, Asia have 27 %, Europe have 23 %, and 9% people affected by NAFLD in India and Pakistan [4, 5]. Genetic variants influence the NAFLD, play very vital role. The first known genetic variation among humans is ABO blood group system which is divided into A, B, AB and O blood groups with respect to RH negative and positive. As such ABO blood system is linked with heart disease and cancer, similarly it is associated with non-alcoholic fatty liver disease (NAFLD) [6]. Lipid profile is effected at very high rate HDL, LDL, VLDL, LDL-C and HDL-C are interlinked [7, 8]. High range of hormone and low adiponectin resistance has been shown to increase the development

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and growth of NAFLD. Adiponectin enhance Fatty Acid Oxidation (FAO) and inhibit De Novo Lipogenesis (DNL) so therefore it increase insulin sensitivity. Increasing the adiponectin level in metabolic syndrome may preventing the serious consequences of NAFLD. HDL (high-density lipoprotein) is often considered "good" cholesterol because it contributes to reverse cholesterol transport. Alternatively, Oxidized HDL (ox-HDL) undergoes structural modifications and might promote atherogenesis instead. HDL can be promoted to oxidation, leading it from protective properties (anti-inflammatory and antioxidant) toward the pathogenic side of the spectrum. Higher levels of ox-HDL have been linked with the development of cardiovascular diseases and metabolic disorders [9, 10].

The main objective of this research was to identify the relationship between the Body Mass Index (BMI) and liver function markers in the study group, as well as Oxidized High-Density Lipoprotein (oxHDL) levels in Lahore population.

METHODS

The study was cross-sectional. This study was carried out in university of The Lahore. The trial lasted six months, from Dec 2023 to May 2024. A total number of participants N=200 were divided into two group healthy group (100) and fatty liver diseases group consist of 100 participants. The age of participants was 40-65 year old. This study was approved by institutional review board (IRB) IMBB/BBB/21/277, the University of Lahore. Making ensuring the informed consent procedure was understandable and transparent for each and every participant. All patients were resident of Lahore Pakistan. 5ml venous blood was extracted and serum was obtained by centrifugation and stored it at -70oC for biochemical analysis. NAFLD grade III along with following Co-morbidities were included in this study: Diabetes Mellitus, COPD, Due to smoking, Hypertension. The following Co-morbidities were not included in this study: alcohol consumption, viral hepatitis (HBV, HCV) and pregnant women. According to Antigen-Antibody agglutination test by slide method blood group with RH factors were determined. Liver function test includes ALT, AST and ALP was estimated. Statistical software or algorithms are typically used in the sample size calculation process. In order to compare the means of two groups, n= $(Z\alpha^{/2}+Z\beta)2*2\ \sigma 2/d^2$). By calculate the significance level, α = 0.05, which gives $Z\alpha/2$=1.96, Power (1- β) = 0.80, which gives $Z\beta$=0.84. Statistical analysis (mean and SD) was done by using SPSS v.26. For the continuous variable analysis, a t independent test was applied. P-value <0.001 was consider as significant value.

RESULTS

Descriptive statistics for Biochemical parameters of patients and controls is tabulated in table 1. Mean age of patients and controls was 58.74 and 52.55 respectively. Values of BMI along with liver enzymes (AST, ALT and ALP) were significantly increased (p<0.001) as compared to controls. Values of AST/ALT ratio and albumin were lower in patients (p<0.001) as compared to controls. Levels of lipid associated parameters such as (c-LDL,d-LDL, Cholesterol, oxHDL, oxLDL, sdLDL, Apolipoprotein-B, triglyceride, V-LDL, adiponectin level) were significantly increased as compared to controls (p<0.001). HDL level was significantly decreased in patients as compared to cases (p<0.001).

Table 1: Biochemical Assay of study participants

S. No.	Variables	Subjects	n	Mean ± SD	Mini-mum	Maxi-mum	P-Value
1	Age	Normal	100	52.55 ± 5.182	45	67	<0.001
		Patient	100	58.74 ± 4.545	45	68	
2	BMI	Normal	100	21.58 ± 2.40	16	30	
		Patient	100	35.67 ± 5.898	26	48	
3	Adiponectin Level	Normal	100	12.360 ± 3.310	7.00	20.00	<0.001
		Patient	100	24.50 ± 4.103	17.00	35.00	
4	V-LDL	Normal	100	25.703 ± 2.386	20.60	34.50	
		Patient	100	48.438 ± 5.017	38.00	56.60	
5	Triglyceride	Normal	100	128.170 ± 6.3	121.172	134.47	
		Patient	100	242.190 ± 4.92	37.27	247.11	
6	Apolipo protein-B	Normal	100	81.937 ± 5.56	76.377	87.49	
		Patient	100	150.624 ± 4.86	145.76	155.48	
7	sdLDL	Normal	100	30.127 ± 4.283	22.39	42.66	
		Patient	100	65.294 ± 5.99	59.3	71.28	
8	oxLDL	Normal	100	50.230 ± 5.745	37.00	60.00	
		Patient	100	96.940 ± 5.52	91.42	102.46	
9	oxHDL	Normal	100	81.920 ± 4.426	73.00	91.00	
		Patient	100	240.680 ± 6.01	243.67	246.69	
10	HDL Level	Normal	100	55.140 ± 5.103	45.00	67.00	
		Patient	100	40.266 ± 6.678	28.00	55.00	
11	Cholesterol	Normal	100	174.54 ± 5.23	169.31	179.77	
		Patient	100	265.350 ± 4.97	260.38	270.32	
12	d-LDL	Normal	100	98.860 ± 5.86	93	104.72	
		Patient	100	182.090 ± 5.94	176.15	188.03	
13	c-LDL	Normal	100	93.766 ± 5.56	88.206	99.321	
		Patient	100	177.066 ± 4.48	172.58	81.54	
14	ALT	Normal	100	33.96 ± 4.865	22	42	
		Patient	100	65.155 ± 3.3	58	73	
15	AST	Normal	100	29.68 ± 4.86	19	38	<0.001
		Patient	100	50.6 ± 4.29	40	60	
16	ALP	Normal	100	81.33 ± 5.76	75.57	87.09	
		Patient	100	95.79 ± 6.482	83	113	
17	Albumin	Normal	100	4.04 ± 0.530	2.80	5.20	
		Patient	100	2.803 ± 0.377	2	3.90	
18	AST/ALT Ratio	Normal	100	1.20 ± 0.12	57	1.15	
		Patient	100	3.13 ± 1.17	62	98	

According to this study it was found that serum oxHDL and Adiponectin with blood groups of cases and controls is tabulated in table 2. It is observed that the level of oxHDL and Adiponectin was significantly high (p<0.001) in patients

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with blood groups A,B,AB,O with Rh factor +ve compared to same blood groups of controls. The level of oxHDL and Adiponectin was also significantly high ($p<0.001$) in patients with blood groups A,B,AB,O with Rh factor -ve compared to same blood groups of controls.

Table 2: Biochemical Assay According to ABO Blood Group

ABO Blood Groups				oxhdL with Blood Groups Mean ± SD		Adiponectin with Blood Groups Mean ± SD	
Blood Group	Normal	Patients	Total	Patients	Normal	Patients	Normal
A+	24	30	54	234 ± 4.06	86 ± 3.09	24 ± 3.62	16 ± 2.83
A-	8	2	10	215 ± 2.82	84 ± 3.2	26 ± 4.24	11 ± 1.85
AB+	12	16	28	260 ± 3.03	79 ± 3.74	29 ± 3.21	10 ± 2.25
AB-	4	6	10	235 ± 4.70	80 ± 4.96	28 ± 3.74	14 ± 3.36
B+	20	26	46	244 ± 4.49	78 ± 2.4	22 ± 3.15	10 ± 1.52
B-	12	4	16	251 ± 4.16	82 ± 3.49	27 ± 1.63	12 ± 2.56
O+	16	12	28	224 ± 4.91	83 ± 3.79	22 ± 2.67	13 ± 2.4
O-	4	4	8	252 ± 3.91	81 ± 4.96	25 ± 3.16	79 ± 1.17
Total	100	100	200	-			

In current reasrch to indicate that for comparison of LDL and oxLDL is tabulated in table 3. The values of LDL and oxLDL was significantly higher in patients ($p<0.001$) as compared to controls.

Table 3: Comparison of LDL and oxLDL in Patients and Normals

Category	Patients (Mean ± SD)	Normals (Mean ± SD)	% increase in patients
LDL	182.09 ± 5.94	98.86 ± 5.86	1.89
oxLDL	96.94 ± 5.52	50.23 ± 5.74	2.08

DISCUSSION

Various investigations have recognized the higher Adiponectin level as independent risk factor of liver damage and NAFLD [11]. Shabalala *et al.*, highlighted the risk of NAFLD by high level of Adiponectin, according to previous reports in this study Adiponectin level mean was 24.5 ± 4.10346 µg/mL (p-value<0.001), minimum value 17 µg/mL and maximum value was 35 µg/ml. Adiponectin normal level was 12.36 ± 3.31078 µg/mL, minimum value 7 µg/mL and maximum value was 20 µg/mL. Adiponectin level was significantly higher. The association of ABO blood group as developing factor of NAFLD is still unclear. Some previous studies exposed the association of ABO blood group with liver injury and also as NAFLD. Different studies reported different result of ABO blood group association to NAFLD, Non-O Blood group was found to be pointedly association to high risk of NAFLD. In this study A+ blood group have higher NAFLD and at 2nd no B+ blood group was reported in NAFLD, O Blood groups was reported very low risk of NAFLD. The obesity epidemic is closely linked with the rising prevalence and severity of nonalcoholic fatty liver disease (NAFLD). Obesity has been associated not only with the simple steatosis (SS), but also with advanced disease i.e., nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis and hepatocellular carcinoma [12]. Consequently, despite of increasing almost all the mortality causes, obesity tends to increase liver-specific mortality especially in NAFLD patients. However, increased Body Mass Index is not an independent risk factor for the development of in NAFLD patients. The BMI mean of our study 35.67 ± 5.898 kg/m^2 (p-value<0.001) verified that obesity was rampant among our subjects weight gaining is the golden indication toward the NAFLD, this result is similar to many previous studies [13]. NAFLD is fairly mutual among elderly population. Intricate process of senescence or aging is complicated in the expansion of a plethora of chronic diseases. Development of senescence includes the pathogenesis and growth of liver steatosis. It includes the development of Nonalcoholic Steatohepatitis (NASH) which is branded by the emergence of inflammation, hepatocyte ballooning, and liver fibrosis. According to Papatheodoridi AM *et al.*, in 2020 the development of Nonalcoholic Fatty Liver Disease (NAFLD) and its progression to NASH are commonly accompanied by several pathological as well as physiological events that include metabolic dysregulation and inflammatory changes occurring within the liver [14]. The average age of cases according to our study was 58.74 ± 4.54 (p-value<0.001), this relatively almost same age is associated with NAFLD which is reported onto several studies [14, 15]. Oxidized High-density lipoprotein (oxHDL) is an emerging biomarker of NAFLD patients. Miura K *et al.*, study reported that Oxidized High-density lipoprotein (oxHDL) level is higher in NAFLD patients similarly in this study Oxidized High-Density Lipoprotein (oxHDL) level in patients was 240.68 ± 6.01 mg/dl (p-value<0.001), minimum value 243.64 mg/dl and maximum value was 246.69 mg/dl. oxHDL normal level was 81.92 ± 4.426 mg/dl, minimum value 73 mg/dl and maximum value was 91 mg/dl. oxHDL level was significantly higher in cases than controls [16]. Increasing oxLDL levels linked to an amplified risk of acute coronary events, metabolic syndrome and hepatocellular damage in clinical cholestasis and fibrosis. oxLDL has been established to increase the production of inflammatory cytokines and chemokines by macrophages and to cause coronary smooth muscle cells to overexpress interleukin, an

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essential gatekeeper of inflammation and tissue damage. oxLDL discovered to increase apoptosis by activating apoptotic signaling pathways like the Fas system [17]. In apoptotic cells, physiologically active oxidized lipids were also discovered. As a result, because oxLDL causes apoptosis, it is not only an inflammatory trigger but also increases cell damage. Furthermore, oxLDL causes inflammation by increasing the production of Reactive Oxygen Species (ROS) and the expression of metalloproteinases. Oxidized Low-Density Lipoprotein (oxLDL) higher value have high risk of NAFLD, similarly in this study Oxidized Low-Density Lipoprotein (oxLDL) level mean in patients was 96.94 ± 5.52 mg/dl (p-value<0.001), minimum value 91.42 mg/dl and maximum value was 102.46 mg/dl . oxLDL level was significantly higher in cases than controls [18]. Dyslipidemia is the most common situation present in NAFLD patients and considered as increasing the level of Small Dense Low-density lipoprotein (sd-LDL) and lower the level of HDL. Hwang HW *et al.*, showed that Small Dense Low-density lipoprotein (sd-LDL) is increased in NAFLD patients, similar to this study in our research sdLDL level mean in patients was 65.294 ± 5.99 mg/dl (p-value<0.001) that is higher than normal range which is less than 40mg/dl (<40 mg/dl) [19]. Apolipoproteins like ApoE, ApoA, ApoC and ApoB are associated with swear diseases of liver especially with NAFLD. In this study Apolipoprotein-B level mean in patients was 150.624 ± 4.86 mg/dl, minimum value 145.76 mg/dl and maximum value was 155.48 mg/dl (p-value<0.001), Apolipoprotein-B level was significantly higher which highlight the high risk of NAFLD [20]. Triglyceride is the independent marker of NAFLD. In this study Triglyceride level was 242.19 ± 4.92 mg/dl (p-value<0.001) and normal value was less than 150 mg/gL (<150 mg/dL) [21]. As earlier reported that maximum patients exhibited the dyslipidemia profile and have abnormal lipid profile which is more frequently in NAFLD patients. Some previous studies reported a significant association of V-LDL with inflammation or liver damages. Mendez-Sanchez N *et al.*, also showed that liver fibrosis (NAFLD) more likely high V-LDL. Similarly, in our study V-LDL was 48.438 ± 5.0174 mg/dl (p-value<0.001), V-LDL level was significantly higher in cases than normal [5]. Earlier studies described the association of low HDL with occurrence of NAFLD. Lower HDL have higher risk of NAFLD and our study HDL mean in cases was 40.266 ± 6.678 mg/dl (p-value<0.001), HDL level was significantly lower [22]. Calculated Low-Density Lipoprotein (c-LDL) is also higher in hepatosytosis and it is the significant reason for the development of NAFLD. In this study the calculated Low-Density Lipoprotein (c-LDL) average level was 177.066 ± 4.48 mg/dl (p-value<0.001). The Desired normal range of this was less than 100 (<100), optimal value was 100-129 and higher than 130 was abnormal condition. This study also verified the previous studies results that Calculated LDL level was significantly higher. Direct Low-density Lipoprotein (d-LDL) Level in NAFLD patients has higher. Normal range of d-LDL was up to 130 mg/dl. Our study stated the d-LDL level mean in patients were 182.09 ± 5.94 mg/dl (p-value<0.001), that was significantly higher than normal [23]. Normal value of cholesterol is less than 200 (<200). In this study Total Cholesterol level mean in patients were 265.35 ± 4.97 mg/dl, minimum value 260.38 mg/dl and maximum value was 270.32 mg/dl. Average result of Cholesterol level was significantly higher (p-value<0.001). Same results were highlighted in Ganjooei NA *et al.*, studies. The concentration of serum albumin reported lower when the intensity of NAFLD increased. The normal level of albumin in serum is 3.5-5 g/dl. In our study Albumin mean in cases was 2.8 ± .377 g/dl, minimum value 2 g/dl and maximum value was 3.9 g/dl (p-Value < 0.001), these results were significantly verified by previous studies [24]. Alkaline Phosphatase (ALP) is also considered as biomarker related to the hepatic fibrosis in the patients. Range of Alkaline Phosphatase is 41 – 133 U/L, 41 U/L is lower and 133 U/L is higher range, in NAFLD patients have higher range and normal people have lower value. In our study ALP average range in cases was 95.79 ± 6.48 U/L, minimum value 83 U/L and maximum value was 113 U/L (p-value <0.001). Other studies also verified our results to describe high range of ALP. AST is also play significant role in diagnosis of liver disorders. The normal value of AST is up to 40 U/L, in our study the mean of AST level was 50.61 ± 4.29 U/L (p-value<0.001) this result show AST values were significantly higher which exposed the high risk of NAFLD. Some NAFLD patients have normal ALT value and some have higher than normal. The normal value of ALT is up to 40 U/L, in our study the mean of ALT level was 65.155 ± 3.316 U/L (p-value<0.001) this result show high level of ALT which shown the high risk of NAFLD. The AST/ALT Ratio mean in patients were 3.13± 1.17 U/L (p-value<0.001), normal valve of AST/ALT ratio is less than 1 (<1 U/L) and in NAFLD this ratio is less than 0.8 U/L (<0.8 U/L). Our study shows AST/ALT value less than 0.8 U/L which is indication of NAFLD [25].

CONCLUSIONS

This study played a vital role to better understanding the association of adiponectin and oxidizes HDL with ABO blood groups in fatty liver patients. Comparing blood group O to other blood groups, higher adiponectin levels may offer protection against severe non-alcoholic Fatty Liver Disease. Different ABO blood groups were linked to genetic and environmental factors that were associated with variable oxHDL levels. These factors could have an impact on oxidative stress and inflammation in patients with fatty livers.

Authors Contribution

Conceptualization: NN
Methodology: RA, AR
Formal analysis: SA, AA
Writing, review and editing: RJ

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Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Assessment of Psychological Well-being of Doctors Working in Public and Private Hospitals of Gilgit-Baltistan, Pakistan

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ABSTRACT

Healthcare workers are prone to develop psychological distress due to overwhelming responsibilities. This can lower their job performance as well as patient satisfaction. **Objectives:** To assess the psychological well-being of doctors who were working in public and private hospitals of Gilgit-Baltistan, Pakistan. **Methods:** A cross-sectional study was conducted for six months, during which data were gathered from a sample of 214 participants chosen through non-probability convenient sampling at various public and private hospitals in the region. Data were analyzed using SPSS version 26.0. An Independent sample t-test was applied to compare the psychological well-being of doctors working in the public and private sectors. DASS scale and self-rated held were used to assess the mental health of doctors. **Results:** Among the 214 respondents, the majority were male doctors. Moreover, the study population's majority was working in the public sector. It was noted that the majority of the study population lies in the normal to mild range of depression, anxiety, and stress. Results also revealed that there was no significant difference in the psychological health of doctors in public and private hospitals. **Conclusions:** It was concluded that the psychological health of doctors working in public and private hospitals of Gilgit Baltistan has no significant difference.

INTRODUCTION

Psychological well-being is an important aspect of health. World Health Organization (WHO) describes health as a combination of multiple factors and not merely the lack of disease. Psychological well-being and mental health are crucial tenets of the definition of health as developed by WHO [1]. Mental well-being is the mental state of an individual, how they feel, and how well they can handle day-to-day life challenges [2]. Healthcare providers are disposed to burnout due to their exhausting schedules. Burnout develops gradually and takes some time to show its symptoms. Twelve different phases of burnout are verified in literature: an obligation to prove oneself, doing hard work, undermining personal needs, shifting disputes, revising standards, not being able to accept new issues, withdrawal, significant alteration in attitude, depersonalization, loneliness, despair, and fatigue [3]. The time of these phases differs from person to person and sometimes, various stages occur simultaneously. This can greatly disturb the physician himself, his family, and the patients. Nowadays, due to increasing struggles and competition, the stressors have increased leading to the corrosion of mental health. Workplace stress is usually caused by increased demands, pressure, competition, and expectations at the workplace. Healthcare professionals are more susceptible to developing stress [4]. A load of different diseases, epidemics, developing and reemerging health problems, multitasking, and job responsibilities make it even more difficult for doctors to accomplish their

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jobs competently and proficiently. These issues contribute to the departure from normal mental state among health care professionals [5]. Healthcare professionals require improved mental wellness so that they can complete their duties professionally. This is mainly important in primary healthcare where health professionals are exhausted with increased work, unsatisfactory working places, and family conflicts which can probably impact their mental and psychological well-being and disturb their work performance [6]. The frequency of psychological issues among health professionals all over the world is increasing day by day. These depressive symptoms start developing during medical school and undergraduate training years [7]. This causes an absence, where health professionals skip their duties because of disturbed mental health; presentism where they perform their duties regardless of their poor psychological health; and a decreased number of staff where health professionals quit the medical profession completely. [7, 8]. Satisfaction with work-life equilibrium has declined extremely from 2011 to 2014 among physicians in the United States (48.5% versus 40.9%) with increased reported burnout. In Pakistan, mild to moderate anxiety and depression are reported by 34% and 24.8% of health professionals respectively [2] and these levels are continuously increasing. Persons with good mental health can understand and properly operate their abilities, can manage ordinary pressures of life, work efficiently and effectively, and are proficient in contributing towards the economy of the society as well as the country. In recent years, psychological well-being has come to attention due to its role in handling and protecting against different psychiatric illnesses [9]. Xiao *et al.*, carried out research in 2020 in China. The main objective of this study was to find out the frequency of psychological issues among different health professionals during the COVID-19 pandemic. The results indicated that 40% of respondents reported having anxiety, 45% of them reported symptoms of depression, 29% of the participants indicated that they have insomnia, and 57% of the respondents reported overall psychological problems. Higher levels of psychological problems were reported by nurses and public health professionals [10]. Azoulay et al., conducted research in France in 2020. The primary objective was to assess the mental health problems among healthcare providers. The findings of the study showed that, out of the total participants, 50.4% showed anxiety and 30.4% were suffering from depression [11]. Jalili et al., carried out research in Iran in 2021. The research was aimed at determining the level of burnout among healthcare professionals dealing with COVID-19 patients. Findings revealed that, out of the total participants, 53% experienced extreme levels of burnout [12]. Rasool *et al.*, carried out research in 2020 in Pakistan. The main objective of the study was to determine the level of anxiety, depression, and stress among healthcare workers during COVID-19. The findings revealed that out of the total participants, 41% experienced a moderate level of depression, extreme levels of anxiety were reported by 30% of the respondents while moderate levels of stress were found in 22% of the participants [13]. Various studies have been conducted worldwide to address the hidden aspects of this vital public health issue however, in Pakistan, there is still a lack of literature regarding this important issue. The present study was conducted in Gilgit-Baltistan, Pakistan to determine the levels of psychological well-being among doctors practicing there and also determine the different socio-demographic characteristics that can affect their subjective well-being. The results of the study have provided important insights regarding psychological well-being among doctors. The study also highlighted some subgroups among the study population that need more attention while developing policies for the betterment of the psychological well-being of doctors.

This research aimed to find the psychological well-being of doctors working in a remote area of Pakistan creating a path for future researchers to explore more aspects of this issue.

METHODS

A cross-sectional study design was used to assess the psychological well-being of doctors who are working in public and private hospitals in Gilgit-Baltistan, Pakistan. The research was conducted for a period of six months from March 2022 to August 2022. Ethical Approval Letter was taken from the Institutional Review Board (MSPH-IRB/13-19). Moreover, consent was taken from every respondent before the data collection. The respondents from public and private hospitals in Gilgit-Baltistan were included in the study through a non-random convenient sample strategy (Figure 1). A total of 25 hospitals were included in the study of which 15 were public sector hospitals. The sample size was determined using OpenEpi Menu software. The prevalence of psychological issues among healthcare workers used in the formula as a reference was 16.7% [14]. Taking a 95% confidence interval, the sample size was 214 for this study. Data were collected using self-administered questionnaire from the respondents. Doctors from all departments and those who were permanent residents of Gilgit-Baltistan were not included in the study. Doctors with diagnosed psychiatric disorders and who were on leave were excluded. The desired sample was collected using non-probability convenient sampling. A questionnaire was developed to collect data regarding the sociodemographic characteristics of the doctors to assess psychological distress, depressive and anxiety symptoms, stress, and

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well-being, a validated, widely used instrument was used including a 21-item Depression, Anxiety, Stress Scale (DASS-21)[15]. For determining subjective self-rated health status, a single-item question was included with five response options ranging from excellent to poor. Scoring of the DASS scale (Table 1).

Table 1: Scoring of Depression, Anxiety and Stress

Score	Depression	Anxiety	Stress
Normal	0-9	0-7	0-14
Mild	10-13	8-9	15-18
Moderate	14-20	10-14	19-25
Severe	21-27	15-19	26-33
Extremely severe	28+	20+	34+

It is a 4-point Likert scale ranging from 1 (did not apply to me) to 4 (applied to me very much or most of the time). Pilot testing was performed before starting the formal data collection procedure by including 10% of the actual sample size. Performa was tested for any future changes; no major changes were made after pilot testing. Cronbach alpha of DASS-21 was found to be 0.91 (Figure 1).

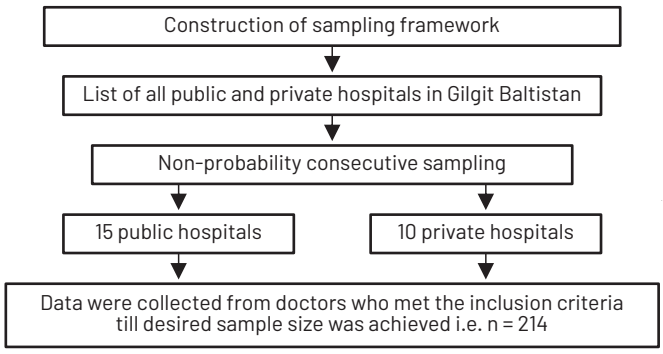

Figure 1: Non-Probability Convenient Sampling Strategy

RESULTS

Results indicate that out of 214 respondents, a larger proportion lies between 25-35 years of age (n= 123, 57.5%). Similarly, more than half of the respondents belong to public health sector (n=124, 58%). A detail of the sociodemographic characters of the respondents (Table 2)

Table 2: Sociodemographic Characters of Respondents

Variables	n (%)
Age	
Less than 25 Years	13 (6.1)
25-35 Years	123 (57.5)
36-45 Years	48 (22.4)
46-55 Years	16 (7.5)
More than 55 Years	14 (6.5)
Gender	
Male	146 (98%)
Female	68 (32%)
Marital Status	
Single	61 (28.5)
Married	150 (70.1)
Widow	3 (1.4)
Qualification	
MBBS	94 (43.9)
BDS	29 (13.6)
FCPS	53 (24.8)
MCPS	12 (5.6)
MPhil	26 (12.1)
Education of Spouse	
Illiterate	3 (1.4)
Matric	12 (5.6)
Graduation	30 (14.0)
Masters	73 (34.1)
Higher	96 (46.9)
Working Status of Spouse	
Working	95 (44.4)
Non-Working	119 (55.6)
Working Hours in a Week	
Less than10 Hours	6 (2.8)
10-20 Hours	22 (10.3)
21-30 Hours	55 (27.6)
More than 30 Hours	127 (59.3)
No. of Patients in a Month	
Less than 100	37 (17.3)
100-500	87 (40.7)
More than 500	90 (42.1)
Job Sector of Respondents	
Public	124 (58)
Private	90 (42)
Work Experience	
Less than 1 Year	22 (10.3)
1-5 Years	84 (39.3)
6-10 Years	43 (20.1)
More than 10 Years	65 (30.4)

The mean and standard deviation of the computed score for psychological well-being. These results revealed that overall depression, anxiety, and stress levels among respondents are normal to mild (Table 3).

Table 3: Mean and Standard Deviation of Psychological Well-Being of the Doctors

Variables	Range	Mean ± SD
Overall Psychological Well-Being of the Doctors	55	13.81 ± 10.19
Depression Among Doctors	16	7.02 ± 3.37
Anxiety Among Doctors	17	7.74 ± 3.31
Stress Among Doctors	25	11.92 ± 4.10

Self-rated health of respondents was reported as very good by the majority (Figure 2).

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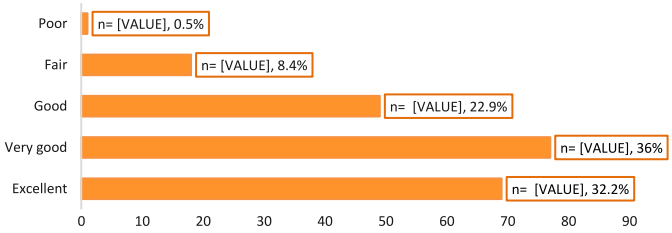

Figure 2: Self-rated Health of the Doctors

A comparison of public and private hospitals showed that there is no significant difference between doctors working in public and private sectors (Table 4).

Table 4: Comparison of Psychological Well-Being of Doctors in Public and Private Sectors

Sector of Job	n	Mean ± SD	t-test (df)	p-value
Public	124	14.55 ± 10.07	1.16 (212)	0.245
Private	90	12.90 ± 10.33		

DISCUSSION

In the present study, the psychological well-being of doctors working at public and private hospitals was assessed. The study was carried out in hospitals in Gilgit Baltistan, Pakistan. A valid questionnaire was used to collect data from doctors. The study tool was adapted from a previous study, which was a 21-item Depression, Anxiety, Stress Scale (DASS-21). The main objective of the study was to assess the psychological well-being of doctors working in public and private hospitals. In the current study, different sociodemographic characteristics and psychological well-being of doctors were tested. It was found that the mean score of depression among the study population was (7.02 ± 3.37). Similarly, anxiety levels were reported to be (7.74 ± 3.31) among the study population. Stress levels were also reported to be (11.92 ± 4.10). These findings are somehow consistent with the previous studies. A study that was conducted in India in 2020 found that a moderate level of stress was reported among doctors during the COVID-10 lockdown [16]. Similarly, some other studies also indicate that the stress level of healthcare workers is reported in a moderate range [17, 18]. The mean score of overall psychological well-being among the study population was (13.81 ± 10.19) on a scale ranging between 0-55. This shows that the current study population experienced an overall good psychological well-being. In the present study, mild and moderate level of stress, depression, and anxiety was testified. As the current study was conducted in remote areas of Pakistan, the burden of disease and also the burden on the healthcare system is low and people follow a healthy lifestyle. Due to all these reasons, the workload on healthcare workers is very low and overall, they have good mental health. It was also observed that the psychological well-being of doctors who worked in public and private hospitals, there was no statistically significant difference between their mean scores ($p < 0.050$) but the mean score of psychological well-being of the doctors who were working in public hospitals was reported more (14.55 ± 10.07) as compared to the doctors who are working in private hospitals (12.90 ± 10.33). The current study results did not follow the previous study. A study that was conducted in Ethiopia in 2022 found that healthcare workers have more stress work who are working in the public sector as compared to the private sector [19]. Furthermore, a study conducted in Punjab, Pakistan found that healthcare workers working in the public sector reported comparatively less stress and anxiety than those working in the private sector [20]. The possible reason for this could be that the workload on doctors is maximum in public hospitals as compared to private hospitals. Due to this reason, the psychological well-being of doctors is more chances to be affected.

CONCLUSIONS

Doctors and other healthcare providers work simultaneously for the well-being of the community and strive to provide a disease-free society with a healthy lifestyle. The results of the current study found that doctors working at public and private hospitals in Gilgit Baltistan presented mild symptoms of depression, anxiety, and stress.

Authors Contribution

Conceptualization: NUS, ABK
Methodology: NUS, ABK, YK, SB
Formal analysis: NUS, ABK, SJ
Writing-review and editing: NUS, SAK

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of Bimatoprost and Timolol for Treatment of Chronic Angle Closure Glaucoma

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ABSTRACT

Angle-closure glaucoma occurs when the normal drainage of fluid within the eye, specifically the aqueous humor, is obstructed or restricted. **Objective:** To assess and compare bimatoprost 0.03% administered once daily versus timolol 0.5% administered twice daily in patients diagnosed with chronic angle closure glaucoma (CACG). **Methods:** This randomized controlled study was performed at the Department of Ophthalmology, Bahawalpur Victoria Hospital, Bahawalpur, Pakistan, from August 2023 to January 2024. Patients of either gender, aged 18 years or older, and diagnosed with unilateral or bilateral CACG were included. Patients were randomly allocated to either Bimatoprost 0.03% (once daily at night) or Timolol malete 0.5% (two times morning and night daily) adopting a lottery method. Patients were asked to visit after one and 3 months (final outcome) and intraocular pressure (IOP) measurements were taken between 8 to 10 am using an applanation tonometer. **Results:** A total of 110 patients of which 64 (58.2%) were female. The mean age was 58.9 ± 10.5 years. At baseline, the mean intraocular pressure was calculated to be 24.2 ± 5.7 mmHg. After 1-month (18.7 ± 4.2 mmHg vs. 20.5 ± 4.7 mmHg, p=0.0418) and 3-months of treatment (16.8±4.6 mmHg vs. 19.6 ± 4.3 mmHg, p=0.0030), the mean IOP were significantly less in Bimatoprost group when compared to Timolol group. The commonest adverse events were conjunctival hyperaemia, and pruritus reported by 19 (17.3%), and 9 (8.2%) patients respectively. **Conclusions:** Bimatoprost exhibited a significantly better reduction in IOP compared to timolol in chronic angle closure glaucoma. Both drugs showed relatively good safety and tolerability profiles.

INTRODUCTION

The prevalence of angle closure glaucoma is an important ocular disorder with an estimated prevalence of 0.6% in the general population [1]. Data from Asia shows the prevalence of angle-closure glaucoma ranging between 0.6 to 1.9% [2-4]. Angle-closure glaucoma occurs when the normal drainage of fluid within the eye, specifically the aqueous humor, is obstructed or restricted. This blockage can damage the trabecular meshwork, a crucial part of the eye's drainage system, causing an increase in intraocular pressure (IOP) [5]. This elevated pressure can result in damage to the optic nerve, a condition known as glaucomatous optic neuropathy. The contact between the iris and the trabecular meshwork can gradually close off the drainage angle, often leading to the formation of adhesions between the iris and the trabecular meshwork, known as peripheral anterior synechiae [6]. This closure can further impede the outflow of aqueous humor, exacerbating the rise in intraocular pressure. When angle-closure glaucoma progresses to cause damage to the optic nerve, it is termed chronic angle-closure glaucoma (CACG). CACG can lead to permanent vision loss if not treated, making early detection and appropriate management crucial in preserving vision and preventing further damage to the optic nerve [7]. CACG is primarily treated with laser

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iridotomy at present, which alleviates pupillary blockage and hinders synechial closure [8]. Presently, the primary CACG treatment involves laser iridotomy to alleviate pupillary blockage and hinder synechial closure, along with pharmaceutical measures that lower IOP [9]. Combining laser with drug therapy does not consistently achieve success in treating CACG among Asian patients, with a majority eventually requiring additional surgery to alleviate the condition [10]. Literature shows latanoprost (a prostaglandin analog) to have a lesser incidence of systemic adverse events and greater efficacy in CACG patients to lower IOP compared to timolol alone or in combination with dorzolamide [11]. Bimatoprost (synthetic prostamide analog) enhances the aqueous humor drainage through the trabecular meshwork and uveoscleral route. The effectiveness and tolerance of bimatoprost has been evident in the past [12]. There is a dearth of information regarding the most suitable interventions for treating CACG, especially in Pakistan. The current study consisted of patients diagnosed with CACG and spanned over a treatment and evaluation period of three months.

The study aimed to assess and compare bimatoprost 0.03% administered once daily versus timolol 0.5% administered twice daily in patients diagnosed with chronic angle closure glaucoma.

METHODS

This randomized controlled study was carried out at the Department of Ophthalmology, Bahawalpur Victoria Hospital, Bahawalpur, Pakistan from August 2023 to January 2024, with prior approval from the "Institutional Ethical Committee" (2351/DME/QAMC Bahawalpur). The inclusion criteria was patients of either gender, aged 18 years or older, exhibiting good overall health, and diagnosed with unilateral or bilateral CACG confirmed via indentation gonioscopy. Additionally, patients requiring iridotomy or iridectomy performed in the last 3 months were excluded. The exclusion criteria was patients with other uncontrolled systemic or ocular diseases, substantial ocular discomfort, confirmed sensitivities to research medications or ingredients in formulations, expected alterations to current therapies affecting IOP, or chronic use of non-study ocular medications. Those with corneal abnormalities hindering accurate IOP measurement or recent ocular surgeries or procedures within the prior three months were not included. Patients with specific heart rate or blood pressure concerns based on age or for whom beta-blockers were contraindicated, pregnant or lactating female, or women of reproductive age using unreliable birth control methods were also not included. Open-EPI was used to calculate the sample size and prior informed consent was taken, CACG was diagnosed as damage to the optic nerve indicating glaucoma, along with visual field issues or reduced vision, and at least 180° of synechial angle closure observed during dynamic gonioscopy [13]. At the time of enrollment, gender, age, and residential area were noted in all patients. Patients were randomly allocated (55 patients in each group) to either Bimatoprost 0.03% (once daily at night) or Timolol maleate 0.5% (two times [morning and night] daily) adopting the lottery method. Patients underwent a suitable washout period before initiating treatment at the baseline visit. For topical beta-blockers or prostaglandins, the washout period was 4-weeks; for alpha-agonists or sympathomimetics, it was 2-weeks; and for carbonic anhydrase inhibitors or parasympathomimetics, it was 4-days. The administration of study medications involved the self-instillation of one drop for every eye between 7-9 am and 7-9 pm (in cases using Timolol). During subsequent study visits, the study medications were administered in the morning by investigators immediately following the measurement of IOP and the examination of the patient's eyes. Throughout the study, data from the eye exhibiting the most severe condition was utilized. Patients were asked to visit after one and 3 months (final outcome) and IOP measurements were taken between 8 to 10 am using an applanation tonometer. Treatment-related adverse events were also noted during the course of the study. Patients missing follow-up visits were left out of the subsequent analysis plans. Data analysis was done utilizing "IBM-SPSS Statistics" version 26.0. The qualitative data were shown as frequency and percentages and a chi-square test was used for the comparisons. Means and standard deviation were calculated to demonstrate the quantitative variables, while comparisons were made employing an independent sample t-test. A $p < 0.05$ was considered standard for significance.

RESULTS

In a total of 110 patients, 64 (58.2%) were female. The mean age was 58.9 ± 10.5 years, ranging between 35 to 85 years. Residential status was rural in 72 (65.5%) patients. Diabetes mellitus was noted in 25 (22.7%) patients. At baseline, the mean IOP was calculated to be 24.2 ± 5.7 mmHg (Table 1).

Table 1: Comparison of Baseline Characteristics (n=110)

Characteristics		Groups		p-Value
		Bimatoprost (n=55)	Timolol (n=55)	
Gender	Male	24 (43.6%)	22 (40.0%)	0.699
	Female	31 (56.4%)	33 (60.0%)	
Age in Years, (Mean ± SD)		58.4 ± 11.4	59.6 ± 9.2	0.545
Residence	Rural	35 (63.6%)	37 (67.3%)	0.688
	Urban	20 (36.4%)	18 (32.7%)	
Diabetes Mellitus		11 (20.0%)	14 (25.5%)	0.495
Intraocular Pressure		23.8 ± 6.2	24.6 ± 5.5	0.475

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At the 1-month follow-up, 2 patients in the Bimatoprost group and 4 patients in Timolol group did not appear for follow-up evaluation. After 3 months of treatment, 7 patients in Timolol group and 9 patients in Bimatoprost group left the final evaluation so these patients were excluded from the final analysis. After 1-month (18.7 ± 4.2 mmHg vs. 20.5 ± 4.7 mmHg, p = 0.0418) and 3-months treatment (16.8 ± 4.6 mmHg vs. 19.6 ± 4.3 mmHg, p = 0.0030), the mean IOP were significantly less in Bimatoprost group when compared to Timolol group (Table 2).

Table 2: Comparison of Mean IOP (mmHg) at Different Study Intervals in Both Study Groups

Group	IOP (mmHg) at Different Study Intervals		
	Baseline (n=110)	After 1-Month (n=104)	After 3-Months (n=94)
Bimatoprost (Mean ± SD)	23.8 ± 6.2	18.7 ± 4.2	16.8 ± 4.6
Timolol (Mean ± SD)	24.6 ± 5.5	20.5 ± 4.7	19.6 ± 4.3
p-Value	0.4756	0.0418	0.0030

The commonest adverse events were conjunctival hyperaemia, and pruritus reported by 19 (17.3%), and 9 (8.2%) patients respectively. Pruritus was significantly more common among Bimatoprost group patients (14.5% vs. 1.8%, p=0.0149). Comparison of most common adverse events during the course of study among patients of both study groups (Table 3).

Table 3: Frequency of Adverse Events among study participants

Adverse Events	Bimatoprost	Timolol	p-Value
Conjunctival Hyperaemia	12 (21.8%)	7 (12.7%)	0.2073
Pruritus	8 (14.5%)	1 (1.8%)	0.0149
Conjunctival Congestion	4 (7.3%)	-	0.0416
Eye Irritation	3 (5.5%)	3 (5.5%)	1
Eyelash Growth	3 (5.5%)	-	0.0791
Punctate Keratitis	-	3 (5.5%)	0.0791
Headache	2 (3.6%)	1 (1.8%)	0.5583

DISCUSSION

This study unveiled novel insights into bimatoprost effectiveness, safety, and tolerability among CACG patients. Bimatoprost was well-tolerated and showcased superior efficacy compared to timolol in reducing IOP and ensuring diurnal IOP control. Our findings stand aligned with Pongpun PR *et al* from Thailand where the researcher noted that the bimatoprost group showed a significantly higher mean reduction in IOP in comparison to timolol after 2 weeks (31% vs 19%; $p < 0.05$), 6-weeks (30% vs. 19%; $p < 0.001$), and 12-weeks (28% vs 18%, $p < 0.001$) [14]. Till now, the majority of research on bimatoprost's efficacy and tolerability has primarily involved open-angle glaucoma patients [15, 16]. A study by Agarwal *et al.*, analyzing CACG patients from India revealed that bimatoprost was demonstrated to reduce IOP by 31% in those patients who were previously taking timolol [17]. Chen *et al.*, reported both Bimatoprost and Timolol to impart significant reduction among CACG patients following iridotomy [15]. Chew *et al.*, reported similar findings to us when they documented one daily Bimatoprost to reduce IOP significantly greater than twice a day Timolol [18]. Higginbotham from UK noted Bimatoprost taken once a day offered a continuous reduction in IOP that surpassed the effects of both timolol and bimatoprost taken twice a day. Additionally, Bimatoprost helped more patients achieve the desired low IOP targets [19]. Collectively, these findings emphasize the excellent efficacy of synthetic prostaglandins Bimatoprost over timolol in reducing IOP among CACG patients. While these results reflect mean responses from patient groups and not the individual range of responses, the consistent and significantly greater reductions in IOP observed throughout the day with bimatoprost are noteworthy. The outcomes of this study offer reassurance to clinicians regarding the effectiveness of bimatoprost as a viable therapy for CACG, positioning it as a credible alternative to timolol. Bimatoprost's distinct mechanisms in reducing IOP make it a promising option for individuals who might not respond favorably to other synthetic prostaglandin analogues. These results also echo similar conclusions drawn from trials predominantly involving Caucasian patients with open-angle glaucoma [11]. The positive safety and tolerability records noted in Asian patients with CACG using both bimatoprost and timolol align with earlier research findings, and support bimatoprost's efficacy in diverse populations [14, 17]. This study showed that both bimatoprost and timolol had good tolerability, with reports of minimal systemic side effects, the majority being mild. There have been reports of withdrawal from the timolol treatment due to symptoms like breathlessness and bronchospasm and these observations underscore the possibility of respiratory side effects linked to timolol use, especially among patients with undetected respiratory conditions but this needs further research [14]. This emphasizes the importance of assessing respiratory function in patients, especially the elderly, undergoing topical timolol treatment [20]. In our study, localized adverse effects were slightly more frequent among patients on bimatoprost than in timolol-receiving patients. Despite the higher occurrence of local adverse effects with bimatoprost, the benefits of achieving a reduction in IOP to a greater extent may outweigh most of these local adverse events that may arise.

CONCLUSIONS

Bimatoprost exhibited a significantly better reduction in IOP compared to timolol in chronic angle closure glaucoma. Both drugs showed relatively good safety and tolerability profiles.

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Authors Contribution

Conceptualization: ZA, SF, MK
Methodology: ZA, NN, SAM, MJK
Formal analysis: ZA, NN, MK, SAM, MJK
Writing-review and editing: SF, MK, SAM, MJK

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

Conflicts of Interest

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Original Article

Changes in Liver Function and Lipid Profile during Underactive Thyroid Phase in Patients after Subtotal Thyroidectomy

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ABSTRACT

Underactive Thyroid Phase or Hypothyroidism is a very common biochemical complication after sub-total thyroidectomy. **Objectives:** To investigate lipid profile and liver function in patients who developed hypothyroidism following sub-total thyroidectomy. **Methods:** Total 100 individuals were selected for present study and divided them into two different groups i.e. Group-A in which 37 healthy individuals were placed whereas in Group-B 63 individuals were adopted surgical process, sub-total thyroidectomy. The study was conducted in Surgical and Medical Units of Ghurki Trust & Teaching Hospital, Lahore from December 2023 to April 2024. Thyroid-stimulating hormone (TSH) levels were extremely high in individuals in the hypothyroid stage. **Results:** The comparative findings of this study showed a significant ($p < 0.05$) change in cholesterol, triglyceride, LDL and HDL blood serum levels of Group-B individuals as compared to the Group-B. While a significant ($p < 0.05$) amplification in enzymes of liver such as aspartate aminotransferase (AST), alanine transaminase (ALT), and decrease in alkaline phosphatase (ALP) in Group-B subjects were seen as compared to normal individuals. **Conclusions:** Sub-total thyroidectomy is associated with hypothyroidism, which correlates with disruptions in liver enzyme activity and lipid metabolism, potentially leading to secondary hyperlipidemia and liver dysfunction.

INTRODUCTION

The mode of action of thyroid hormone is to control the number of biochemical and physiological functions in biological system such as lipid metabolism, growth and liver functions. Hypothyroidism is the prevailing chronic outcome after complete thyroidectomy [1]. Thyroid hormone is crucial for the proper growth of various human tissues and controls the metabolic processes of almost all cells and organs in the human body throughout one's lifetime [2]. Hypothyroidism, a prevalent illness characterized by a shortage of thyroid hormones, is a frequently occurring ailment among the general population. Primary hypothyroidism is a prevalent condition globally, mostly caused by iodine deficiency and Hashimoto thyroiditis [3]. The liver is involved in the conjugation, excretion, peripheral deiodination, and metabolism of thyroid hormones, which plays a significant role in the production of globulin that binds thyroxine. Previous investigations have demonstrated some anomalies in circulating hormone concentrations, despite the fact that nearly all patients with liver disease are clinically thyroid [4]. The thyroid gland and liver have a complicated interaction in both health and illness. Through

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the selenium deiodinase enzyme system, the liver contributes to the activation and inactivation of thyroid hormones. It also produces transport proteins such albumin, transthyretin, and thyroxine-binding globulin, which helps to increase the absorption of thyroid hormones [5]. Different researchers described after the findings of their studies that blood serum cholesterol, triglycerides, low density lipoproteins and high-density lipoproteins levels have correlation with thyroidectomy. During biosynthesis of cholesterol the step 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity in the liver stimulated by Thyroid hormone [6]. Although blood total cholesterol and low-density lipoprotein cholesterol (LDL-C) concentrations drop due to improved LDL-C metabolism, cholesterol production rises in hyperthyroidism. Atherosclerosis resembles a plaque that has accumulated calcium, fat, cholesterol, and other compounds. As a result, while cholesterol production is elevated in hyperthyroidism, increased LDL metabolism causes a decrease in blood total cholesterol and LDL-C levels[7, 8]. This study is very important as it uniquely contributes to the existing scientific literature by being one of the first to systematically analyze the biochemical changes in the liver function and lipid metabolism in patients with hypothyroidism following subtotal thyroidectomy [9,10]. Whereas Previous studies have focused on general thyroid dysfunction, but this research uncovers specific outcomes of a commonly performed surgical procedure, hence providing valuable insights into the management and long-term care of these patients.

The present study aimed to uncover Biochemical and Physiological changes those leads to deficiency of thyroid hormones secretion, current research provided health awareness about low quantity secretion of thyroid hormones. Therefore, sub-total thyroidectomy, a common surgical procedure for managing thyroid disorders, often leads to hypothyroidism, affecting liver function and lipid metabolism. This study investigates these biochemical and physiological changes.

METHODS

The present comparative cross-sectional study was conducted in Surgical and Medical Units of Ghurki Trust & Teaching Hospital, Lahore from December 2023 to April 2024. Ethical Approval Certificate (ERC) (Ref no. ERC/2023/28B) was taken from Ethical Review Board of Lahore University of Biological & Applied Sciences (Lahore-UBAS) a project of Lahore Medical & Dental College Lahore, Pakistan. All patients provided informed consent form prior to their participation in the study, open EPI software was used for sample size calculation. Regarding inclusive criteria all participants were in between 18-60 years and only those patients were selected who adopted the procedure of sub-total thyroidectomy. To examine acute or subacute phase changes, patient inclusion criteria was restricted to individuals who underwent surgery within a specified timeframe prior to the study, such as within the last six months. Those who have a medical history of thyroid disorders other than Hashimoto's thyroiditis, Graves' disease, or thyroid malignancy are excluded from the study. Due to the potential hazards associated with study procedures and the variable effects of pregnancy on thyroid function, pregnant women are frequently excluded. The study used a purposive sampling technique for the selection of participants. The study was conducted from December 2023 to April 2024. During this period, all patients who underwent sub-total thyroidectomy and met the inclusion and exclusion criteria were enrolled in the study. Group-A in which 37 healthy individuals were placed whereas in Group-B 63 individuals were adopted surgical process, sub-total thyroidectomy. Auto-analyzer was used for the biochemical tests of blood serum cholesterol, triglycerides , LDL, HDL and liver enzymes such as ALT, AST and ALP levels measurements. While independent t-test was applied to compare biochemical biomarkers between the groups. Raw data were analyzed by SPSS version 27.0. For continuous variables, the mean and standard deviation were calculated. While continuous variables such as age, BMI, triglycerides, cholesterol, LDL, HDL, ALT, AST, and ALP blood serum levels were compared between Group A and Group B by applying independent t-tests. To compare categorical variables, including gender, age and BMI between the two groups, chi-square tests were applied whereas ($p \leq 0.05$) value considered as statistical significance.

RESULTS

A significant ($P<0.05$) changes in cholesterol, triglycerides, Low density lipoprotein, high density lipoprotein blood serum levels in Group-B individuals were seen as compared with individuals of Group-A. While a significant ($P<0.05$) increase of blood serum alanine transaminase, aspartate aminotransferase and decrease in alkaline phosphatase levels were concluded in Group-B as compared with Group-A participants. Mean standard Deviation and chi-square tests were applied and P- Value as ($p\leq0.05$) was considered for the considering Criteria of significance (Table 1).

Table 1: Characteristics of Group-A and Group-B Individuals

Parameter	Group-A (n=37)	Group-B (n=63)	Statistical Test	P-value
Age (Years, Mean ± SD)	52.04 ± 4.02	53.01 ± 4.01	Independent t-test	0.01
Gender	-	-	Chi-square test	0.01
Male (n, %)	19 (51.4%)	35 (55.6%)	-	0.01
Female (n, %)	18 (48.6%)	28 (44.4%)	-	0.02
BMI (kg/m^2, Mean ± SD)	19.11 ± 1.01	30.05 ± 1.01	Independent t-test	0.01

(Continuous Variables (Age, BMI) Independent t-test was applied and Mean and Standard deviation was used between group A and B, Categorical variable (Gender) chi-square test was applied, $p\leq0.05$)

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Blood serum cholesterol, Low density lipoprotein, triglycerides, high density lipoprotein, aspartate aminotransferase, alanine transaminase, aspartate aminotransferase and alkaline phosphatase levels of Group-B (298.10 ± 23.1, 219.01 ± 21.3, 167.4 ± 7.2, 37.04 ± 1.03, 25.10 ± 3.01, 35.12 ± 1.04, 105.10 ± 2.04) showed a significant (P≤0.05) change than Group-A. Further comparative description of Group-A and Group-B were elaborated by applying independent t-test for response of two groups and test findings were significant (P≤0.05). Blood serum cholesterol, triglycerides, Low density lipoprotein, high density lipoprotein of Group-B presented a significant (P≤0.05) increase and alkaline phosphatase levels indicated significant (P≤0.05) decreased as compared than Group-A respectively. P-value, independent t-test with mean standard deviation were applied for the Comparative description of data separately (Table 2)

Table 2. Differences in lipid profile and liver enzymes of Group-A and Group-B Individual

Parameter	Units	Group-A (n=37)	Group-B (n=63)	T-Test	P-value (P≤0.05)
Serum Cholesterol levels	mg/dl	220.2 ± 12.2	298.10 ± 23.1	0.05	0.01
Serum triglycerides levels	mg/dl	149.02 ± 15.5	219.01 ± 21.3	0.04	0.02
Serum LDL	mg/dl	139.2 ± 8.6	167.4 ± 7.2	0.014	0.01
Serum HLD	mg/dl	43.19 ± 1.06	37.04 ± 1.03	0.03	0.02
Serum ALT	IU/L	16.12 ± 2.04	25.10 ± 3.01	0.017	0.05
Serum AST	IU/L	22.11 ± 1.01	35.12 ± 1.04	0.013	0.03
Serum ALP	U/L	132.01 ± 2.03	105.10 ± 2.04	0.021	0.04

DISCUSSION

Ming J *et al.*, in their study claimed that Sub-Total thyroidectomy is a major type of thyroidectomy before complete thyroidectomy, which can lead to significant morbidity and increased costs. Previous research has connected secondary dyslipidemia to thyroid problems, and acute hypothyroidism following thyroid surgery might negatively impact lipid profile and endothelial function [11, 12]. An analysis of sixteen observational studies revealed that clients with subclinical hypothyroidism had significantly higher levels of total cholesterol, Low density lipoprotein, and triglycerides compared to those with euthyroidism. This suggests a link between hypothyroidism and higher lipid profile. Even in those with clinically normal thyroid function, little variations in TSH levels can elevate fat findings and raise the risk of hyper-Cholesterolemia [13]. The only traditional serum lipid confounding factors taken into account in these studies were BMI, gender, and age. Hypothyroid individuals have significantly higher blood lipid levels compared to healthy controls. Subclinical hypothyroidism can lead to higher TC and LDL-C levels, as well as higher TG and lower HDL-C levels, according to certain research [14]. In line with earlier research, TSH levels and total and low-density lipoprotein cholesterol levels were shown to be strongly positively correlated in the current investigation. The data of different studies indicate that even within the normal range, blood thyroid hormone levels significantly impact serum lipid levels [15]. Thyroid hormones may significantly impact the connection between lipid indicators and TSH. It's important to evaluate the influence of TSH on lipid profiles, independent of thyroid hormone level. Without taking these parameters into account, the correlation between TSH and lipid profile is questionable [16, 17]. Increased levels of ALT or AST activity in the serum were more common in patients with TSH ≤ 0.2 IU/l. These results were mostly unchanged when age, gender, fasting hyperglycemia, and lipid characteristics were taken into account. TSH influences TC levels by means of thyroid hormones, both directly and indirectly [18, 19]. The finding of present research have similarities with the findings of previous studies by different researchers [20]. Research found considerably lower blood alkaline phosphatase levels (P<0.001) in hypothyroid individuals compared to controls. The current study found a decrease in serum ALP levels in hypothyroid patients, which is consistent with previous findings by other researchers [21].

CONCLUSIONS

The results of the current study suggest that sub-total thyroidectomy is associated with the development of hypothyroidism in most patients of Group B, which in turn correlates with altered liver enzyme activity and lipid metabolism. Patients who underwent sub-total thyroidectomy exhibited higher serum cholesterol, triglycerides, LDL, liver enzymes (ALT and AST), and lower HDL and ALP levels. These biochemical alterations suggest a potential link between sub-total thyroidectomy and secondary hyperlipidemia and possible hepatotoxicity in hypothyroid patients.

Authors Contribution

Conceptualization: MNS, AI
Methodology: ZH, SUSZ,
Formal analysis: MU, MSA
Writing, review and editing: ABW, MSA, MU

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

Conflicts of Interest

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Original Article

Assessment of Immunomarker Profiling in Bone Marrow Trephine Biopsy (BMTB) for Lymphoma Diagnosis

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ABSTRACT

Lymphomas are characterized by clonal abnormality of the lymphatic system resulting in malignant neoplasms, classified into Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL). The immunophenotyping and genetic features of the lymphomas play a major role in its classification. **Objective**: To determine the immunohistochemical profiles for multiple types of Lymphoma by using the primary (CD30, CD20, CD3) and secondary (CD15, CD5, CD10, Ki67, BCL6,) panel of immunomarker. **Methods:** This cross-sectional study was done over a period of 1 year from 1st January 2023 to 31st December 2023. A consecutive sampling technique was used. Bone marrow aspiration, and trephine biopsy samples were taken from each patient. Immunohistochemical (IHC) profiling was done on Trephine biopsy to diagnose Lymphomas. **Results:** Out of 57 lymphoma cases, 41 were male and 16 were female patients. The most affected age group was 45-60 years. Among total cases, 43 (75.4%) were of NHL while only 14 (24.6%) cases were of HL. Among 43 cases of NHL, 38 (88.4%) were found of B-cell type while only 5 (11.6%) were of T-cell origin. CD30 (85.7%) was the most expressed immunomarker in HL while CD20 (92%), CD3 (60%), CD5 (47%), and Ki67 showed the highest positivity rate in NHL. IHC was found to be significant by statistical analysis (p-value < 0.05). **Conclusions:** In addition to morphological findings, another crucial step in lymphoma diagnosis is the selection of relevant immunomarkers after clinicopathological correlation with the patient. Therefore, based on our experience, we suggest the use of a limited, cost-effective immunomarker panel for optimal diagnosis of lymphomas and subtypes.

INTRODUCTION

Lymphomas are characterized by the clonal abnormality of the lymphatic system in which the architecture of lymph nodes may be destroyed because of metastasis or due to malignant neoplasia which initiates in the lymph nodes itself [1, 2]. From a hematopathological point of view, malignant lymphomas are defined as the presence of a homogenous population of neoplastic cells as well as a tumor growth pattern which may be either a nodular or follicular pattern or it could be a diffuse pattern of infiltration [3]. From an immunological perspective, lymphomas are expanded clonal proliferation of lymphocytes or B or T cell types of lymphocytic series. Generally, lymphoid tissue-associated malignant neoplasms are classified into two main classes including Hodgkin lymphoma and Non-Hodgkin lymphoma [4]. The distinguishing feature of Hodgkin lymphoma from other lymphomas lies in their exceptional cellular composition including atypical large neoplastic cells mainly Reed-Sternberg and Hodgkin (HRS) cells along with their variants and nonneoplastic reactive cells. According to classification by the World Health Organization (WHO 2016), four different histological variants including nodular sclerosis, lymphocyte depleted, lymphocyte rich, and mixed cellularity were proposed for classical Hodgkin's lymphoma [5]. The immunophenotyping and genetic features of the lymphomas play a major role in its classification. The most common markers useful for the confirmation of classical Hodgkin lymphoma included

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CD30+, CD45+, and CD15+ [6]. On the other hand, non-Hodgkin lymphomas represent various categories of lymphoid malignancies linked with multiple causes. It is estimated that NHL accounted for 5.1% of entire malignant neoplasms and 2.7% of cancer-related fatalities [7]. The origin of NHL may be either B or T cell types. According to WHO 2016 classification, NHL comprises usual and usual subtypes including CLL/SLL (small lymphocytic lymphoma, mantle cell lymphoma (MCL) MALT lymphoma, and follicular lymphoma (FL). Other categories include Diffuse Large B cell lymphoma (DLBCL) and Burkitt lymphoma (BL) [8]. The literature revealed that the distribution of the subtypes of lymphomas varies geographically either within or between the countries. Another study reported a lower frequency of mantle cell lymphoma and follicular lymphoma in Asian countries as compared to the Western population [9]. It was also reported that in the Indian population, the most common subtypes of B-cell NHL were found to be DLBCL [10]. It was also found that the cases of lymphomas associated with Natural killer cells or peripheral T cells were more prevalent in Western countries as compared to Asian countries [11]. Immunophenotyping by immunohistochemistry plays an important role in the diagnosis of the disease along with two other important tools like genetic profiling and morphological examination. The most common markers used for the differentiation of B and T cell lymphomas include CD3, CD30, and CD45 [12]. Lymphoma is included in the top five most prevalent cancers in Pakistan and the disease burden is high with huge financial implications in an under-resource country like ours.

This study aimed to determine the immunohistochemical profiles of multiple types of lymphomas by using different immunomarkers in the patients who visited tertiary care hospital. As a secondary objective, the current study also analyzed the minimum low-cost essential immunomarkers required to reach an appropriate diagnosis of lymphoma with their types and subtypes.

METHODS

The study was conducted at the Department of Pathology, King Edward Medical University/Mayo Hospital Lahore over the study period of 1 year from 1st January to 31st December 2023. Ethical approval (No.329/RC/KEMU) was taken from the Institutional Review Board. It was a cross-sectional study design and samples were collected through consecutive sampling techniques. The sample size was calculated with win-pepi ver: 11.15 to estimate a proportion with confidence level of 95%, acceptable difference = 0.105, and assumed proportion = 0.785 (B-NHL formed 78.5%) [30]. Total 72 samples which fulfilled the inclusion criteria were selected in the study period. Written, informed consent was taken from each of the study participants. Demographic data like age and gender were recorded from all the included cases. Bone marrow aspiration and trephine biopsy were taken from each patient according to the standard PGMIER protocol of bone marrow sample collection [13]. For the processing of bone marrow aspirate, air dried smear slide was stained with May-Grunwald Giemsa stain after fixation. For processing of bone marrow trephine biopsy, formalin-fixed tissue was embedded in paraffin wax, thin sections were cut through microtomy and after de-paraffinization, slides were prepared for hematoxylin and eosin staining procedure for morphological examination were observed by expert Pathologists under light microscope Olympus CX43 five head Microscope using 10x, 20x, 40x and 100x magnification to visualize the lymphoma infiltration pattern of bone marrow. For immunohistochemistry, avidin-biotin peroxidase complex method was used after microwaving was performed for antigen retrieval and washing in TRIS buffer. Different panels of immunohistochemistry markers were selected according to morphological diagnosis. These include CD20, CD23, CD5, BCL6, Ki67, CYCLIN D1, CD25, CD3, CD30, CD79a, CD45, CD10, CD15. Mouse monoclonal antibodies (BioGenex) were used for the binding of these antigens. Lymphomas were identified and categorized according to the infiltration pattern and immunomarkers chosen. For Hodgkin lymphoma: CD30, CD15. For Non-Hodgkin B cell lymphoma: CD20, CD23, CD19 Cyclin D1, Ki67 and BCL6. For Non-Hodgkin T cell lymphoma: CD5, CD30, CD3, CD10, TDT. Interpretation of all cases was done by experienced Pathologists. Results were analyzed using SPSS 28. Percentages and frequencies were calculated for the demographic data, clinical presentation of the patients, and bone marrow infiltration patterns. The chi-square test was used to evaluate qualitative data and validity parameters were calculated.

RESULTS

A total of 72 patients with clinical suspicion of lymphoma were enrolled, out of which 57 cases were diagnosed as lymphomas. Among Lymphoma patients, 41(71.9%) were male while 16 (28.1%) were female. Age distribution showed that the maximum patients were in the age group of 45 to 60 years (44%) followed by the patients from the age group of more than 60 years of age (21%) (Figure 1).

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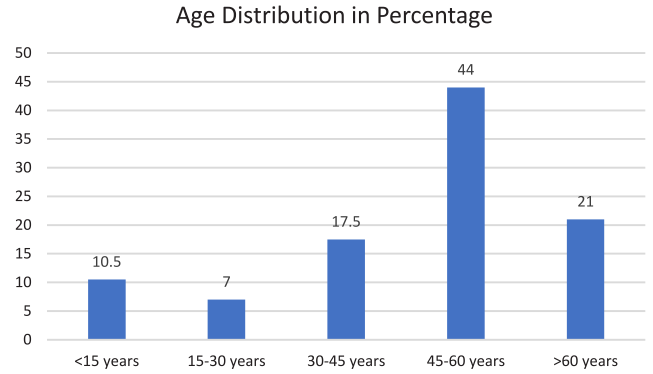

Figure 1: Age Distribution of Lymphoma Cases

CBC findings of the selected cases showed that all the patients were suffering from the cytopenia of cell lines. Maximum patients showed the picture of anemia (31.6%), followed by Bicytopenia (26.3%) and Pancytopenia (22.8%) (Figure 2).

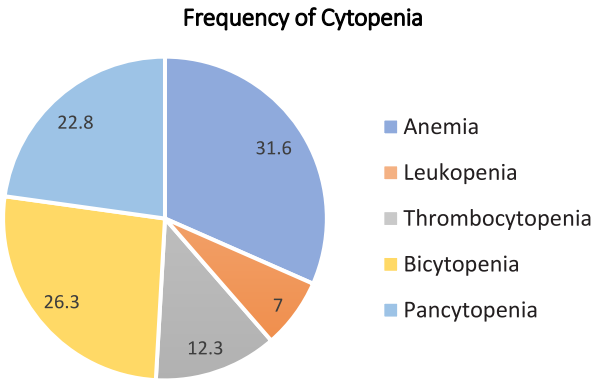

Figure 2: Frequency of the Patients Represented with Different Types of Cytopenia

Clinically, all the patients were affected by organomegaly amongst which maximum patients showed hepatosplenomegaly at 43.9% (n=25), followed by lymph node enlargement at 26.3% (n=15), Splenomegaly at 19.3% (n=11) and 10.5% cases (n=6) showed hepatomegaly. Out of a total 72 enrolled patients with clinical suspicion of Lymphoma, 15 cases were of normal morphology and were thus labeled as Controls. Out of the remaining 57 cases of lymphomas, 43 (75.4%) cases were of Non-Hodgkin Lymphomas (NHL) while only 14 (24.6%) cases were of Hodgkin Lymphomas (HL). Among 43 cases of Non-Hodgkin Lymphomas, 38 (88.4%) were found of B-cell type while only 5 (11.6%) were of T-cell origin. Bone marrow infiltration pattern of the lymphoma cases (Figure 3).

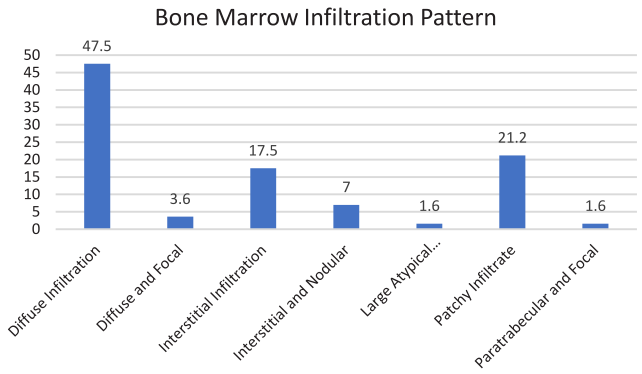

Figure 3: Percentage of Various Bone Marrow Infiltration Patterns in Lymphoma Cases

Immunophenotyping showed CD30 was found to be a more efficient marker for the identification and confirmation of Hodgkin lymphoma. 12 cases (85.7%) out of the 14 total cases of Hodgkin lymphoma were found to be positive for CD30. In the case of non-Hodgkin lymphoma, CD20 was the most efficient marker for the identification of B-cell non-Hodgkin lymphoma while in the case of T-cell CD3 was found to be positive in 3 cases (60%) out of 5 cases. Further categorization of both the T-cell and B-cell non-Hodgkin lymphomas showed their subtypes. A minimum panel of immunohistochemistry for the diagnosis of the above-mentioned lymphomas was further divided into primary and secondary panels. The primary panel included CD20, CD30, and CD3. While CD5, CD10, CD23, BCL6, and Ki67 were nominated as secondary panels. Positive and negative CD markers for the subtypes of B-cell and T-cell Non-Hodgkin lymphoma found in this study were as follows as well a comparison of both bone marrow morphology and immunohistochemistry was done for the identification of Non-Hodgkin lymphoma. p-value of less than 0.05 was considered statistically significant (Table 1).

Table 1: Immunohistochemical Profile and Comparison of Diagnostic Ability of Bone Marrow and Immunohistochemistry for Diagnosis of Non-Hodgkin Lymphoma

Diagnosis	Positive markers	Negative markers	NHL identified by BMM	NHL identified by IHC	p-Value
B-cell Non-Hodgkin Lymphoma					p < 0.05
Chronic Lymphocytic Leukemia (CLL) n=9	CD20 CD5, Ki67<20%	CD3 CD10	3	9	
Mantle Cell Leukemia (MCL) n=4	CD20 CD5 Ki67>30% CD23	CD3 CD10	1	4	
Diffuse Large B-cell lymphoma (DLBCL) n=15	CD20 CD10 KI67>80% BCL6	CD3 CD5	4	14	
Burkitt's Lymphoma (BL) n=6	CD20 CD10 BCL6	CD3 CD5	2	5	

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Follicular Lymphoma (FL) n=4	CD20 CD10 Ki67<40%	CD3 CD5	1	4	
T-cell Non-Hodgkin Lymphoma					
Angio Immunoblastic Lymphoma n=2	CD3 CD10	CD30	1	2	
Anaplastic Large T-cell Lymphoma n=1	CD30 CD5 CD2	CD3	0	1	
Lymphoblastic Lymphoma n=2	CD3 CD5 Tdt	CD20 CD4 CD8	0	2	
Total	-	-	11	41	-

NHL: Non-Hodgkin Lymphoma, IHC: Immunohistochemistry, BMM: Bone Marrow Morphology

A contingency table was drawn to check the association of bone marrow morphology and immunohistochemistry with the diagnosis of non-Hodgkin lymphoma. This statistical analysis shows that the p-value is 0.0001. Since the p-value is less than 0.05, this suggests that there is a statistically significant difference between the BM and IHC diagnoses (Table 2).

Table 2: NHL Cases Detected by Bone Marrow Morphology Vs IHC

-	Diagnosis Done NHL (Positive)	Diagnosis Missed NHL (Negative)	Total	p-value (chi sq test)
BMM	11	32	43	0.0001
IHC	41	2	43	

Validity parameters showed sensitivity and specificity of IHC to be 95% and 86% respectively with diagnostic accuracy of 93%. IHC was found to be extremely significant by the chi-square test (Table 3).

Table 3: Diagnostic Utility of IHC in NHL Diagnosis

-	NHL Positive Cases - 43	NHL Negative Cases (Normal Control) 15
IHC Detected	41 TP	2 FP
IHC Not Detected	2 FN	15 TN

DISCUSSION

Out of 57 samples, 41 were male and 16 were female patients. The most affected age group was 45-60 years. Among total cases, 43 (75.4%) were of NHL while only 14 (24.6%) cases were of HL. Among 43 cases of NHL, 38 (88.4%) were found of B-cell type while only 5 (11.6%) were of T-cell origin. CD30 (85.7%) was the most expressed immunomarker in HL while CD20, CD3, CD5, and Ki67 showed the highest positivity rate in NHL. IHC was statistically significant (p-value < 0.05) with a sensitivity of 95%. In various studies, geographical variations in the incidence rate and distribution of multiple subtypes of lymphomas are very well documented. Burkitt's lymphoma is reported to be endemic in the African region, while adult T-cell lymphomas and gastric lymphomas are much more frequent in Japan and Italy respectively [1]. In India, a high incidence rate of NHL was reported [14]. In the present study, the prevalence of lymphomas was found to be higher in male as compared to female, which was in accordance with various other studies [15, 16]. Age distribution showed that maximum cases were reported in the age group of 45-60 years. Similarly, to our results, a study reported a median age of 50 years about the prevalence of lymphomas [17]. Padhi *et al.*, also reported that 30 to 50 years was the most commonly affected group with lymphomas [18]. Non-Hodgkin lymphomas were found to be more prevalent than Hodgkin lymphomas in the ratio of 3:1 in our study. A South Indian study also reported a ratio of 3.6:1 concerning NHL to HL, which was in accordance with our results [19]. Similar results were reported in other studies as well [16, 20]. In the present study, B-cell lymphomas were found to be more prevalent than T-cell lymphomas. Various other studies also reported the predominance of subtypes of B-cell lymphomas like DLBCL and Burkitt lymphomas [10, 20]. Another study conducted in Amritsar also reported the predominance of DLBCL, a B-cell NHL among all cases of lymphomas [20]. The most common clinical presentation in the current study was hepatosplenomegaly followed by lymph nodes enlargements. Similar results were also reported in various other studies in which lymphadenopathy was the most common clinical sign examined in lymphoma cases [11, 21]. For the diagnosis of Hodgkin lymphoma, CD30 was found to be the most effective marker. Recently, Fromm and Wood reported the panel of six immune markers including CD3, CD30, CD40, CD20, CD95, and CD 64 for the diagnosis of classical Hodgkin lymphoma among which CD30, CD95, and CD40 were found to be positive in most cases of HL which was in concordance with our results. While other markers represented variable positivity rates [22]. Another study reported similar results of a high positivity rate of CD30 in cases of HL [23]. CD3 and CD5 immune markers were positive in most cases of T-cell NHL. To our results, a study reported the expression of CD3 and CD5 markers in cases of T-cell NHL [5]. In the case of anaplastic large cell lymphoma, expression of CD30, CD5 and CD2 was observed in the present study. Das *et al* also reported similar results [6]. Immunophenotyping of B cell NHL lymphomas showed the positivity rate of CD20, CD10, K167, and BCL2 in subtypes of B-cell NHL. A study conducted in 2021 also reported the strong expression of CD20 in B-cell NHL cases [24]. In cases of Mantle cell lymphoma, expression of CD5 was observed in the current study. Another study reported the high positivity rate of CD5 in cases of Mantle cell lymphoma [25]. Another study in 2020 also reported the expression of CD5, and CD20 immunomarkers in Mantle cell lymphoma and CD10 was a negative marker. This was in accordance with our results. However, they also reported the negative expression of CD23 while in the current study, CD23 was a positive marker in cases of MCL [26]. In the case of Burkitt's lymphoma, expression of CD10, CD20 and BCL6 was reported which was similar to our results. Expression of CD10 was observed in cases of CLL which

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was also in accordance to our results [27]. According to the data reported in 2020, 60% of cases of follicular lymphoma showed expression of CD10 immunomarker. In our study, similar results were reported in which CD10 was a positive marker among cases of follicular lymphomas [26]. Another subtype of B-cell non-Hodgkin lymphoma, Chronic lymphocytic leukemia (CLL) was also identified in the present study. Immunophenotyping of CLL showed expression of CD20 immunomarker. Similar results were reported in 2022, in which differential diagnosis of CLL showed CD20 as a positive marker. Immunohistochemistry of Diffuse Large B-cell lymphoma (DLBCL) was also reported in the same study and the results were positivity of CD20 and CD79a immunomarker which was also in accordance with our results in which CD20 was a positive marker in cases of DLBCL [28]. In the present study sensitivity and specificity of IHC is 95% and 88% respectively with a diagnostic accuracy of 93%. These results suggest that Immunohistochemistry is a good test for diagnosing lymphoma. This is in line with another study done in 2017 [29].

CONCLUSIONS

It was concluded that in addition to morphological findings, another crucial step in lymphoma diagnosis is the selection of relevant immunomarkers after clinicopathological correlation with the patient. Therefore, on the basis of our experience, we suggest the use of limited and effective panels of immunomarkers for optimal diagnosis of lymphomas and its subtypes. CD20 was most expressed marker in case of B cell NHL while T cell NHL showed the expression of CD3 and CD5. CD30 was an effective marker for diagnosis of Hodgkin lymphoma.

Authors Contribution

Conceptualization: MA

Methodology: MA, SH

Formal analysis: MI

Writing-review and editing: SH, RM, HA, NM

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Predictive Value of Neutrophil Lymphocyte Ratio in Assessing Severity Grades of Knee Osteoarthritis

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ABSTRACT

Osteoarthritis is a disease with a significant inflammatory component. Neutrophil Lymphocyte Ratio (NLR) level is a marker to determine inflammation. **Objective:** To find the value of NLR ratio in assessing severity grades of knee osteoarthritis. **Methods:** Prospective Observational Study was carried out in Tertiary care hospital on 378 patients diagnosed both clinically and radio graphically with Knee osteoarthritis reported to tertiary care hospital were selected. Convenience sampling was performed. Patients were divided into, group A, B and C Mild, moderate and severe Knee osteoarthritis with 126 patients. Blood samples were taken from participants and total and differential leucocyte counts and neutrophil levels were determined. NLR value was determined in each group. Mean value was calculated. **Results:** Out of 378 patients, 172 (45.5%) were female and 206 (54.5%) were male. The mean value of NLR ratio in group A was found to be 2.96 ± 0.84. Mean value in group B was found to be 5.83 ± 1.52 and for grade 3 was found to be 8.86 ± 2.33. **Conclusions:** NLR value is a good indicator for assessing severity grades of Knee osteoarthritis.

INTRODUCTION

Osteoarthritis is an illness marked by bone hyperplasia, articular cartilage degeneration, and joint destruction. It is a degenerative joint disease, involving joints only and sparing internal organs. It is the fourth most common joint disease and the most common form of the arthritis. Joint stiffness and limitation of joint movement is hall mark of the disease [1]. It involves both the genders, male and female but the condition primarily affects women. One of the reason woman are prone to osteoarthritis is there hormonal change and less bone density. Its incidence climbed from 13.8% to 21.6% in 2018 [2, 3]. In Pakistan, knee osteoarthritis (OA) was reported to be diagnosed in 3.6% of rural and 3.1% - 4.6% of urban areas in Northern Pakistan [4]. Knee OA is a degenerative, long-term bone joint illness. The solid and intricate framework of articular cartilage that resists pressure has usually already been destroyed by the time pain and dysfunction is detected [10]. Early diagnosis is now the most important factor in the prevention and management of knee OA. Diagnostic imaging, including radiography, is the most widely used technique. Early knee OA imaging alterations are not readily apparent [5]. These days, complicated joint exams such as MRIs, CT scans, X-rays, rheumatoid factors, mucin, and erythrocyte sedimentation rate are used to diagnose osteoarthritis; however, by the time arthroscopy and bone scanning are used to find the disease, it has usually moved to an advanced level [6]. Knee pain and function are correlated with many synovial cytokines [7]. Through expressing

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modifications to cytokines, microRNAs, and metabolites, inflammatory pathways play a significant role in the pathophysiology of OA [8]. The Neutrophil to Lymphocyte Ratio (NLR) is an easy-to-use indicator of overall inflammation. It has proven effective in forecasting cardiovascular and cancer outcomes [9]. More recently, NLR has been suggested as a separate factor to influence the postoperative phase following an arthroplasty and predict the radiographic severity of the hip and knee [10].
The aim of present study was to determine the predictive value of Neutrophil Lymphocyte ratio in assessing severity grade of knee osteoarthritis.

METHODS

This prospective study was carried out on 378 patients with knee osteoarthritis. Sample size was calculated using WHO sample size calculator using reported prevalence of knee osteoarthritis as 56.7% [11]. Patients aged 20 years or above reporting to medicine Department in Tertiary Care Hospital in Rawalpindi were included in the study. Convenience sampling was performed. The study commenced after due approval of methodology and concept by Ethical Committee of Pak-Emirates Military Hospital Rawalpindi, Pakistan and granted ethical clearance ERC Letter Number: A/28/ER/15/23. Also written permission was taken from patients. The study was conducted from June 2022 to December 2022. Inclusion Criteria Include Patients age 20 years or above, Patient diagnosed clinically and radio graphically with knee osteoarthritis. Exclusion Criteria include Patient with complicated diseases such as tumors, carcinoma, and patients allergic to medicine used in this study, mental and psychologically disable. On enrollment, complete medical and smoking histories, as well as information about current pharmacologic treatments, were acquired. Baseline data was collected related to demographic characteristic, past medical history and co-morbidities. Respondents were divided into 3 groups based on history, clinical, radio graphical, and total time of medication used, with 126 patients in each group, group A, B and C, Grade 1 and 2 as mild, Grade 3 as moderate and Grade 4 as severe knee osteoarthritis based upon Kellgren and Lawrence grading. Blood samples were taken from participants and BMI Index were measured Body Mass Index (BMI) was calculated as the ratio of body weight kg/m^2. [12]. Total and differential leucocyte counts, absolute eosinophil and neutrophil levels were determined. NLR was determined by dividing the neutrophil count by the lymphocyte count. NLR value was determined in each group. Mean value was calculated. Independent T test was applied between Group A vs Group C of NLR, and p value (p <0.0.5) was considered statistical significant. SPSS version 26.0 was used to collect enter, and analyses the data. The mean ± Standard Deviation (SD) was computed for quantitative data, while frequency and percentage were determined for qualitative data.

RESULTS

This prospective study was carried out on 378 patients. Out of which 210 (55.5%) were female and 168 (44.4%) were male (Table 1).

Table 1: Gender Distribution of Respondents

Gender	Female N (%)	Male N (%)
	172 (45.5%)	206 (54.5%)

For age distribution, only 90 (23.8%) had age <30 years, 201 (53.17%) had age 31-60 years and rest 78 (20.6%) had age >60 years. BMI index showed that mean BMI index was 34.23 ± 4.23, out of total 378 patients, only 20 (5.2%) had normal BMI Index, 34 (8.9%) were overweight, 116 (30.6%) were obese I, 112 (29.62%) were obese II and 96 (25.3%) were obese III (Table 2).

Table 2: BMI Index of Respondents

Normal BMI N (%)	Overweight N (%)	Obese I N (%)	Obese II N (%)	Obese III N (%)
20 (5.2%)	34 (8.4%)	116 (30.6%)	112 (29.62%)	96 (25.3%)

They were divided into 3 groups based upon severity grades of Knee Osteoarthritis. The mean value of NLR ratio in group A was found to be 2.96 ± 0.84. Mean value in group B was found to be 5.83 ± 1.52. And for grade 3 mean value was found to be 8.86 ± 2.33 (Table 3).

Table 3: Mean NLR Ratio in Mild, Moderate and Severe Arthritis

Variables	Mean ± SD
Mild (Group A)	2.96 ± 0.84
Moderate (Group B)	5.83 ± 1.52
Severe (Group C)	8.86 ± 2.33

Independent T test was applied between group A and C. P value came out to be p<0.0002. Hence results here proved that NLR ratio is a good indicator in assessing severity grades of knee osteoarthritis.

DISCUSSION

This study was carried out on 378 patients. Group C with Severe osteoarthritis had predictive value of 8.86 + 2.33. This study is first study conducted in Pakistan measuring the predictive value of NLR in assessing severity grades of knee osteoarthritis. The results of present study is in accordance to a study carried out by Shekhar et al., study conducted in India where they found that NLR ratio is a good inflammatory marker in RA, present study focus on NLR predictive values in assessing severity grades of osteoarthritis [13]. Present study found that patients NLR ratio kept on increasing as severity grades increases, the results are in accordance to a study carried out by Marius *et al.* Research conducted in Romania in patients with mild and advanced stage knee NLRs were higher in patients with end disease than in the group with moderate OA [14].

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Present study considered, 1.45 as a normal value for NLR, the results are in accordance to a study carried out by Forget *et al.*, a healthy adult's normal NLR value should be 1.65, but within a wider range of 0.78 – 3.53 [15]. Present study found that NLR is linked to inflammation the results are in accordance to a study where NLR is associated with inflammatory arthritis activities, including lupus, psoriasis, ankylosing spondylitis, and rheumatoid arthritis. Platelet to lymphocyte ratio and mean platelet volume are also linked to this association [16]. Present study found that NLR is associated with presence on OA and its severity the results are in accordance to a meta-analysis and systematic review where only NLR was linked to the severity of the disease, but both PLR and NLR were connected with the presence of OA [17]. Patients with osteoarthritis had considerably higher levels of NLR in their peripheral blood, indicating a possible role for them in the onset and progression of the condition. The results of Cheng *et al.*, and Gundogdu *et al.*, (NLR in osteoarthritis) are in line with this [18, 19]. According to the correlation between the severity of OA and the variables that showed significant connection on univariate analysis in older age and higher NLR were remained strongly linked with severe OA, According to earlier research, old age is a major risk factor for OA and is linked to severe OA [20]. Present study found that, NLR was positively and significantly was associated with Knee osteoarthritis, and values are usually greater than 2.1. The results are in accordance to a study where they found that age and NLR over 2.1 were predictive of advanced OA [21].

CONCLUSIONS

The present study concluded that predictive value of Neutrophils to lymphocyte ratio for severe arthritis is 9.11 ± 2.26. The presence of Osteoarthritis and severity is linked to NLR. The NLR ratio was linked to OA in the knee that was symptomatic.

Authors Contribution

Conceptualization: MWA
Methodology: AA, WA
Formal analysis: SZA, GAKN
Writing, review and editing: FB

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Prevalence and Diagnosis of Rifampicin-Resistant *Mycobacterium Tuberculosis* using the GeneXpert MTB/RIF Assay at a Tertiary Care Children's Hospital

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ABSTRACT

Rifampicin is a primary anti-tuberculosis medication. Diagnosing multidrug-resistant tuberculosis (MDR-TB) remains a persistent challenge when examining both pulmonary and extra-pulmonary samples. Rapid detection of rifampicin resistance is essential for the timely treatment and prevention of the spread of tuberculosis. Recently, GeneXpert MTB/RIF assay has emerged as an advanced technique for the rapid diagnosis of *Mycobacterium tuberculosis*. **Objectives:** To assess the prevalence of rifampicin resistance in samples from pediatric patients in Pakistan, encompassing both pulmonary and extra-pulmonary cases using GeneXpert MTB/RIF assay. **Methods:** A cross-sectional study was conducted in the Children's Hospital, Lahore for a duration of six months. Pulmonary and extra pulmonary samples of patients under age 16 were examined by GeneXpert MTB/RIF assay. **Results:** A total of 1320 samples were examined, and among them, 110 tested positive for *M. tuberculosis* (MTB) infection. Out of these 110 positive samples, 5 exhibited resistances to rifampicin, 18 showed indeterminate resistance, while rifampicin resistance was not detected in the remaining 87 samples. Additionally, 3 of the rifampicin-resistant samples displayed a very low load of MTB, and 2 samples exhibited a low MTB load. **Conclusions:** This study revealed 4.5% prevalence of MDR-TB in pediatric population. The study also showed that GeneXpert is a highly advanced technique for the diagnosis of rifampicin resistance in pulmonary and extra-pulmonary samples.

INTRODUCTION

In spite of many advances in the discipline of medicine, tuberculosis (TB) is still considered as one of the most lethal diseases. Moreover, the increasing trend in multidrug-resistant tuberculosis (MDR-TB) cases also bring significant challenges to control TB [1, 2]. It is concerning that Pakistan ranks fifth among nations with highest TB burden and fourth globally for MDR-TB cases (National TB Control Program - Pakistan) (https://ntp.gov.pk/) [3]. Pakistan has significant tuberculosis (TB) burden, with approximately 510,000 new cases emerging annually and around 15,000 developing drug-resistant TB each year. Pakistan accounts for 61% of the TB burden in the WHO's Eastern Mediterranean Region. The main factors contributing to the rise of drug-resistant TB in Pakistan include delayed diagnosis, inadequate or unsupervised treatment, poor follow-up, and a lack of social support programs for high-risk populations (WHO 2024). Rifampicin is considered to be one of the most effective first line anti-TB drugs. Other drugs used for treatment of TB include pyrazinamide, ethambutol, isoniazid and streptomycin [4]. Rifampicin has its mode of action by halting the transcription and elongation of RNA by binding to the RNA polymerase [5, 6]. Rifampicin resistance is therefore a surrogate marker in diagnosis of MDR-TB. Drug resistance

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against MTB is classified as monoresistance, MDR-TB and extensive drug resistant TB (XDR-TB). TB which is resistant to one of the drugs from first-line therapy (rifampicin, isoniazid, pyrazinamide and ethambutol) is called Mono-resistant TB while resistance against both rifampicin and isoniazid is classified as MDR-TB. XDR-TB is combination of MDR-TB plus resistance to one of the injectable drugs from the second line therapy. Resistance to rifampicin is due to mutation in RNA polymerase subunit B (rpoB gene) [6]. Drug resistant MTB is rapidly transmitted from an infected individual to other healthy individuals which leads to an increase in the frequency of MDR-TB. According to a survey, every undiagnosed, untreated active TB case can infect 10-15 healthy persons per year. So, in order to reduce transmission of infection, early diagnosis and detection of rifampicin resistance is very important [7]. In high incidence environments, where reinforcement is common, an undetermined percentage of previously treated TB patients have acquired MDR-TB unelated to their initial infection. Other risk factors for transmission of MDR-TB include close contact with the infected person and younger age. Minimum 18 to 24 months are required for the current standard treatment of MDR-TB using at least five drugs but none of them is as effective as rifampicin and all more toxic and less well tolerated [7]. Culture method and DST method are the gold standard methods to diagnose TB and drug resistance, but they have limitations as requirement of long time and high costs. The newer and faster technologies include microscopic observation, drug susceptibility assay, MTB growth indicator tube and calorimetric assays but the places where these techniques are most required frequently lack the specific knowledge and biosafety laboratories needed for these techniques [8]. Molecular assays such as GeneXpert have altered the panorama of diagnosis and proved to be economical, time saving solution to this issue worldwide. GeneXpert uses a real time PCR to detect the specific sequence for MTB as well as that of rifampicin resistance [9] and is considered a better approach than the conventional methods as Ziehl-Neelsen technique [10]. GeneXpert is a WHO endorsed, cartridge based novel diagnostic instrument that performs sample processing and real-time PCR analysis in a single cartridge for simultaneous diagnosis of TB infection and RIF resistance by PCR amplification of the resistance responsible fragment of the rpoB gene. It also identifies other possible mutations that are associated with RIF resistance [11]. The specificity and sensitivity of GeneXpert is found to be 98.3% and 93% [12].

This study aimed to detect rifampicin-resistant MTB and assess its prevalence in the pediatric population diagnosed with tuberculosis, using the GeneXpert assay.

METHODS

This cross-sectional study was conducted in the Children's Hospital during the period of six months from August 2022 to February 2023. A total of 1320 samples which were suspected of tuberculosis were examined and out of these 110 samples which were positive for Mycobacterium infection were examined to analyze rifampicin resistance. The patient population consisted of children under age 16 of both genders, admitted to hospital due to any infection. Subjects enrolled were considered irrespective of any other disease or history of disease. Patients with tuberculosis were confirmed with the help of GeneXpert MTB/RIF assay. Sample reagent and sample were added in 2:1 and allowed to stand for 5 min. Sample container was shaken for 10 to 20 min using forth and back movements and incubated for 10 min at room temperature. Xpert MTB/RIF cartridge was labelled with laboratory number on the side of cartridge. With the help of a transfer pipette, 2ml sample was transferred into the sample column of Xpert/MTB cartridge. Then cartridge was installed in the GeneXpert MTB/RIF assay machine. After 1 h and 50 min, results were displayed on the GeneXpert® Dx System. The used cartridge was discarded immediately. PPE kits, safety goggles, nitrile gloves and a procedure mask were used for this purpose. The data were entered and analyzed using IBM-SPSS version 23.0. Categorical variables like gender are described in the form of frequencies. Ethical approval was taken from the Institutional review board of the University of Child Health Sciences, The Children's Hospital, Lahore, under the (Ref no 1221/SAHS) before the conduction of this study. Confidentiality of each patient enrolled in this study was maintained. Patients consent was taken before enrolling in our study.

RESULTS

Total 110 eligible samples were analyzed using GeneXpert MTB/RIF assay following complete safety protocol. Out of 110 MTB detected patients, 5 patients were detected with rifampicin resistant MTB while 18 had indeterminate resistance and 87 patients were not detected with rifampicin resistance (Table 1).

Table 1: Frequency Distribution of Rifampicin Resistance

Rifampicin resistance	Frequency (%)
Not detected	87 (79,1)
Detected	05 (4.5)
Indeterminate	18 (16.4)
Total	110 (100)

In terms of the gender distribution among the patients, almost equal representation of tuberculosis cases in males 54 (49.1%) and 56 females (50.9%) were observed. Out of all the samples that tested positive for tuberculosis, five were found to exhibit rifampicin resistance. Among these cases, four were male patients, while one was female. This result indicates a higher prevalence of rifampicin resistance

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among males (80%) compared to females (20%). It was concluded that both genders exhibit a similar susceptibility to tuberculosis, indicating no discernible gender-based dominance in tuberculosis prevalence. However, when the distribution of rifampicin resistance was assessed among both genders, a higher incidence of resistance was observed among male patients in comparison to their female counterparts (Table 2).

Table 2: Frequency Distribution of Association between Gender and Rifampicin Resistance

Gender	Not Detected	Detected (%)	Indeterminate	Total (%)
Male	39	4 (80)	11	54 (49)
Female	48	1 (20)	7	56 (51)
Total	87	5 (100)	18	110 (100)

GeneXpert analysis also provides information on the MTB load in the detected samples. Among the five samples where rifampicin resistance was detected, two samples exhibited a low load of MTB, while three had a very low load of MTB. None of the samples with rifampicin resistant samples showed a high or medium load (Table 3).

Table 3: Frequency Distribution of Load of Rifampicin Resistant MTB in Patients with Tuberculosis

Load	Frequency (%)
Very low	3 (60)
Low	2 (40)
Total	5 (100)

Out of 110 MTB samples, 81 samples were pulmonary and 29 were extra pulmonary (frequency distribution given in Table 4). Out of these, 4 pulmonary and 1 extra pulmonary sample was detected with rifampicin resistance. Among rifampicin resistant pulmonary samples, one was sputum and 3 were gastric aspirate. While in extra pulmonary samples, only CSF was detected with rifampicin resistance (Table 4).

Table 4: Frequency Distribution of Rifampicin Resistant MTB in Specimens Collected from Patients with Tuberculosis

-	Specimen	Frequency	Rifampicin Resistant (%)
Pulmonary samples	Sputum	23	1 (1.2)
	Gastric Aspartate	57	3 (3.7)
	NG Aspirate	1	-
	Total	81	4 (4.9)
Extrapulmonary samples	Cerebrospinal Fluid	24	1 (3.4)
	Pericardial Fluid	1	-
	Pleural Fluid	4	-
	Total	29	1 (3.4)
	Sum Total	110	5 (4.5)

DISCUSSION

Diagnosing MDR-TB is consistently challenging in healthcare settings. The primary reason for the spread of TB is our inability to detect drug-resistant TB using current diagnostic methods. Rapid diagnosis, on the other hand, results in timely treatment, ultimately contributing to better epidemiological control [13]. Moreover, there are many disputations regarding the diagnosis of childhood TB, and it is often ignored by TB control programs [14]. Consequently, TB remains a leading cause of pediatric mortality, posing numerous threats that drive TB progression [15]. Here in this study, we utilized the GeneXpert MTB/RIF assay to diagnose rifampicin-resistant TB in samples from both the pulmonary and extra-pulmonary sources of children under the age of 16. Out of the 1320 suspected samples obtained from patients, 8.33% were confirmed to have tuberculosis. Among these confirmed TB cases, 4.5% displayed rifampicin resistance. Previously, somehow similar prevalence of rifampicin resistance has been reported in similar studies from the African countries as, Zambia (5.9%) [15], Nigeria (6.9%) [16] and Ethiopia (5.7-9 %) [16-17]. In present study, we observed an approximately equal distribution of male and female patients with tuberculosis. However, rifampicin resistant *Mycobacterium* exhibited a higher prevalence, with 80% of cases occurring in male patients. This gender-based disparity is consistent with findings from a similar study conducted in Nigeria, where rifampicin resistance was predominantly identified in the male population (65.5%) [17]. Furthermore, when examining the load of MTB in the rifampicin-resistant MTB samples, it was observed that the majority had very low or low MTB load. None of the samples exhibited a high load of MTB. This observation suggests that effective control of drug resistance can be achieved through improved and early diagnosis, as well as the appropriate use of antibiotics. Nevertheless, the specific factors contributing to this predominance of rifampicin resistance among male remain unidentified [18-19]. The prevalence of rifampicin resistance in pulmonary samples was determined to be 4.9% in this study, which closely aligns with findings from a previous study conducted in a Nigerian population (4%) [20]. In extrapulmonary samples, we observed a prevalence of 3.4% rifampicin resistance. It is also worth noting that in this study, the prevalence of indeterminate rifampicin resistance was substantially higher (16.3%) compared to findings from a study in an Indian rural community where a prevalence of 1.5% was reported [21].

CONCLUSIONS

The prevalence of rifampicin-resistant MTB in pediatric population of Pakistan as diagnosed using the GeneXpert assay is 4.5%. Notably, all the patients included in this study who exhibited rifampicin-resistant MTB had low or very low MTB load. This finding underscores that the rifampicin resistance is posing a fitness cost on *Mycobacterium* and the resistant organisms are weakly stable in nature till date. The rifampicin-resistant MTB in our community can,

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therefore, be controlled through the implementation of precise antibiotic dosing protocols.

Authors Contribution

Conceptualization: AZ, NM[1]
Methodology: RJ, IA
Formal analysis: NM[2], AT
Writing, review and editing: IA, AT

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

Conflicts of Interest

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Original Article

Comparison of Frequency of Pathogenic Micro-Organisms Causing Bloodstream Infections in Patients Admitted at Tertiary Care Hospital Rawalpindi

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ABSTRACT

Blood Stream Infections (BSI) are frequently occurring thing in hospital setting and if not tested and appropriate medicine not used, it has significant mortality and also adds an extra burden on health care. **Objective:** To find the frequency of various pathogenic micro-organisms causing bloodstream infections. **Methods:** Cross-sectional study was done in tertiary Care Hospital Rawalpindi from April 23 to August 23. Blood samples of 50 patients from two age groups were collected (n=25 above 60 years and n=25 ages 30-60 years). Blood samples were drawn into glass vial containing 20% EDTA to prevent blood clotting and then culture studies were performed. **Results:** Mean participant age in both study groups was 75.76 ± 8.9 and 46.88 ± 7.7 years ($p<0.001$). Blood culture analysis revealed that 42 isolates of *Staphylococcus aureus* was present in >60 years of patients and 55 isolates of *Staphylococcus aureus* were present in 30-60 years age group. 255 isolates of *Escherichia coli.* was present in >60 years' patients and 312 isolates of *Escherichia coli* were present in 30-60 years' age group. 9 isolates of *Klebsiella* was present in >60 years patients and 05 isolates of *Klebsiella* were present in 30-60 years age group years. **Conclusions:** Study showed that significant number of microorganism were present in collected blood culture samples. Among various strains of microorganisms, most common is *Escherichia coli*. Followed by *Staphylococcus aureus*. Study also highlights that BSI is a frequent occurring problem in hospital setting and if proper antibiotic administered, early cure can be achieved.

INTRODUCTION

Blood Stream Infections (BSI) include the presence of live microorganisms in the bloodstream, resulting in inflammation inside the host. This occurrence may significantly impact the clinical and hemodynamic characteristics, potentially leading to adverse outcomes [1]. The temporary presence of microbes in the circulation offers a potential hazard to several organs inside the body. If bloodstream infections are left untreated, they may result in severe outcomes such as shock, multiple organ failure, Disseminated Intravascular Coagulation (DIC), and ultimately, death [2]. Bloodstream infections represent a substantial global public health concern and have been linked to considerable morbidity and death [3]. While the prevalence of this phenomenon remains significant in industrialized nations, it is most pronounced in the least developed and emerging countries [4]. There exists a notable diversity in the epidemiology and pathogen profile of bacteria that are responsible for bloodstream infections [5]. Studies conducted in several countries including Canada, Australia, Finland, Denmark, Iceland, Sweden, New Zealand, and the United States have shown that the primary causes of Blood Stream Infections (BSI) are *Escherichia coli*, *Streptococcus pneumoniae*, and *Staphylococcus aureus* [3]. In contrast, there are variations

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in the pathogen profiles between Africa and Asia. *Salmonella enterica* has been identified as a significant causative agent of BSI in several African and Asian countries [6]. Empirical therapy is often used due to the possible consequences of BSI and the associated delays in conducting and obtaining culture results. The absence of treatment recommendations and the unavailability of susceptibility patterns for local isolates may potentially contribute to this phenomenon in poor countries [3]. An understanding of local antibiotic resistance trends may be beneficial in the selection of appropriate empirical medication, even within healthcare systems that have limitations or constraints [7]. There is now a growing phenomenon of BSI caused by Gram-negative germs, accompanied by a rise in the prevalence of drug-resistant strains [8]. Given the increasing prevalence of BSI worldwide and the emergence of antibiotic resistance among the organisms involved.

It is imperative to undertake research endeavors aimed at examining the pathogen profiles specific to Pakistan. Furthermore, it should be noted that there is a scarcity of published data pertaining to the nation in question. Consequently, there exists a pressing need for doing baseline investigations in this particular field. Consequently, a retrospective investigation was undertaken in order to ascertain the prevailing bacterial pathogens responsible for bloodstream infections in patients admitted at PEMH Rawalpindi.

METHODS

After the ethical approval from the institutional review board, this cross-sectional study was carried out at Territory Care Hospital Rawalpindi from April 2023 to August 2023. Ethical Committee approval was taken from Hospital Ethical Committee under Letter Number A/28/226/EC/522/23 dated 20th March 2023. A sample size of 50 was calculated using WHO EPI sample size calculator, keeping confidence of interval 95% and margin of error 5% and using a study conducted by Bandy *et al.*, in 2020 [9]. It was the hospital-based survey conducted to estimate the frequency of pathogens resulting in the progression of bloodstream infection. For this purpose, 25 admitted patients were above years and 25 hospitalized patients of 30-60 years were selected for this research study. Patients with age above 30 years, of either gender, and with bloodstream infection in soft tissues due to microbial manifestations were included in this research study. Patients with blood cancer, thrombocytopenia, severely compromised immune system, other malignancy, and surgery were excluded from the study. A formal consent form was provided to the respective patients before the collection of blood. The questionnaire was also used to collect the clinical laboratory data in the blood culture data of BSI patients. Standardized protocols designed by the hospital's research committee in Pakistan were thoroughly followed. To determine the presence of a pathogen, blood culture samples were put into a blood culture system and cultured at 37°C for 7 days. Plates of MacConkey agar and blood agar were inoculated immediately with positive culture materials. After 18-24 hours of aerobic incubation at 37 degrees Celsius, the plates were inspected. Bacteria were isolated using methods recommended by the most recent Clinical and Laboratory Standards Institute (CLSI) guideline (2014-2017). Statistical Package for the Social Sciences (SPSS) version 23.0 was used for the quantitative analysis of collected data from Territory Care Hospital. The data underwent analysis via the use of statistical methods including chi-square, independent samples t-test, and frequency distributions. A study was undertaken to determine the notable disparity among bacterial isolates in relation to different age groups. The p values ≤0.05 was considered statistically significant.

RESULTS

A total of 50 patients full filling the inclusion criteria were included in the present study table 1 represent the clinical and demographic parameters of the study participants in study groups. Mean of participants age in both study groups was 75.76 ± 8.9 and 46.88 ± 7.7 years (p<0.001). Majority of the study participants in both study groups were males. Mean ± S.D of participants leucocytes in both study groups was 10.24 ± 1.5 and 14.6 ± 1.5109/l (p<0.001). Mean of participants neutrophils in both study groups was 70.68 ± 2.9 and 77.4 ± 1.4% (p<0.001). Mean of participants blood urea nitrogen in both study groups was 30.28 ± 2.35 and 33.6 ± 2.2 mg/L (p<0.001). Mean of participants creatinine in both study groups was 1.39 ± 0.20 and 1.7 ± 0.22 mg/L (p<0.001). Mean of participants albumin in both study groups was 2.80 ± 0.63 and 3.06 ± 0.44 mg/L (p=0.025). Mean of participants cholesterol in both study groups was 331.04 ± 106.5 and 448 ± 102.2 mg/L (p<0.001).

Table 1: Clinical Laboratory Data in the Blood Culture (n=50)

Variables	>60 Years of Patients (Mean ± S.D)	30-60 Years (Mean ± S.D)	p-Value
Age (Years)	75.76 ± 8.9	46.88 ± 7.7	<0.001
Leucocytes 109/L	10.24 ± 1.56	14.6 ± 1.5	<0.001
Neutrophils	70.68 ± 2.9	77.4 ± 1.4	<0.001
Blood Urea Nitrogen (mg/L)	30.28 ± 2.35	33.6 ± 2.2	<0.001
Creatinine (mg/L)	1.39 ± 0.20	1.7 ± 0.22	<0.001
Albumin (mg/L)	2.80 ± 0.63	3.06 ± 0.44	0.025
Cholesterol (mg/L)	331.04 ± 106.5	448 ± 102.2	<0.001
Gender N (%)			
Male	17 (68%)	18 (72%)	0.802
Female	8 (32%)	7 (28%)	

Blood culture analysis revealed that among 30 BSI patients, no *Staphylococcus* (-), *Acinetobacter*, and fungi were

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isolated in both study groups. 42 isolates of *Staphylococcus aureus* were present in >60 years of patients and 55 isolates of *Staphylococcus aureus* were present in 30-60 years age group. 25 isolates of *Streptococcus pneumoniae* was present in >60 years patients and 32 isolates of *Streptococcus pneumoniae* were present in 30-60 years age group. 25 isolates of other *Streptococcus species* were present in >60 years' patients and 26 isolates *Streptococcus species* were present in 30-60 years age group. 255 isolates of *Escherichia coli* was present in >60 years patients and 312 isolates of *Escherichia coli* were present in 30-60 years age group. 9 isolates of *Klebsiella* was present in >60 years patients and 05 isolates of *Klebsiella* were present in 30-60 years age group years. No Pseudomonas was isolated in >60 years patients and 08 isolates of Pseudomonas were present in 30-60 years age group. 01 isolates of *Enterobacter* was present in >60 years patients and 03 isolates of *Enterobacter* were present in 30-60 years age group. The same number of Proteus isolates were present in >60 years and 30-60 years BSI patients. 15 other gram-negative bacteria were present in >60 years patients and 05 isolates of other gram-negative bacteria were present in 30-60 years. 30 anaerobic micro-organisms present in >60 years patients but no anaerobic pathogenic bacteria were present in 30-60 years age group (Table 2).

Table 2: Frequency of Pathogenic Micro-Organisms Causing Bloodstream Infections in Soft Tissues of Patients, Admitted at Territory Care Hospital Rawalpindi (n=50)

Micro-Organisms Encountered in Hospital	Pathogens	
	>60 Years of Patients (n=25)	30-60 Years of Patients (n=25)
Number of Patients	15	15
Staphylococcus coccus (-)	0	0
Staphylococcus aureus	42	55
Streptococcus pneumoniae	25	32
Other Streptococcus Species	25	26
Enterococcus	0	7
Escherichia coli	285	312
Klebsiella	09	5
Pseudomonas	0	8
Enterobacter	01	3
Acinetobacter	0	0
Proteus	8	8
Other gram (-)	15	5
Anaerobes	30	0
Fungi	0	0

DISCUSSION

The rise of antibiotic-resistant bacteria, both acquired in the community and in hospitals, is posing a growing threat to the effectiveness of antimicrobial therapy. This is especially evident in the selection of empiric antimicrobial treatment. The occurrence of Multi Drug Resistant (MDR) pathogens is often attributed to the overutilization of broad-spectrum antimicrobial drugs, as shown by the fact that over 60% of patients in Intensive Care Units (ICUs) are administered antimicrobials throughout their critical care stay [10]. In contrast to infections produced by bacteria that are not MDR, studies have indicated that MDR infections in hospitalized patients incur an extra cost ranging from $6,000 to $30,000 per patient [11, 12]. Various behavioral modifications have been suggested in the ongoing effort to combat MDR organisms, with the aim of mitigating the negative impact on antimicrobial treatment [13]. Strategies such as antimicrobial cycling and de-escalation systems have been employed in ICUs [14]. Nevertheless, the administration of broad-spectrum antimicrobials in patients with critical illnesses is considered essential owing to the limited room for mistake in selecting appropriate medication [15]. In such cases, the first choice of antimicrobials that effectively target the causative bacteria is of utmost significance [16]. According to the findings of Lipsitch *et al.*, the utilization of antimicrobials that do not currently have resistance will exhibit a positive correlation at the individual level with the presence of bacteria that are resistant to a different antimicrobial. However, at the population level, this utilization will have a negative correlation with the overall prevalence of resistance to the aforementioned antimicrobial [17]. The outcome of Blood Stream Infections (BSIs) is influenced by many variables. The correlation between mortality and several factors such as the severity of infection, underlying disorders, advanced age, and poor antimicrobial treatment seems to be significant [18]. The epidemiology of microbial pathogens causing Blood Stream Infections (BSIs) has undergone significant changes throughout the years, accompanied by a simultaneous rise in antibiotic resistance [19]. Overall in the present study, the most frequent bacterium was Escherichia coli in the bloodstream followed by Staphylococcus aureus and Anaerobes in soft tissues of BSI patients. Similar to our findings, A. Santaro *et al.*, reported a higher frequency for Escherichia coli and aureus species of bacteria in BSI patients [20]. In contrast to our research study, the recent findings of Gonzalez et al., reported that Pseudomonas aeruginosa were frequently involved in causing BSI infection [21].The rise of antibiotic-resistant bacteria, both acquired in the community and in hospitals, is posing a growing threat to the effectiveness of antimicrobial therapy. This is especially evident in the selection of empiric antimicrobial treatment. The occurrence of Multi Drug Resistant (MDR) pathogens is often attributed to the overutilization of broad-spectrum antimicrobial drugs, as shown by the fact that over 60% of patients in Intensive Care Units (ICUs) are administered antimicrobials throughout their critical care stay [10]. In contrast to infections produced by bacteria that are not

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CONCLUSIONS

Blood Stream Infections (BSI) are a frequently occurring and challenging thing in hospital setting, especially in indoor settings of a hospital. They carry significant morbidity and mortality and if not treated properly and diagnosed at right time, they are the source of extra burden on health care. Our study showed that significant microorganism was present in the tested samples and among them, the most common occurring microorganism was *Escherichia coli* followed by *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Klebseilla species.* The other rare includes aneorobes and *Enterobacter.*

Authors Contribution

Conceptualization: SS
Methodology: SN, KN
Formal analysis: HR
Writing, review and editing: AM, MA

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

Conflicts of Interest

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Original Article

The Risks of Early Complications from Level II Axillary Clearance in Modified Radical Mastectomy

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ABSTRACT

The second leading cause of cancer fatalities in women is breast cancer. Complete breast tissue removal and axillary lymph node removal are performed in a modified radical mastectomy. Seroma is the most frequent surgical complication. Due to inadequate data, our study would give significant data on this issue and wound infection. **Objective:** To determine the most prevalent early difficulties observed by early breast cancer patients after a modified radical mastectomy with axillary clearing. **Methods:** This descriptive research included 135 women who had a modified radical mastectomy with level II axillary clearance for early-stage breast cancer. After surgery, we monitored these patients in the Breast Clinic for up to a month for any issues. This data set used SPSS version 24.0. **Results:** The patients' average age was 50.12 ± 7.44 years. Seroma development was the most prevalent consequence found in 47 (34.8%) patients, while 35 patients (24.9%) experienced edema of the arm. In 15 patients (11.1%) wound infection was noted, 12 patients (8.9%) had paresthesia, 8 patients (5.9%) had a hemorrhage, in 7 patients (5.2%) hematoma was noted, and 7 patients (5.2%) developed skin flap necrosis. In 5 patients (3.7%), paralysis of the serratus anterior and Latissimus Dorsi muscles was detected. **Conclusions:** A modified radical mastectomy can cause complications like seroma formation, wound infection, arm edema, hemorrhage, skin flap necrosis, serratus anterior muscle paralysis, intercostobrachial nerve paresthesia, and axillary dissection. Correct postoperative care can detect these issues.

INTRODUCTION

Cancer of the breast affects 1 in 5 women. It is the second leading cause of death for female globally [1, 2]. These days, breast cancer treatment requires a multi-specialty group. Modified radical mastectomy, plain mastectomy, and conservative breast surgery are a few surgical options for breast cancer therapy [3]. Breast cancer patients often have axillary dissection and wide local excision in addition to modified radical mastectomy. Common early problems after breast surgery include seroma formation, skin flap necrosis, wound infection, and a high rate of morbidity and mortality. An infection in the wound is considered postoperative wound infection if it appears within one month after surgery [4]. Since it was initially documented as a component of radical mastectomy, axillary dissection for breast cancer has persisted with radical mastectomy modifications [5]. From the medial boundary of the axilla to the second to sixth ribs along the chest wall, all external mammary nodes were carefully removed as part of this framework, which also required the removal of lymph nodes at three levels. A transection of the pectoralis minor muscle was performed to access the level III apical nodes [6]. This muscle was originally attached to the coracoid process. The sternal part of the pectoralis major was also laterally removed to open up more space in the axillary

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area. In the next steps, the muscle was rebuilt. As more information about the location of nodal micrometastases became available and breast-conserving treatments gained popularity, the scope of elective axillary dissection was often modified [7]. Little more than one percent of cases had level III micro-metastases in the absence of level I or II metastases. The prevalence of solo metastases to level II was found to be less than 2% in certain research, whereas over 20% of "skip" metastases were reported in other publications [8, 9]. As a result, most publications now show level I and II dissection as the anatomic extent of axillary lymphadenectomy, while the pectoralis minor is preserved [10]. From what we can tell from their medical records, 20% of patients suffered seroma development, 18% wound infections, and 2% skin flap necrosis [11]. A 100% seroma formation rate, a 6-14% wound infection rate, and an 8-60% necrosis rate have been reported by various sources. These issues are not life-threatening because patients fully recover with the right administration of antibiotics, drainage, and flap implantation and removal. The leading complication following breast cancer surgery, seroma, has an unknown origin. Seromas occurred in 15.8% of patients overall, 19.9% of patients undergoing MRM, and 9.2% of patients undergoing breast-conserving surgery (p=0.01)[10]. In cases of breast cancer, seroma formation is the most common wound complication following axillary lymph node dissection and modified radical mastectomy. About 50% of patients who get a mastectomy will experience this [12].

A modified radical mastectomy with axillary clearance at level II was performed on patients with breast cancer.

This study aimed to determine the frequency of early post-procedure complications.

METHODS

A descriptive study was conducted at the Department of Surgery, Bakhtawar Amin Trust Teaching Hospital, Multan after getting approval from the ethical review board with reference number (2767/MD/BATTH). The duration was 14 months from February 2023 to April 2024, with the established diagnosis of carcinoma of the breast and underwent modified radical mastectomy with axillary clearance. Exclusion criteria included patients who had a history of palliative mastectomy (LABC with metastatic lesion) or who had undergone a modified radical mastectomy operation. Because the needed sample size was 135 patients, the estimation of the sample size was based on the prevalence of 18%, the margin of error was 10%, and the confidence interval was 95%. The non-probability purposive sampling approach was modified to fit the situation. Each patient underwent a thorough clinical examination, baseline testing, and an informed consent process before a thorough medical history was obtained. For individuals who may have distant metastasis, it was recommended to undergo bone scans and abdominal ultrasounds. Both FNAC and open biopsy were used to confirm the diagnosis of breast cancer in individuals. All of these patients were observed for postoperative complications for one month at the Breast Clinic on an outpatient basis after undergoing modified radical mastectomy with axillary clearance. We recorded all of the following findings in a specially constructed proforma. All patients had their clinical and demographic details recorded. A confirmation of breast cancer was achieved using an open biopsy, which also served to assign a staging system. When doing MRM, standard surgical procedures were adhered to. Notable outcomes included early problems, comorbidities, and risk factors. Complications that occurred within 30 days after MRM were considered to be early complications. "Statistical Package for the Social Sciences (SPSS)" version 24.0 was used for data analysis. While quantitative data were shown with means and standard deviations (SDs), qualitative variables were indicated with frequencies and percentages. The association between the research variables was determined using Pearson correlation, with a significance level of $p < 0.05$ being deemed statistically significant.

RESULTS

The patient's average age was 50.12 ± 7.44 years. 108 (80%) of the patients were married and the mean duration of marriage was 25.7 ± 4.26 years. 55 (40.7%) cases were educated and 80 (59.3%) cases were non-educated. Most cases were from urban areas. Family history of disease was found in 37 (27.4%) cases. Frequency of breastfeeding cases was 73 (54.1%) (Table 1).

Table 1: Characteristics of the Cases

Variables	Frequency/Percentage (135)
Mean Age (Years)	50.12
Mean Duration of Marriage (Years)	25.7
Marital Status	
Yes	108 (80%)
No	27 (20%)
Education Status	
Yes	80 (59.3%)
No	55 (40.7%)
Residency	
Rural	60 (44.4%)
Urban	75 (55.6%)
Family History of Disease	
Yes	37 (27.4%)
No	98 (62.6%)
Breast Feeding	
Yes	73 (54.1%)
No	62 (45.9%)

The most common comorbidity was hypertension (HTN), diabetes mellitus (DM), obesity, and smoking. There were 63 (46.7%) patients had tumor stage II, 52 (38.5%) cases had

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tumor stage III, and 20 (14.8%) cases had stage I cancer (Table 2).

Table 2: Comorbidities and Stages of Cancer Among all Cases

Variables	Frequency/Percentage (135)
Comorbidities	
HTN	48 (35.6%)
DM	40 (29.6%)
Obesity	18 (13.3%)
Smoking	29 (21.5%)
Stage of Tumor	
I	20 (14.8%)
II	63 (46.7%)
III	52 (38.5%)

Seroma development was the most prevalent consequence found in 47 (34.8%) patients, while 35 patients (24.9%) experienced edema of the arm. In 15 patients (11.1%) wound infection was noted, 12 patients (8.9%) had paresthesia, 8 patients (5.9%) had a hemorrhage, in 7 patients (5.2%) hematoma was noted, and 7 patients (5.2%) developed skin flap necrosis. In 5 individuals (3.7%), paralysis of the serratus anterior and latissimus dorsi muscles was detected (Figure 1).

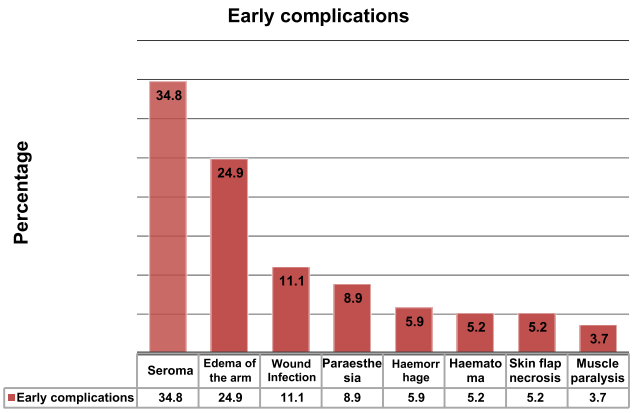

Figure 1: Modified Radical Mastectomy. Potential Risks and Consequences in Patients with Level II Axillary Clearance

In terms of p-values, the association between the most frequently occurring post-surgical compilations and the accompanying comorbidities is being evaluated (Table 3).

Table 3: Associated Risk Variables and Post-Mastectomy Problems Had a p-Value Less Than 0.05

Variables	Wound Infections	Seroma Formation
Comorbidities		
Stage of Cancer	0.579	0.416
HTN	0.512	0.004*
DM	0.612	0.001*
Obesity	0.298	0.003*

DISCUSSION

Nowadays, a multidisciplinary strategy is used to manage breast cancer. The first presenting stage of the disease, the patient's age, the patient's preference, and the surgeon's option all play a role in determining the surgical treatment for breast cancers. The technique with the highest frequency of occurrence is modified radical mastectomy with axillary clearance [13]. Significant morbidity and death are inherent to all surgical procedures. Consistent with Moo *et al.*, 47 individuals (34.8%) experienced seroma development as a complication. According to the research, seroma production rates range from 4.2% to 89% in axillae that have not been drained, and they reach 53% in drained axillae. One way to avoid this problem is to put a suction drain deep into the axilla, where the mastectomy flaps [14]. Seroma is more common in older patients, those with larger breasts, those with axillary lymph nodes, those who have had a prior surgical biopsy, those with hypertension, and those who used heparin [15]. Similarly, this study found that seroma more commonly occurred in elderly patients, those with hypertension, and those whose axillary lymph nodes tested positive for metastasis. After multiple aspirations, every single one of our patients made a full recovery. Prior reports indicated instances of fibrous encapsulated seroma following radical mastectomy, which ultimately necessitated surgical removal due to its resistance to conservative treatment. Nonetheless, we could not find any evidence of seroma development in our research. Therefore, seroma is a "necessary evil" that will affect a predicted percentage of people in an unpredictable way [16]. By performing a modified radical mastectomy, the surgeon removes breast tissue while also surgically clearing the axilla. So, for these people, axillary radiation following a mastectomy is not required. Although the extent can vary, most surgeons do level 1 and level 2 axillary clearance. Level 1 clearance requires the removal of lymph nodes situated laterally to the lateral border of the Pectoralis minor muscle. Lymph nodes between the medial and lateral borders of the Pectoralis minor muscle and inter-pectoral lymph nodes need to be excised for level 2 clearance. In most cases, a nosocomial or hospital-acquired bacteria is to blame for the wound infection. Smoking, fluid accumulation, and wound separation are the causes of wound infections. Of the two organisms that caused the disease, Staphylococcus aureus was far more frequent than pseudomonas aeruginosa [17]. In a previous research, wound infections occurred in 3.6% of patients in a combination of a sterile dressing changed daily and antibiotics prescribed based on the patient's culture and sensitivity results used to treat wound infections. It is reported that approximately 50% of individuals experience early arm edema following axillary dissection [18]. The majority get edema, however it is usually so mild that people do not even notice it. The likelihood of lymphedema increases with both the pre-and post-operative body mass index being higher. This issue was noted in 24.9% of the

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cases. Lymphedema was observed in 28.8% and 27.8% of participants in the other two investigations, respectively [19, 20]. Extensive mobilization was associated with 5.2% of cases of skin flap necrosis. After having the skin margins removed, another patient who had diabetes, hypertension, and a stroke resolved the flap necrosis. Repetitive excision of skin was necessary in one patient with comorbid. The most likely theory is that successful wound healing necessitates the activation of immune cells, the production of proteins, and a healthy nutritional state. During a mastectomy, a patient with locally advanced breast cancer who was experiencing bleeding, ulceration, and a low hemoglobin level had a big defect covered with a rotational skin flap. Half of the flap had necrosis. Reducing the amount of cautery used, injecting adrenaline-containing solutions into subcutaneous tissue, using suction drains routinely, and applying pressure garments can all reduce the incidence of skin flap problems following radical breast cancer surgery [21, 22]. There is substantial psychological morbidity in the years after a mastectomy for breast cancer, according to studies. Possible causes include a decline in her health, sense of self-worth, femininity, or purpose in life [23]. Acute depression was also experienced by two of our patients following surgery. However, after much deliberation and consultation, antipsychotic medication was ultimately chosen.

CONCLUSIONS

Early warning signs of complications from a modified radical mastectomy with axillary dissection include seroma formation, wound infection, edema of the arm, paresthesia from the involvement of the intercosto-brachial nerve, hemorrhage, necrosis of the skin flap, and paralysis of the serratus anterior muscles. These issues can be identified with correct postoperative care.

Authors Contribution

Conceptualization: TJ

Methodology: TJ

Formal analysis: MMZ, AA

Writing-review and editing: JMT, FN

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of Transvaginal Ultrasound Cervical Length with Bishop Score in Predicting Cesarean Section after Labor Induction

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ABSTRACT

A critical aspect of obstetric care aimed at initiating or augmenting childbirth when natural processes are deemed insufficient or unsafe, employing various methods to ensure maternal and fetal well-being **Objective:** To compare the transvaginal ultrasound cervical length with bishop score in predicting cesarean section after labor induction. **Methods:** A comparative cross-sectional study was conducted at the Department of Gynecology and Obstetrics Azad Jammu Kashmir Medical College (AJKMC), Muzaffarabad from January 2023 to June 2023. A total of 110 pregnant women aged 18 to 35 years having gestational age ≤ 40 weeks were included who underwent transvaginal ultrasound (TVS) for measuring cervical length (CL) measurement and Bishop Score assessment before labor induction. Primary outcomes included cesarean section rates post-induction, with secondary outcomes covering maternal and neonatal variables. **Results:** The study involved 110 participants, with a mean age of 25.9 ± 4.00 years. Mean Bishop Score was 4.53 ± 2.06, and the mean cervical length measured by transvaginal ultrasound was 26.6 ± 7.37 mm. Misoprostol was the primary induction method (65.5%), with an overall Cesarean Section rate of 35.5%. Comparing CS and VD groups, BS was lower in CS (3.74 ± 2.20 vs. 4.96 ± 1.86, p = 0.005), while CL was higher (31.1 ± 6.70 mm vs. 24.1 ± 6.53 mm, p < 0.001). **Conclusions:** Our study found that transvaginal ultrasound (TVUS) measurement of cervical length (CL)>27 mm demonstrated superior predictive ability for cesarean section (CS) following labor induction compared to the Bishop Score (BS)≤5.

INTRODUCTION

Induction of labor, a medical intervention to initiate uterine contractions artificially, has become increasingly common in contemporary obstetric practice [1]. It is used where there is a delayed onset of the natural labor process or where a medical condition requires that the baby be delivered before actual labor. Bennett's case highlights several critical aspects of labor induction: the associated risks for both the mother and fetus, revised calculations according to the gestational age, and the unique conditions of the patient [2, 3]. Induction of labor should be attempted when there are risks associated with continued pregnancy for the mother or fetus. Some of the most frequent indications of a maternal kind include preeclampsia, gestational diabetes, cholestasis, and post-term pregnancy. Fetal indications may include small for gestational age, poor weight gain, range of movement restriction, reduced fluid, and placental dysfunction [4]. In general, induction of labor is nowadays considered safe but as is always the case with any medical procedure, there are not without risks and possible complications. The risks

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may affect the mother and include uterine hyperstimulation. This condition is characterized by the excessive and forceful contraction of the uterus following the administration of a drug or injection. Uterine rupture refers to a tear that occurs in the uterine wall. Postpartum hemorrhage is defined as excessive bleeding that occurs after childbirth. Maternal risks may be further categorized into short-term and long-term risks and include; Pregnancy-induced hypertension, placenta abruption, preterm labor, anemia, mode of delivery, and death. Fetal risks include birth trauma, fetal distress, and NICU admission [5]. Originally, performing cervical length examination has posed some concerns due to its invasiveness; however, with the advancement of transvaginal ultrasound (TVS), assessing cervical length has become much more effective and accurate before labor induction. The non-stiff cervix can be measured accurately with the help of TVS. Short cervical length and poor perinatal outcomes have also been found to be linked to the risk of Cesarean section and hence cervical length measurements using TVS are useful in obstetric practice [6, 7]. The Bishop Score, first introduced in the mid-1960s is a cervical scoring system employed to evaluate the cervix in preparation for artificial rupture of membranes (ARM). The Bishop Score is a tool used in evaluating cervical ripeness, with a higher score being an indication of increased inducibility and successful vaginal birth [9]. This research aims to address the challenge of effectively combining the Bishop Score with transvaginal ultrasound assessment of cervical length (CL) to improve the accuracy of predicting cesarean sections (CS) after labor induction (LI). Detailed data on this cumulative assessment and its predictive value are scarce, particularly in countries like Pakistan, where the risks of cesarean sections are high. Thus, this study is well-positioned to fill this research gap. The findings of this research are useful for clinicians and might help to enhance existing programs thereby improving safety in childbirth as well as the use of resources.

This study aimed to comparison of transvaginal ultrasound cervical length with bishop score in predicting cesarean section after labor induction.

METHODS

The current cross-sectional comparative study was conducted in the Department of Gynecology and Obstetrics of Azad Jammu Kashmir Medical College, Muzaffarabad after getting permission from the respective ethical review board of the hospital (AJKMC/IRB/86) from January to June 2023. Written informed consent to participate in the study was taken from each patient. Pregnant women with age between 18 and 35 years, pregnant with a single baby, and those with gestational age not exceeding 40 weeks formed the target study group under the Inclusion criteria. Exclusion criteria involved multiple pregnancies (twins, triplets), known fetal anomalies incompatible with vaginal delivery, a history of uterine surgery (cesarean section, myomectomy), pre-existing medical conditions complicating labor induction (placenta previa, severe preeclampsia), and an inability to undergo transvaginal ultrasound examination or Bishop Score assessment. The sample size of 110 women was calculated using the WHO calculator taking cesarean section rates post-labor induction based on prior research, a significance level (α) of 0.05, and a power of 80%. Data encompassing demographic and clinical information such as maternal age, gestational age, parity, medical history, and obstetric history were gathered from the medical records of patients. Bishop Score and cervical length (CL) were measured by transvaginal ultrasonography before labor induction. TVS was conducted by experienced sonographers using a high-resolution ultrasound machine (GE Voluson E10, 7.5 MHz). CL was measured in millimeters from the inside to the outside, with the participant in the lithotomy position. The average of three consecutive measurements was recorded. The induction methods included the administration of Misoprostol (25 mcg every 4 hours up to 200 mcg total) for cervical ripening and Oxytocin (starting at 1-2 mU/min, titrated based on response) for labor stimulation. Delivery methods included Cesarean section for indications such as fetal distress or failed induction, and Vaginal delivery for successful inductions or spontaneous labor. The indications for labor induction were determined through a comprehensive review of patient records, including gestational diabetes, antepartum hemorrhage, fetal growth restriction, intra-hepatic cholestasis, intra-uterine demise, oligohydramnios, polyhydramnios, post maturity, preeclampsia, and Rh-negative grade through isoimmunization. Bishop Score assessment was performed by obstetricians using standard criteria, evaluating cervical dilation, effacement, consistency, position, and fetal station. Each parameter in the Bishop Score is scored on a scale from 0 to 3. This includes cervical dilation, effacement, consistency, position, and fetal station. Higher scores indicate increased cervical ripeness and a greater likelihood of successful labor induction. The primary outcome of this study is the rate of cesarean section following labor induction, as predicted by transvaginal ultrasound (TVS) measurement of cervical length (CL) and Bishop Score (BS). The secondary outcome was the determination of the predictive value of a cervical length cutoff of >27 mm compared to a Bishop Score of ≤5 for cesarean section following labor induction, as indicated by the superior predictive ability of CL. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated using standard 2x2 contingency tables comparing predicted outcomes (CS or VD) with actual outcomes. Sensitivity was

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the ratio of true positives to the sum of true positives and false negatives, specificity was the ratio of true negatives to the sum of true negatives and false positives, PPV was the ratio of true positives to the sum of true positives and false positives, NPV was the ratio of true negatives to the sum of true negatives and false negatives, and accuracy was the ratio of the sum of true positives and true negatives to the total number of cases. Statistical analysis was done with IBM SPSS 27. Continuous variables were shown as mean ± SD, whereas categorical variables were shown as frequencies and percentages. The Chi-square test compared categorical variables, while the Mann-Whitney U test examined continuous variables. The Kolmogorov-Smirnov Test determined data normality. To evaluate the predictive value of transvaginal ultrasound-measured cervical length for cesarean section after labor induction, we performed a Receiver Operating Characteristic (ROC) curve analysis. The ROC curve was generated using IBM SPSS version 27.0. The ROC curve plots sensitivity (true positive rate) against 1-specificity (false positive rate) at various threshold settings. The Area Under the Curve (AUC) was calculated to quantify the overall ability of the test to discriminate between those who would require a cesarean section and those who would not. An AUC of 1 represents perfect discrimination, whereas an AUC of 0.5 suggests no discriminative ability.

RESULTS

There were 110 participants in the study, with a mean age of 25.9 ± 4.00 years. Most of the participants were 18-25 years old (n=62, 56.4%), followed by 26-30 years (n=37, 33.6%) and 31-35 years (n=11, 10%). The average Bishop Score was 4.53 ± 2.06 and transvaginal ultrasonography indicated 26.6 ± 7.37 mm cervical length. The majority of participants (n=67, 60.9%) were multigravida and had gestational ages ≤ 40 weeks (n=71, 64.5%). Misoprostol induction predominated (n= 72, 65.5%). The overall prevalence of Cesarean Section was 35.5% (Table 1).

Table 1: Study Participant Characteristics and Outcomes (n = 110)

Variables	n (%) / Mean ± SD
Age Groups (Years)	
18-25	62 (56.4%)
26-30	37 (33.6%)
31-35	11 (10.0%)
Age (Years)	25.9 ± 4.00
Bishop Score	4.53 ± 2.06
Cervical Length (mm)	26.6 ± 7.37
Gravida Status	
Multigravida	67 (60.9%)
Primigravida	43 (39.1%)
Duration of Pregnancy	
≤40 Weeks	71 (64.5%)
>40 Weeks	39 (35.5%)
Period of Gestation (Weeks)	
Mean ± SD	39.5 ± 1.69
Method of Induction	
Misoprostol	72 (65.5%)
Oxytocin	38 (34.55)

Out of all the grounds for induction, the most common ones were foetal growth restriction (9.1%), oligohydramnios (10.9%), intrahepatic cholestasis (14.5%), post-maturity (28.2%), and pre-eclampsia (17.3%). Table 2 showed that less common reasons included factors such as intrauterine death (5.5%), Rh-negative status with isoimmunization (5.5%), antepartum haemorrhage (4.5%), polyhydramnios (0.9%) and gestational diabetes mellitus (3.6%) (Table 2).

Table 2: Reasons for Labor Induction among Study Participants

Indications	n (%)
Gestational Diabetes (GDM)	4 (3.6%)
Antepartum Hemorrhage	5 (4.5%)
Fetal Growth Restriction (FGR)	10 (9.1%)
Intra-Hepatic Cholestasis of Pregnancy	16 (14.55)
Intra-Uterine Demise	6 (5.5%)
Oligohydramnios	12 (10.9%)
Polyhydramnios	1 (0.9%)
Post Maturity	31 (28.2%)
Preeclampsia	19 (17.3%)
Rh-Negative Grade Through Isoimmunization	6 (5.5%)

The majority of scores (55.5%) were in the 4-6 range, with 29.1% scoring above 6. With an average BS of 4.53 ± 2.06, fifteen cases (15.5% of the total) had a BS less than four. The cervical length varied between 15 and 44 mm, with 50.9 percent having a CL less than 25 mm, 25.5 percent between 25 and 30 mm, and 23.6 percent greater than 30 mm. The average CL, as shown in Table 3, was 26.6 ± 7.37 mm (Table 3).

Table 3: Distribution of participants according to Bishop score and TVS measurement of cervical length

Variables	n (%)
Bishop Score	
<4	17 (15.5%)
4-6	61 (55.5%)
>6	32 (29.1%)
Cervical Length	
≤25 mm	56 (50.9%)
25.1 to 30 mm	28 (25.5%)
>30 mm	26 (23.6%)

The average ages of women having a caesarean section (CS) and those having a vaginal delivery (VD) were 25.3 ± 4.02 and 26.23 ± 3.98 years, respectively, with a p-value of 0.312. Compared to the VD group, the CS group had a lower Bishop Score (BS) (3.74 ± 2.20 vs. 4.96 ± 1.86, p = 0.005) and higher cervical length (31.1 ± 6.70 mm vs. 24.1 ± 6.53 mm, p < 0.001). The CS group had 53.8% primigravida compared to 31% in the VD group (p = 0.019). The two groups did not differ

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in gestation period (39.3 ± 1.56 weeks vs. 39.6 ± 1.76 weeks, p = 0.355) or induction method (p > 0.05) (Table 4).

Table 4: Comparison of demographic and clinical parameters between cesarean section (CS) and vaginal delivery (VD) groups

Variables	CS (n=39) n (%)	VD (n=71) n (%)	p - value
Age (Mean ± SD)	25.3 ± 4.02	26.23 ± 3.98	0.312[a]
Bishop Score (Mean ± SD)	3.74 ± 2.20	4.96 ± 1.86	0.005[a]
Cervical Length (mm) (Mean ± SD)	31.1 ± 6.70	24.13 ± 6.53	< 0.001[a]
Gravida Status			
Multigravida	18 (46.2%)	49 (69.0%)	0.019[b]
Primigravida	21 (53.8%)	22 (31.0%)	-
Pregnancy Duration			
≤40 weeks	27 (69.2%)	44 (62.0%)	0.446[b]
>40 weeks	12 (30.8%)	27 (38.0%)	-
Weeks of Gestation (Mean ± SD)	39.3 ± 1.56	39.65 ± 1.76	0.355[a]
Method of Induction			
Misoprostol	26 (66.7%)	46 (64.8%)	0.843[b]
Oxytocin	13 (33.3%)	25 (35.2%)	-

[a] Mann-Whitney U test; [b] Chi-square test.

Table 5 presents the cross-tabulation of mode of delivery with Bishop scores of ≤ 5, indicating 32 (29%) true positive cases and 26 (23.6%) true negative cases. Additionally, the table illustrates that a cervical length cutoff of > 27 mm identified 31 (28.2%) true positive participants and 58 (52.7%) true negative participants.

Table 5: Cross-tabulation of the mode of delivery with Bishop score and Cervical length

Variables		Mode of Delivery	
		Cesarian Section (n=39)	Vaginal Delivery (n=71)
Bishop Score (≤5)	Yes	32	45
	No	7	26
Cervical Length (>27 mm)	Yes	31	13
	No	8	58

The strong predictive ability was indicated by the ROC curve analysis for cervical length (CL), which produced an AUC of 0.797 (95% CI = 0.712-0.881, p < 0.001). The overall accuracy was 80.9% with a sensitivity of 79.5% and a specificity of 81.7% when the CL cutoff was > 27 mm. In contrast, Following IOL, the Bishop Score (BS) showed less predictive power for CS, with an area under the curve (AUC) of 0.347 (95% CI = 0.238-0.456, p = 0.008). Comparison of the AUC of both ROC curves highlighted cervical length (CL) as the superior predictor of Cesarean Section (CS) post-induction of Labor (IOL). CL demonstrated higher specificity (81.7% vs. 36.6%), a greater PPV (70.5% vs. 41.6%), and increased overall accuracy (80.9% vs. 52.7%) compared to the Bishop Score (BS). Comparing the two predictors, we found no statistically significant variations in sensitivities (79.5% vs. 82.1%) or NPV (87.9% vs. 78.8%) (Table 6).

Table 6: Comparison of accuracy of bishop score and cervical length for predicting likelihood of cesarean section

Parameters	Formula	Cervical Length (>27 mm)	Bishop Score (≤5)
Sensitivity	$\frac{TP}{TP+FN} \times 100$	79.5%	82.1%
Specificity	$\frac{TN}{TN+FP} \times 100$	81.7%	36.6%
PPV	$\frac{TP}{TP+FP} \times 100$	70.5%	41.6%
NPV	$\frac{TN}{TN+FN} \times 100$	87.9%	78.8%
Accuracy	$\frac{TP+TN}{TP+TN+FP+FN} \times 100$	80.9%	52.7%

Where: TP = True Positives, TN = True Negatives, FP = False Positive, FN = False Negatives

Figure 3 ROC curve illustrates the diagnostic performance of cervical length measurement in predicting cesarean section after labor induction. The y-axis represents sensitivity (true positive rate), and the x-axis represents 1-specificity (false positive rate). The Area Under the Curve (AUC) is 0.797 (95% CI: 0.712-0.881) with a p-value of <0.001, indicating a significant predictive value (Figure 1).

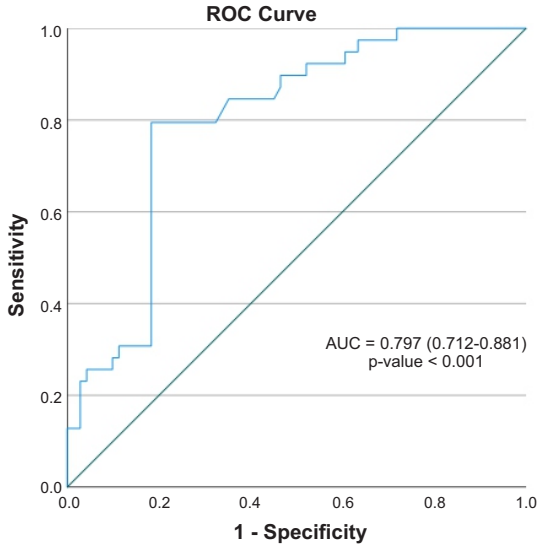

Figure 1: ROC Curve for Predicting Cesarean Section Based on Transvaginal Ultrasound Measured Cervical Length

The ROC curve for the Bishop score-predicted cesarean section is shown in Figure 4. The curve demonstrates the trade-off between sensitivity and specificity for different threshold values. The AUC of 0.347 (95% CI: 0.238-0.466) indicates that the model has limited discriminative ability. The p-value of 0.008 suggests that the model's performance is significantly different from random guessing, although the overall performance is poor. The x-axis represents 1–Specificity1–Specificity (also known as the False Positive Rate). The y-axis represents Sensitivity (also known as the True Positive Rate). Both axes are unitless as they represent proportions or probabilities ranging from 0 to 1 (Figure 2).

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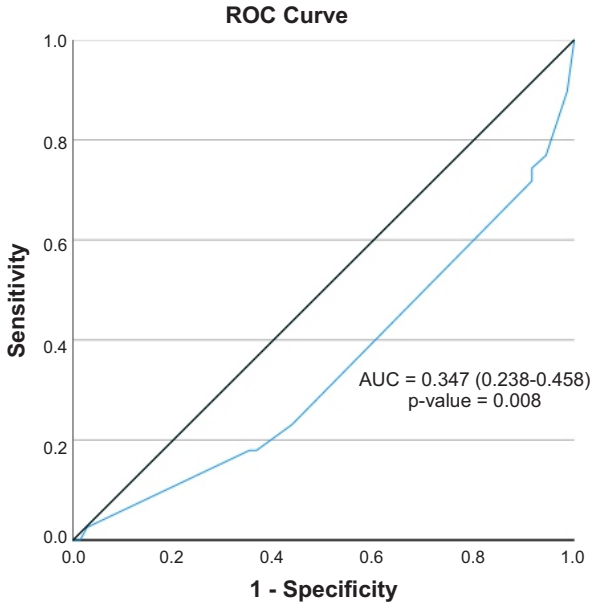

Figure 2: Bishop Score-Predicted Cesarean Section ROC Curve

DISCUSSION

In Cesarean sections following induction of labor, TVS (transvaginal ultrasound) of cervical length (CL) provides crucial insights into cervical readiness, aiding in assessing the feasibility of vaginal delivery. Adding CL measurements to the Bishop Score improves the accuracy of the decisions to be taken to get the best deliveries possible [10]. In the primary findings of our study, the average age of the respondents was 25 years. 60% of them are within the ages of 18-25 years, whereas the rest is equally distributed within the remaining age bracket of the next three decades. This stands in agreement with what Sinha *et al.*, conducted, which stated that the mean age was 25 years. Years of work was 56 years and the majority of them were in the age group of 20-25 years (56.7%) [11]. Nikbakht *et al.*, however, reported a slightly lower mean age of 25.5±4.4 years among their participants. Regarding gravidity, our study predominantly included multigravida participants (60.9%), which is consistent with the findings of Nikbakht *et al.*, where 59.5% of the participants were nulliparous [12]. Sinha *et al.*, reported a higher proportion of multigravida participants (57.5%) compared to primigravida and grand multigravida individuals. Interestingly, our study had a higher percentage of participants with a gestational age of ≤ 40 weeks (64.5%) compared to Sinha *et al.*, findings. The prevalent use of misoprostol for induction in our study (65.5%) aligns with their observation of 65.8%. In our analysis, 28.2% of inductions were for post-maturity, which is consistent with Sinha *et al.*, findings (28.3%). Additionally, our study's mean cervical length of 26.6 ± 7.37 mm is comparable to Nikbakht *et al.*, median cervical length of 24.5 ± 7.9 mm among pregnant women undergoing pregnancy termination [11, 12]. Both our study and Sinha *et al.*, found a predominant proportion of cases with a Bishop score falling within the moderate range (55.5% and 55.8%, respectively), indicating moderate cervical readiness. Similarly, a comparable percentage of cases had a cervical length of 25 mm or less (50.9% in our study, 51.7% in Sinha *et al.*, suggesting potential challenges in induction[11,12]. In our study, mean ages were comparable between Cesarean Section (CS) and Vaginal Delivery (VD) groups (25.3 ± 4.02 years vs. 26.23 ± 3.98 years, p = 0.312), whereas Kamran *et al.*, found a significant higher mean age in the CS group (30.21 ± 4.55 years) compared to the VD group (28.32 ± 4.87 years). Additionally, our CS group had a significantly lower Bishop Score (BS) compared to the VD group (3.74 ± 2.20 vs. 4.96 ± 1.86, p = 0.005), contrasting with Kamran *et al.*, findings of a higher mean cervical length in the CS group (27.95 ± 7.24 mm) compared to the VD group (24.85 ± 7.68 mm). Both studies reported a higher proportion of primigravida in the CS group, reflecting potential obstetric risk factors [13]. The findings of the current study align with Kamran *et al.*, who reported 48% true positive and 13.74% true negative patients using a Bishop Score > 5. In contrast, cervical length with a cutoff of < 27 mm showed higher true positives (53.43%) and true negatives (22.14%). Similarly, our study found cervical length (CL) to be a better predictor, with an AUC of 0.797, 79.5% sensitivity, 81.7% specificity, 70.5% PPV, and 87.9% NPV, compared to the Bishop Score (BS) with lower predictive power (AUC of 0.347). Kamran et al., also noted higher sensitivity (87.5% vs. 80.0%) and specificity (56.86% vs. 35.29%) for CL, reinforcing that CL is more accurate for predicting successful labor induction [13]. Our study's findings regarding cervical length corroborate those of the Al-Adwy *et al.*, study where the mean cervical length was significantly lower in women with successful induction of labor (28.76 ± 3.93 mm) compared to those with unsuccessful induction (34.67 ± 2.40 mm). This consistency underscores the clinical significance of cervical length as a predictive factor in labor induction outcomes [14]. Current study found no significant associations between maternal age, gestational duration, or induction method with delivery mode. However, a notably higher cesarean rate was observed in primigravida (48.9%) compared to multigravida (27.4%), consistent with findings by Cubal *et al.* This underscores parity's influential role in determining delivery mode, warranting further investigation for tailored obstetric management strategies [15]. Using a Bishop Score (BS) cutoff of ≤ 5, we observed 82.1% sensitivity, 36.6% specificity, 41.6% PPV, 78.8% NPV, and 52.7% accuracy. In comparison to Hafeez *et al.*, our study demonstrated higher specificity (81.7% vs. 59%) and NPV (87.9% vs. 80%) for CL, indicating its enhanced ability to correctly identify cases not requiring CS following IOL [16]. Agrawal *et al.*, reported lower sensitivity (67.57%) and specificity (65.38%) for BS, contrasting with our findings

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for both predictors [17]. Similarly, Wajid *et al.*, showed inferior specificity (58.9%) and PPV (76%) for CL compared to our study, suggesting variations in predictive performance across different populations [18]. Our study supports findings from Iftikhar *et al.*, who noted that TVS outperforms the Bishop Score in predicting successful labor induction, with TVS showing higher accuracy and F1 Score. Similarly, Chauhan *et al.*, reported that cervical length is more predictive of successful induction compared to the Bishop Score, a result consistent with our higher sensitivity and specificity for cervical length [19, 20]. In contrast to Bahadori *et al.*, who found the Bishop Score to have higher sensitivity (77%) and lower specificity (56%) compared to cervical length (66% sensitivity, 76% specificity), our study found cervical length to be superior overall, with an accuracy of 80.9%, sensitivity of 79.5%, and specificity of 81.7% [21]. Study strengths include the robust sample size, precise methodology adhering to standardized protocols, and comprehensive analysis employing receiver operating characteristic (ROC) curve assessment. Study limitations involve the lack of diversity in the study population and limited generalizability to different healthcare settings.

CONCLUSIONS

Our study found that transvaginal ultrasound (TVUS) measurement of cervical length (CL) >27 mm demonstrated superior predictive ability for cesarean section (CS) following labor induction compared to the Bishop Score (BS) ≤5. This highlights the potential of CL measurement as an objective, reliable tool for better predicting CS likelihood and optimizing labor induction decisions.

Authors Contribution

Conceptualization: NS
Methodology: HP, NS, RA, SK
Formal analysis: IA, SH
Writing review and editing: HP

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Clinical Study of the Manifestations of Diabetes Mellitus in Oral Cavity

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ABSTRACT

Diabetes Mellitus, a chronic illness affecting all ages, contributes to worldwide mortality and morbidity. Oral consequences of diabetes are less well-documented than microvascular and macrovascular issues. It's been called a growing endemic disease. About 285 million people worldwide have diabetes. **Objectives:** To enhance the understandings of oral signs and the complications associated particularly with Diabetes Mellitus. **Methods:** Patients aged 40 to 75 were included in the study without gender discrimination All patients were known diabetic (NIDDM) and having the disease from at least last 7 years. clinical values and labs (RBS and HbA1C were taken to assess the control level of the disease) were taken from their record files. **Results:** Family history of non-idiopathic diabetic retinopathy (NIDDM) was found in (59.44%) of the population. NIDDM caused oral lesions in close to (79.34%) of individuals. 13 patients presented with white lesions. Buccal mucosa remained the most common site of involvement, with desquamative gingival involvement in 3 patients. Oral Lichen Planus was seen in 13 patients (2.53%). Halitosis in 309 patients (60.23%), Mild xerostomia in 184 patients (35.87%), tooth mobility>2mm was found in 106 patients (20.66%), Angular Cheilitis seen in 51 patients (9.94%), and oral ulcers / RAS were reported in 117 patients (22.81%). **Conclusions:** NIDDM can cause oral mucosal pathologies. Routine dental screenings and early detection of these alterations may improve oral health, medication adherence, and problems in afflicted persons.

INTRODUCTION

The endocrine condition known as diabetes is characterized by an abnormal metabolism of carbohydrates, protein, glucose, and fat or lipids. Diabetes is a condition that does not ever go away [1]. The inability to either produce or respond to insulin is the hallmark of this disease, which is characterized by persistently high levels of glucose in the bloodstream. These levels, if allowed to remain elevated for an extended period of time, have the potential to cause damage to a number of vital organs in the body, including the kidneys, blood vessels, nerves, and heart. Idiopathic diabetic retinopathy (IDDM) and non-idiopathic diabetic retinopathy (NIDDM) are the two primary types of diabetes [2, 3]. IDDM, also known as Type 1, is a form of diabetes that first manifests itself in infants or young children and accounts for approximately 10 to 15 percent of all patients who are diagnosed with diabetes mellitus. This is because to the elimination of beta islets of Langerhan cells in the pancreas, which is caused by an autoimmune response. Diabetes mellitus type 1 (NIDDM), also known as adult-onset diabetes, is a form of diabetes that is more prevalent and recurrent [4]. A wide variety of oral manifestations have been observed in patients who are medically compromised, according to the findings of a number of researchers. Individuals who have diabetes that is not under control are at a greater risk of developing certain infections, such as fungal and viral infections, which are essential to the consequences of hyperglycemia that has been present for a long time. To achieve the goal of achieving a world free of diabetes and obesity by the year 2025, everyone is fully committed to meeting this objective

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[5, 6]. Problems can arise in many different parts of the body, including the mouth, when blood sugar levels remain consistently high for an extended period of time. As a consequence of this, it is possible to effectively avoid these consequences by maintaining proper control of the levels of glucose in the blood. There are a number of potential mechanisms that are associated with diabetic oral complications. Some of these mechanisms include hypoxia, microangiopathy, neuropathy, microvascular changes, increased glucose levels in saliva, dehydration, and impaired neutrophil function (chemotaxis steps) [7]. It is possible for this kind of infection to take place when the pH is low and the saliva is low. SIAG, C-reactive protein, serum amyloid A, interleukin-6, cortisol, and sialic acid alpha-1 acid glycoprotein are inflammatory indicators related with NIDDM. For this reason, the sick note should include oral symptoms [8]. Xerostomia, tooth and root caries, periodontal lesions, gingivitis, gum disease, oral candidiasis, B.M.S., altered taste feelings, oral lichen planus, recurrent aphthous a condition called raised infection risk, and poor wound healing following minor oral surgical procedures are all oral manifestations and complications that can respond to D.M. High blood sugar levels, both in terms of length and intensity, are often connected with the severity of diabetic complications [9, 10]. The diagnosis of Diabetes Mellitus is established by examining blood glucose levels. For F.B.S. levels> 126mg/dl or R.B.S. levels > 200mg/dl, the diagnosis of D.M. is established, cemented by a HbA1C level > 6.4%. A normal HbA1C level is below 5.7%. 5.7% to 6.4% suggests prediabetes, whereas levels greater than 6.5% indicate diabetes. The bigger the HbA1C with pre-diabetic readings, the greater is the chance of developing NIDDM [11].

This study aimed to increase our understanding of oral symptoms and the repercussions that are frequently linked with diabetes mellitus that does not depend on insulin.

METHODS

This descriptive study was comprised of 513 patients. The data were collected over a time period of 11 months Feb 2023-Dec 2023. Ethical review board of CIMS Dental College Multan approved research on with (Ref no 786/CDC-20MDC/IRB 2-07). All patients were known diabetic (NIDDM) and having the disease from at least last 7 years. Patients aged 40 to 75 were included in the study without gender discrimination. Also patients who regularly used oral stimulants such as pan, betel nut, snuff, tobacco, or alcohol were excluded. Their clinical values and labs (RBS and HbA1C were taken to assess the control level of the disease) were taken from their record files. Patient details encompassing demographic data, oral hygiene practices, and past medical and dental history were documented. Examination was conducted using a mouth mirror and CPITN probe. All oral anatomical sites (soft and hard tissues including lips, gingiva, tongue, alveolar bone, dental tissues and palate) were examined, and relevant information was recorded. Consent of the patients was obtained and appointment for biopsy was given. After successfully managing diabetes mellitus, the patient's physician gave their authorization for the biopsy to be taken. In order to administer the local anesthetic solution, the patient was positioned in a dental chair and instructed to sit still. Injecting 0.2% lidocaine around the biopsy site allowed for precise histological analysis. The buccal mucosa was then carefully removed using tissue forceps after a tiny section had been sliced with a Bard-Parker blade. The tissue was fixed in a 10% formalin solution after the biopsy site was sutured. The standard protocols were used to prepare 5µm paraffin slices from the tissue. The sections were stained using the H and E procedure, which stands for hematoxylin and eosin. Statistical test was applied to check oral manifestation in gender, which was determined by analyzing the data using SPSS software version 27.0 for comprehensive elaboration and comparison. In order to show the data, the mean and standard deviation were utilized.

RESULTS

Out of 513 patients in studies, 193 were male (37.62%), and females 320 were (62.38%). The male-to-female ratio was 1:1.66 The Mean age of patients was 54.16 years with an age range of 50-80 years. The study revealed that 383 patients (74.66%) had poor oral hygiene, 96 patients (18.71%) had moderate oral hygiene, and only 34 patients (6.63%) had good oral hygiene. Family history of NIDDM was found in 59.4% of the population. NIDDM caused oral lesions in close to 79.34% of individuals (Table 1).

Table 1: Demographics of the Enrolled Cases

Variables	Frequency (%)
Male	193
Female	320
Total	513
Mean Age (Years)	54.16
Oral Hygiened	
Poor	383 (74.66%)
Moderate	96 (18.71%)
Good	34 (6.63%)
Family History of NIDDM	
Yes	305 (59.4%)
No	208 (40.6%)
Oral Lesions	
Yes	407 (79.34%)
No	106 (20.66%)

It was found that, mean HbA1c was 7.6%, mean RBS was 201.15 mg/dl and mean RBS was 177.13mg/dl. These findings indicated that presence of DM in patients (Table 2).

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Table 2: Blood Glucose Levels among Presented Cases

Variables	Mean Value
HbA1c %	7.6%
RBS mg/dl	201.15
RBS mg/dl	177.13

Different oral mucosal lesions were present as an effect of NIDDM in 407 patients (79.33 %). 13 patients presented with white lesions. Buccal mucosa remained the most common site of involvement, with desquamative gingival involvement in 3 patients. These lesions were regarded as Oral lichen planus (OLP) or Lichenoid drug reactions (LDR) based on their clinical presentations and the long-term history of drug intake (oral hypoglycemics). The oral pathologist studied the microscopic examination of 6 cases to confirm them as an erosive type of OLP., and three as a reticular type. Four patients refused h/p (Table 3).

Table 3: Oral Manifestations of NIDDM

Oral Manifestations	Male	Female	Total
	N 193 (%)	N 320 (%)	N 513 (%)
Oral Mucosal lesions	39 (7.61)	67 (13.1)	407 (79.33)
OLP	8 (1.55)	5 (1)	13 (2.53)
Chronic Periodontitis	147 (28.65)	81 (1.58)	228 (44.44)
Oral Candidosis	17 (3.31)	21 (4.1)	38 (7.41)
Dental Caries	60 (11.69)	67 (13.1)	127 (24.76)
BMS	0 (0)	58 (11.31)	58 (11.31)
Delayed / Defective Healing	11 (2.14)	32 (6.24)	43 (8.39)
Hallitosis	193 (37.62)	116 (22.61)	309 (60.23)
Mild Xerostomia	47 (9.16)	137 (26.7)	184 (35.87)
Tooth Mobility	63 (12.28)	43 (8.38)	106 (20.66)
Angular Cheilitis	23 (4.48)	28 (5.46)	51 (9.94)
RAS	43 (8.38)	74 (14.42)	117 (22.81)

Chronic periodontitis (pocket depths >4mm with bleeding gums and Halitosis) was found in 228 patients (44.44%), oral candidiasis was seen in 38 patients (7.41%), significant dental caries was reported in 127 patients (24.76%), burning sensations /BMS was present in 58 patients (11.31%), defective or delayed wound healing after minor oral surgical procedures was found in 43 patients (8.39%), Oral Lichen Planus was seen in 13 patients (2.53%). Halitosis in 309 patients (60.23%), Mild xerostomia in 184 patients (35.87%), tooth mobility>2mm was found in 106 patients (20.66%), Angular Cheilitis seen in 51 patients (9.94%), and oral ulcers / RAS were reported in 117 patients (22.81%). One patient had multiple findings in these results (Figure 1).

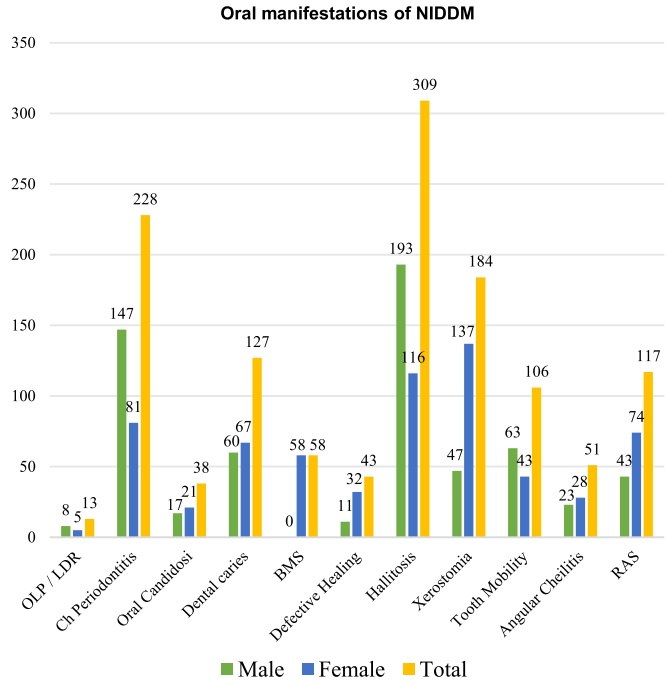

Figure 1: Oral Manifestation of NIDDM with respect to Gender

DISCUSSION

There are over 537 million diabetic patients worldwide, almost 1 in every 10 individuals. Even this number is expected to rise up to over 643 million in 2030. Being a developing country with limited resources, Pakistan ranks at number 3 in global diabetes prevalence. Over 19 million people are living with diabetes in Pakistan. Diabetes Mellitus comprises a range of metabolic disorders that impact nearly every part of the body, including a wide range of presentations in the oral cavity, affecting oral mucosal linings. In the current study, the Mean age of patients is 54.16 years, with the age group of 40-75 years. Bastos [10] and co-workers from Brazil reported the mean age of NIDDM patients as 50.3 years. In another study from Pakistan, the mean age of D.M. is 53.1 years, aged 40-70 [11]. The global disparities in such data occur due to geographical differences, other environmental factors like diet and lifestyle, and the health awareness facilities available. In addition, this difference may also be because we have included a wide range of mucosal lesions in the oral cavity in the study and not any single entity [12]. Advanced glycation end products are formed in hyperglycemia, which is characterized by chronically elevated blood sugar levels. Substances (A.G.E.s) in the tissues and other metabolic disorders [13]. The mouth and teeth are vulnerable to the unanticipated consequences of these A.E.G.s. Delays in wound healing occur when fibroblasts, which are responsible for periodontium repair, connect with A.G.E.s in an environment with high glucose levels, rendering them unable to repair the damaged collagen [14, 15]. As a result, periodontal support is compromised and teeth become

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more mobile, and bone resorption and collagen fiber breakdown occur. Periodontal tissues are more susceptible to infections when blood sugar levels are high (hyperglycemia), which causes oxidative stress to build up. The inflammation in periodontal tissues, which is characteristic of periodontitis, is worsened by diabetes since the disease is intrinsically pro-inflammatory. This is demonstrated by elevated levels of reactive oxygen species (ROS) and inflammatory cytokines [16-20]. Because of both the disease itself and the medications used as oral hypoglycemics, there is a strong correlation between oral lichen planus and lichenoid drug reactions in patients with diabetes mellitus [21-23]. Nevertheless, additional research is need to confirm the connection and associations. The sixth main consequence of poorly controlled diabetes in both NIDDM and IDDM patients is aggressive periodontitis, which is now widely acknowledged.

CONCLUSIONS

Dental issues and oral mucosal problems are significant yet often overlooked complications of diabetes, which escalate with the duration and management of the condition. Regular dental check-ups for routine screening and prompt identification of these changes can enhance oral health, promote adherence to drug therapy, and mitigate complications in affected individuals. Additional research, in collaboration with physicians and endocrinologists, and thorough examinations are necessary to ascertain the precise types and frequency of dental issues related to diabetes. Moreover, evaluating the management of diabetes alongside periodontal disease treatment is essential.

Authors Contribution

Conceptualization: MTK, BK

Methodology: BK

Formal analysis: MH, SN

Writing, review and editing: EH, AN

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Perceived Stress and Its Physical Presentation During Exam: A Study of Central Park Medical College

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ABSTRACT

Stress during examination is a global issue. Researches show that the physical impact of stress includes various clinical symptoms and diseases. This study was designed to analyze the clinical presentation of stress in medical students during professional examination and the coping strategies practiced by them. **Objective:** To evaluate the causes of stress during exams and its physical presentation in medical students. **Methods:** A cross-sectional survey was conducted at Central Park Medical College, from November 2022 to February 2023. A validated questionnaire was used as a data collection tool. Medical students from 1st year to the 4th year of the age group 18 to 25 years were selected using the convenient sampling method. The data were transcribed into SPSS version 26.0. The significance of the results was decided at a p-value of ≤ 0.05. **Results:** The most frequent clinical symptom during stress was fatigue, followed by headache. These symptoms varied significantly among male and female students ($p \leq 0.05$) for headache, tense muscles, depression, and decreased blood pressure. The portion regarding coping mechanisms exercised by students during stress, revealed religious activities (35%) followed by music (22%) and sleep (18%) respectively. The study also revealed that the biggest support medical graduates get during stress is from their friends (45%). **Conclusions:** This study concluded that the main cause of stress during professional exams is fear of disappointing parents. This stress presents in the form of physical symptoms like excessive fatigue, headache, and anxiety. Where the support system during this time is friends for most respondents, the most commonly exercised coping mechanism is performing religious activities.

INTRODUCTION

Stress during examinations or assessments is a global issue with alarming statistics showing high suicide attempts during exams, in many developed countries of the world [1]. It is the emotional disturbance that is experienced by students during test preparation and test-taking situations. Since medical studies are considered among the most difficult ones, the exam stress is also very severe. It leaves many adverse effects on the mental as well as physical health of students [2]. During their studies, many medical students may face a variety of academic and personal obstacles, but little data are available about their experiences. The influence of stress, involvement in school, and how they relate to medical students' general well-being is concerning. A study conducted by Buch *et al.*, on school-going children in Surat city of India, documented the factors that lead to examination stress. The findings revealed that anxiety, dread of forgetting, nervousness, and fear of failure in exams were the most prevalent stressors [3]. Research shows that the physical impact of stress includes headaches, weight issues, disturbance of the menstrual cycle, and sleep disorders [4-7]. Some studies have proven its impact on mental health, including attention deficit disorder, anxiety, depression, fear, eating disorders, etc [8]. Exam stress is often accompanied by the triad of cynicism, helplessness, and burnout. A cynical attitude has a negative outlook on one's studies, peers, teachers, and patients. According to a study that was conducted in 2021, medical students were found to have a

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higher prevalence of burnout compared to students in other educational courses [9]. The emotional anguish and health problems, as well as the loss of time, energy, and money, are just some of the personal, psychological, and financial effects that are relevant as a result of exam stress, burnout, and dropping out among medical students [10]. Another variable of significance regarding exam-induced anxiety is the "coping mechanism" chosen by students. According to research, these coping strategies can be divided into adaptive and maladaptive ones. Adaptive coping strategies include seeking assistance, knowledge, and support from others, acknowledging, scheduling, and redefining problems with levity or faith. Student participation in school is mostly associated with adaptive coping. Non-adaptive coping strategies include distraction, disassociation, self-pity, denial, and drug abuse. Non-adaptive coping strategies are linked to burnout [11]. Spending time with close companions has an adverse association with fatigue, burnout, and general distress manifested as depression and anxiety [12]. It is reasonable to anticipate that not all coping methods will be equally efficient in the management of stress. Some coping techniques might be beneficial to one's health (adaptive), whereas maladaptive coping approaches can be harmful to one's health [13]. The curriculum and workload of medical education is stress provoking. Despite being aware of the causes and consequences of stress and anxiety on their physical and mental health, medical students are still most prone to it. Therefore, awareness of the matter is very important, along with an analysis of the factors leading to it and the actual effects of exam stress on mental and physical health, to come up with ways to prevent it. The rationale of the study was to identify different presentations of stress so that it can be identified earlier and addressed with appropriate help and support.

This study aimed to analyze the causes and symptomatic presentation of stress experienced during professional examination by medical students of Central Park Medical College and its impact on the individual's mental and physical health as well as the coping strategies practiced by them.

METHODS

A cross-sectional survey was conducted at Central Park Medical College, from November 2022 to February 2023. This study was approved by the Institutional Review Board of Central Park Medical College (CPMC/IRB-No/1368). The sample size was calculated as 329, using the WHO sample size calculator, and for better accuracy of results, more data were collected than the calculated sample size. A total of 298 medical students of MBBS from 1st year to 4th year, age group 18 to 25 years were selected using the convenient sampling method. Participants outside of the age group and students of other allied health sciences, graduates, and post-graduates were not included in the study. The participants were explained the aim of the research and written as well as verbal consent was obtained. The perceived stress scale and Stress symptoms-frequency assessment scale were modified by adding the possible causes of stress for a medical college undergraduate student, validated with a cronbach alpha of 0.84, and was distributed among the participants to assess the causes and clinical symptoms experienced during their professional examinations as well as the coping strategies practiced by them. The data were collected during the preparatory leave of respective exams, after the completion of the session when students were preparing and appearing in their final professional exam. The questionnaire was divided into three sections. The first part estimated the stress level of respondents according to the standard perceived stress scale [14]. At the end of the section, the score was calculated by adding the selected value against each item. Score 0-13 was considered low stress, 14-26 was considered moderate while score 27-40 was considered high perceived stress. The second component evaluated the symptomatic manifestations in the students during the exam stress [14]. The list included a total of 20 different symptoms on a Likert scale from 0-4 with 0 as never, 1 as rarely, 2 as sometimes, 3 as often, and 4 as very often. The third section evaluated the coping mechanisms and emotional support for medical students. Microsoft Excel was used to organize the data, and the software Statistical Package for Social Sciences (SPSS) version 26.0 was used to perform the analysis of the data. Statistical significance was set at P value ≤ 0.05. For descriptive analysis, data were assessed and presented in the form of frequency and percentage, and the results are presented in the form of tables and figures. The data on the Likert scale were presented as mean scores. The statistical significance between the mean scores in both genders was compared by using non-parametric tests like chi-square and Mann-Whitney U test.

RESULTS

A total of 60 students from 1st year, 59 students from 2nd year, 91 students from 3rd year, and 88 students from 4th year participated in the research. Among 298 students, 187 (62.75%) students were female, and 111 (37.24%) students were male (Table 1).

Table 1: Demographic Data of Research Participants

Parameter	1st year	2nd year	3rd year	4th year
Male	15	20	30	46
Female	45	39	61	42
Total	60	59	91	88
Average Age	20.0	20.8	21.8	24.2
Average Weight	60.4	61.6	63.1	69.9

The stress levels of students were calculated by using the perceived stress scale. Score 0-13 was considered low

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stress, 14-26 was considered moderate while score 27-40 was considered high perceived stress (Table 2).

Table 2: Perceived Stress Scale Score in Both Genders

Score	Total	Males	Female
0-13 (Low Stress)	0	0	0
14-26 (Moderate Stress)	145 (49%)	54 (48%)	91 (49%)
27-40 (High Stress)	153 (51%)	59 (52%)	94 (51%)
Total	298	113	185

The most common symptom is fatigue with the highest mean of 3.76 whereas in gender vise observation the most common symptom in male is fatigue, followed by anxiety and headaches. In female, the most common symptom is fatigue followed by anxiety headache, depression, and tense muscles (Table 3).

Table 3: Mean Scores and Gender Distribution of Clinical Symptoms of Stress in Undergraduate Medical Students

Symptoms	Mean Score (Likert Scale)	Mean Score in Male	Mean Score in Female	p-Value
Headache	3.36	1.87	2.17	≤0.05*
Tense Muscles	3.42	1.77	2.06	≤0.05*
Fatigue	3.76	2.23	2.42	≥0.05
Diarrhea	1.91	0.97	1.03	≥0.05
Cramps	1.41	1.32	1.46	≥0.05
Flatulence	1.56	1.02	.93	≥0.05
Constipation	.96	.86	1.01	≥0.05
Weight Gain	1.02	1.06	.99	≥0.05
Weight Loss	1.04	.92	1.12	≥0.05
Increased BP	1.33	1.23	1.13	≥0.05
Decreased BP	1.07	.80	1.24	≤0.05*
Restlessness/Tics	1.83	1.72	1.89	≥0.05
Anxiety/Phobias	2.18	2.14	2.20	≥0.05
Irritability	1.99	1.86	2.07	≥0.05
Difficulty Falling Asleep	1.79	1.75	1.81	≥0.05
Insomnia	1.61	1.57	1.63	≥0.05
Excessive Sleep	2.09	1.83	1.58	≥0.05
Anger/Hostility	1.91	1.85	1.95	≥0.05
Depression	2.03	1.86	2.13	≤0.05*
Eating Too Much	1.73	1.68	1.76	≥0.05
Eating Too Little	1.23	1.15	1.27	≥0.05

*significant difference between the two genders

Religious activities were the most commonly practiced coping mechanism followed by listening to music and sleep (Figure 1).

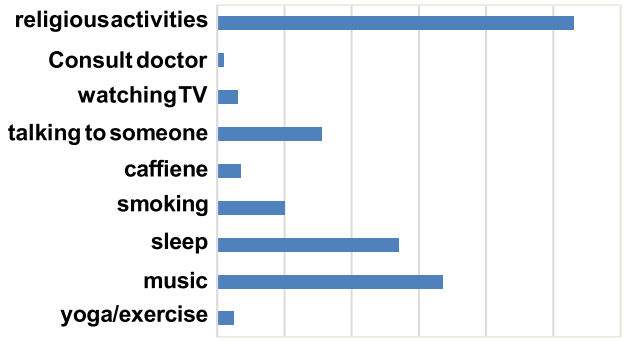

Figure 1: Frequency Distribution of Coping Mechanisms Adopted to Relieve Stress

When asked about the human support during stress, most common source was friends, followed by parents and siblings (Figure 2).

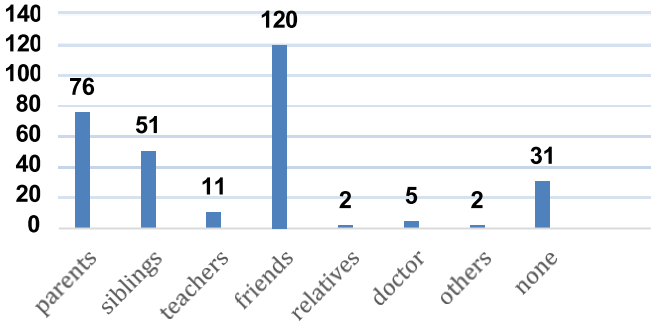

Figure 2: Frequency Distribution of Support Sources During Stress

DISCUSSION

Medical studies are considered stressful due to the expanse of syllabus and the depth and significance of material to be learned. The examination process is also rigorous and nerve racking. According to a study conducted in the Middle east, by Ragab *et al.*, the estimated prevalence of stress in medical students is up to 31.7% ($p < 0.05$) [15]. This study aimed to examine the etiology and clinical presentations of stress among medical students during professional examinations, and its effects on their mental and physical well-being. Additionally, the study sought to explore the coping mechanisms employed by these students. Similar studies have been conducted in the past on students of different fields. In 2021, a descriptive cross-sectional survey was carried out at Pakistani Medical Colleges, and the results revealed that stress, anxiety, and depression were quite common among medical students. Undergraduate medical students had depression in 67.4%, anxiety in 62.6%, and stress in 72.5% of cases. Compared to men, women were more likely to experience stress, anxiety, and depression [16]. Psychological diseases like anxiety and depression, in addition to physiological issues like high blood pressure and delayed wound healing, can all be influenced or caused by stress. Among physical issues brought on by stress, the most common complaint was a persistent headache, as reported by 84.5% of the

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participants of a study [17]. Gender was shown to be significantly associated in a comparative analysis with disrupted sleep, breathing difficulties, persistent headaches, and muscle pains; on the other hand, there was a significant relationship between age and weight increase, TMJ discomfort, and oral cavity ulcers. Age and weight increase were shown to be significantly correlated by regression analysis [17]. This is very similar to current research which showed that exam stress leads to headache, fatigue, diarrhea, depression and many other serious complications. The purpose of present study was to highlight the effects of exam stress on body and understand how young generation deals with it so that it could be controlled and dealt at an administrative level. If we as educationists, fail to comprehend the significance of it, this stress is proven to be potent enough to lead to suicidal attempts by medical students [18]. Research conducted has shown that suicide rates among medical students are sharply rising. Numerous factors, such as exam failures, rejection from desired subjects or institutions, bullying, sexual abuse, life dissatisfaction, bullying, depressive disorders, psychological disorders, family issues, parental separation, forced subject selection, pressure from teachers, an overwhelming workload of coursework, the actions of teachers, and numerous other factors, are forcing students to consider suicide. It's not only alarming but highly disturbing to consider that the burden of studies can cause enough stress to influence young brains to end their own lives. This study reflects that students consider help from their family & friends, to ease their trouble yet many students never seek help. Around 40% of participants in this research said that their friends were their biggest support system. This is probably because they are going through similar situations and can understand each other better as compared to others. This indicates that parents and teachers need to develop a more empathetic relationship with the children so that they can seek guidance and strength from them. This will also help in relieving the cause of stress in the students as the main fear or stressful factor for students during exams was that they were afraid of disappointing their parents. Research proved that Systems of passing and failing grades as well as long-term, collaborative learning strategies supported by peers seem to be beneficial for students' overall wellbeing. Furthermore, engaging in fulfilling hobbies, building social support systems, and strengthening resilience can help medical students feel less distressed on a personal level. To ensure student welfare, faculty and administrative development is equally essential [19]. This study provides a solid basis for policy-makers in the medical field to improve present assessment practices while simultaneously boosting the well-being of students. Rigorous interventions in the medical curriculum, teaching methodology, grading system, and development of student support system can help reduce the stress and associated illnesses to a great extent and overall student performance may also improve [20]. Instead of concentrating efforts on achieving success in exams and making progress, it is necessary to first establish a level of trust with students and then collaborate with them to improve their sense of who they are and how they engage with their education.

CONCLUSIONS

The main cause of stress during professional exams is fear of disappointing parents. This stress presents in the form of physical symptoms like excessive fatigue, headache, and anxiety. Where the support system during this time is friends for most respondents, the most commonly exercised coping mechanism is performing religious activities. There is a need for further research to broaden the sampling and expand its coverage beyond medical institutions to include groups from other educational fields.

Authors Contribution

Conceptualization: K
Methodology: MM, FA, LG
Formal analysis: MM, FA
Writing-review and editing: K, MM

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of Therapeutic Outcomes: Two Triple-Therapy Approaches for *H. pylori* Eradication in Gastric Ulcer Disease

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ABSTRACT

Gastric ulcer is a prevalent digestive disease, primarily caused by *Helicobacter pylori* infection. *H. pylori* infection poses a substantial challenge for medical practitioners due to increased antibiotic resistance. **Objectives:** To compare the efficacy of a 14-days clarithromycin-based triple therapy (TRT) with a moxifloxacin-based TRT for eradicating Helicobacter pylori in gastric ulcer disease. **Methods:** A quasi experimental study was conducted with 294 positive *H. pylori* patients divided into two groups. Group A was given standard triple therapy while Group B received moxifloxacin-based triple therapy. Data collection commenced after obtaining IRB approval and informed consent from all participants. Descriptive statistics was used to calculate frequency and percentages. Differences between the two groups were compared using the fisher exact analysis at a significance level, p-value < 0.05. **Results:** In the group with standard triple therapy (TRT), the eradication rates of *H. pylori* were reported as 67.3 % intention-to-treat (ITT) and 76.1% per-protocol (PP) analysis. In contrast, in the moxifloxacin-based triple therapy (MAO) group, the eradication rates were 86.3% ITT and 92.7% PP analysis. The eradication rates with moxifloxacin-containing triple therapy were statistically significant than standard TRT (p = 0.001). Furthermore, few side effects were evident in the moxifloxacin TRT group (p < 0.001) compared to the standard TRT group. **Conclusions:** In Pakistan, moxifloxacin-containing triple therapy may offer a notably superior treatment option for eradicating *H. pylori* infection compared to standard triple therapy.

INTRODUCTION

Gastric ulcer is a prevalent digestive disease, impacting more than half of the global population [1]. It is usually caused by a *Helicobacter pylori* infection and is marked by the presence of ulcers on the inner lining of the stomach [2]. *H. pylori* infection is an issue of global significance prevailing all over the world. The global prevalence of *H. pylori* is nearly 50%, with more cases observed in developing countries [3]. Due to improved sanitary conditions, the rate is changing in developing countries like Pakistan [4]. H. pylori infection is transmitted through feco-oral route and its prevalence in Pakistan amounts to 22% according to recent research [5]. Gastric ulcer primarily impacts middle-aged and elderly individuals, causing symptoms like loss of appetite, weight loss, stomach pain, and a sensation of fullness after meals. Without prompt treatment, gastric ulcers can lead to serious complications, such as gastric perforation and bleeding, which can be life-threatening [6]. The incidence of gastric ulcers has risen due to dietary and lifestyle changes. Contributing factors include consuming strong tea, *Helicobacter pylori* infection, smoking, using non-steroidal anti-inflammatory drugs, and alcohol consumption [7]. The main symptoms consist of stomach discomfort, stomach pain, loss of appetite, and occasional indigestion. In gastric ulcer disease, patients may experience symptoms such as hematemesis (vomiting

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blood), bloating, belching, and vomiting which can harm their health and lower the quality of life [8]. In Pakistan, the reported prevalence of *H. pylori* varies widely, ranging from 50% to 90% across different regions [9]. Although *H. pylori* shows in vitro sensitivity to several antibiotics, it is challenging to treat the infection in vivo with a single antibiotic. This difficulty is attributed to the bacterium's residence in the low pH environment of the mucinous layer [10]. Clarithromycin, with an efficacy rate of 40% against *H. pylori* is considered as best therapeutic approach. The combination of two antibiotics along with a proton pump inhibitor offers improved eradication by producing a synergistic effect [11]. Antibiotic resistance is the foremost important reason for the failure to eradicate the infection nowadays. The highest resistance rate is reported for clarithromycin owing to its widespread use in routine practice [12]. These incidents lead researchers to search innovations for treatment and preventive purposes. A new combination of therapies has been introduced which are more effective in treating *H. pylori* infection. Multiple studies suggest the use of moxifloxacin as a safe and best therapy with an 85 to 92% cure rate in place of clarithromycin [13]. Due to varying resistance patterns and treatment success rates across different regions, it is crucial to identify the best therapeutic regime for the treatment of gastric infection.

This study aimed to compare the efficacy of a 14-day clarithromycin-based triple therapy (TRT) with a moxifloxacin-based TRT in eradicating *Helicobacter pylori* infection.

METHODS

A quasi-experimental comparative study was carried out at the Niazi Welfare Foundation Teaching Hospital from June 2023 to April 2024 approved by the Institutional Review Board with the reference number (NM&DC/IRB/459). Sample size (n = 264) was calculated using the following formula, n= Z^2pq / e^2at 95% CI, and 0.05 margin of error. *H. pylori* prevalence data (22%) were taken from a prior study conducted in Pakistan [5]. Considering the dropout rate of 10%, a total 294 participants were included. A purposive sampling technique was employed to collect data. 294 *H. pylori*-positive patients having age > 18 years confirmed through stool antigen test using ELISA technique after getting informed consent were included in the study. Patients were excluded if they had age < 18 years, used PPIs or H2 receptor blockers in the last four weeks or antibiotics in the last two weeks, previously received *H. pylori* eradication therapy, liver or kidney insufficiency, pregnancy, severe heart disease, previous gastric surgery, contraindications to the drugs used in this study. Participants were randomly assigned to groups A & B after detailed clinical history and conducting a complete physical examination on a specific Performa. Patients' demographic information, like gender, age, weight, and disease duration, was documented. Group A was given standard triple therapy consisting of clarithromycin 500mg, with amoxicillin 1g, and omeprazole 20mg given bid for 14 days. Group B received triple therapy with moxifloxacin 400mg OD, amoxicillin 1g bid, and omeprazole 20mg two times a day for 14 days. Patients were followed for any side effects related to medication every week. At week 8, patients' stool antigen test was done to evaluate the *H. pylori* eradication status in both groups for cure rate. Descriptive statistics was employed to determine the frequency and percentages for categorical variables. Mean and SD for continuous variable. The fisher exact test was utilized to compare differences between the two groups at a significance level of p-value < 0.05 using SPSS version 24.0.

RESULTS

In group A, there were 68 (46.2%) female and 79 (53.8%) male, while in group B, 65 female (44.2%) and 82 male (55.8%). p-value of 0.725 indicates no significant differences between groups A & B in gender distribution. According to age, participants in group A ranged in age from 23 to 72 years old, with a mean age of 47.29 ± 6.31 years. In group B, ages ranged from 24 to 73 years and an average age of 47.93 ± 6.52 years. p-value of 0.371 depicts insignificant differences in ages between the two groups. The duration of the disease ranged from 0.5 to 11 years, with a mean duration of 4.92 ± 0.68 years in group A and 0.5 to 10 years, with an average duration of 4.86 ± 0.72 years in group B with p-value > 0.05 revealing no significant differences. In group A, participants' weights varied from 39 to 79 kg, with an average of 54.27±7.31 kg. The weights of the participants in group B varied from 39 to 80 kg, with an average weight of 54.48 ± 7.02 kg. p-value indicates no significant differences in participants' weights between the two groups A & B (Table 1).

Table 1: Demographics of Participants in Two Groups

Characteristics	Group A	Group B	p-Value
Male	79 (53.8%)	82 (55.8%)	0.725
Female	68 (46.2%)	65 (44.2%)	
Age (Years)	23-72	24-73	0.371
Mean Range	47.29 ± 6.31	47.93 ± 6.52	
Disease Duration (Years)	0.5-11	0.5-10	0.463
Mean Range	4.92 ± 0.68	4.86 ± 0.72	
Weight Range (kg)	39-79	39-80	0.801
Mean Range	54.27 ± 7.31	54.48 ± 7.02	

H. pylori eradication rate was based on per protocol (PP) and intention to treat (ITT) analysis at a 95% confidence interval. In this study, 267 patients completed the follow-up. 130 patients in group A completed the follow up and the cure rate was 76.1% (99/130) as PP analysis and according to ITT, 67.3% (99/147) cure rate was observed. Whereas, in group B, 137 patients completed the follow-up, and the cure

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rate was 92.7% (127/137) as PP analysis. According to ITT analysis, 86.3% (127/147) cure rate in group B was observed. The total ITT rate in the two groups was 76.8% (226/294) at 95% CI. The entire PP analysis rate was 84.6% (226/267). Fisher exact analysis revealed significant differences in Group A and B at p value of 0.0001 (Table 2).

Table 2: *Helicobacter pylori* Eradication Rate

Eradication Rate	Group A	Group B	p-Value
Intention-to-Treat 95% CI	67.3% (99/147)	86.3 % (127/147)	0.0001
Per Protocol 95% CI	76.1% (99/130)	92.7% (127/137)	0.0001

In our study, the primary reason for dropout was personal issues, with participants missing consecutive follow-up visits. Participants who failed to report weekly were considered lost to follow-up. The statistical analysis revealed that in terms of side effects, frequency was significantly lower in group B participants. In group participants, vomiting and diarrhea were the most frequently reported side effects whereas in group B, diarrhea and nausea were obvious (Table 3).

Table 3: Comparison of Side Effects in Two Groups

Side Effects	Group A	Group B	p-Value
Metallic Taste	6 (4.6%)	3 (2.1%)	< 0.001
Nausea	10 (7.6%)	6 (4.3%)	
Vomiting	18 (13.8%)	5 (3.6%)	
Diarrhea	22 (16.9%)	7 (5.1%)	

DISCUSSION

The rising antibiotic resistance has negatively impacted the success of *H. pylori* eradication treatments. There is now a tenacious need for new and more effective therapeutic approaches to address treatment failures. Recent guidelines no longer recommend clarithromycin-containing triple therapy as a first-line treatment. Among the newer drug combinations for *H. pylori* therapy, moxifloxacin-based triple therapy has demonstrated promising results in several studies [15]. A study reported 31% failure using standard triple therapy (TRT) for *H. pylori* eradication and showed higher resistance to clarithromycin therapy [16]. Completely eradicating *H. pylori* continues to pose a substantial challenge for medical practitioners, as current treatment regimens have not demonstrated consistent effectiveness in curing the infection [17]. In South Asia, there has been a notable rise in antibiotic resistance among *H. pylori* strains [18]. A current meta-analysis highlighted Pakistan as having the cases with the highest resistance to amoxicillin, clarithromycin, and tetracycline [19]. Several studies have been undertaken to assess the most effective treatment regimens for improving eradication rates. This study represents another effort. The findings from this research indicate that both intention-to-treat (ITT) and per-protocol (PP) analysis reveal significantly higher outcomes with the moxifloxacin-containing therapy compared to clarithromycin-based therapy (80.9% vs. 57.8% for ITT and 92.7% vs. 76.1% for PP). These results align with a study comparing triple therapies for *H. pylori* eradication, using moxifloxacin and, clarithromycin, suggesting higher eradication rates with the moxifloxacin-based therapy [20]. Also, Akpinar *et al*. found that moxifloxacin-containing triple therapy is a first-line treatment for *Helicobacter pylori* infection [21]. Similarly, Hassan *et al.* performed a comparative study on the efficacy of therapy in eradicating *H. pylori* infection, with results showing a higher eradication rate (74%) with the moxifloxacin regimen. These studies collectively report that moxifloxacin TRT are superior compared to other therapies [22]. The current study found that the primary side effects due to moxifloxacin-containing TRT were diarrhea and nausea, followed by occurrences of vomiting and a metallic taste. In contrast, diarrhea and vomiting were the most commonly reported adverse events in the clarithromycin group. However, Hwang *et al*. reported that dyspepsia/bloating and altered taste sensation were the common adverse reactions observed during 2 weeks of moxifloxacin treatment [23]. The overall rate of adverse events with the moxifloxacin-based regimen was 15.1%, notably lower than the 42.9% observed with clarithromycin therapy. This study indicates a significant disparity in both the frequency and intensity of side effects between the two groups ($p < 0.001$). Patients receiving moxifloxacin predominantly reported mild to moderate side effects, with none severe enough to necessitate discontinuation of treatment or disrupt daily activities. These findings are consistent with other studies revealing the side effects linked with triple therapy treatment for *H. pylori* infection [24]. The current study has several limitations, including the absence of antimicrobial sensitivity testing before treatment for both study drugs. Patients were not stratified based on ethnicity, BMI, or bacterial load, factors known to impact cure rates. Genetic polymorphism, which can influence eradication rates, was also not assessed. Future research should include genetic polymorphism analysis in patient's resistant to therapy to better understand these factors.

CONCLUSIONS

In summary, this study suggests that moxifloxacin TRT is the most effective and safe option to combat *H. pylori* infection, in comparison to standard clarithromycin-based therapy. Given its substantial eradication rate and safety profile, moxifloxacin TRT should be highly preferred for clinical practice in Pakistan.

Authors Contribution

Conceptualization: JA
Methodology: JA, RAK, KA
Formal analysis: SS, SM, MAM

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Original Article

Therapeutic Potential of Silodosin for Chronic Prostatitis: Efficacy and Safety Insights

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ABSTRACT

Chronic prostatitis is a common urological condition impacting men globally and poses a considerable clinical challenge due to its diverse symptoms and vague causes. The symptoms significantly affect patients' quality of life. **Objective:** To investigate the efficacy and safety of silodosin in men with chronic prostatitis who have not previously been treated with alpha-blockers for this condition. **Methods:** A quasi-experimental study was conducted from July 2022 to June 2023 at Niazi Welfare Foundation Teaching Hospital, Sargodha. Eighty-two patients with chronic prostatitis were treated with 4 mg of silodosin once daily and monitored for 12 weeks. Data collection commenced following IRB approval (NM&DC-IRB-43) and informed consent from all participants. Descriptive statistics were used to calculate the mean and standard deviation. Mean differences in NIH-CPSI score were computed through paired t-test at p-value < 0.05, using SPSS version 25.0. **Results:** Results show noticeable improvement in CP and NIH-CPSI scores following treatment. The change in symptoms of CP and NIH-CPSI score before and after silodosin indication were statistically significant ($p < 0.05$). Additionally, the treatment was well-tolerated, with minimum adverse events reported. **Conclusions:** Silodosin, a novel selective inhibitor of the α1A-adrenergic receptor, proved to be effective in treating chronic prostatitis without significant side effects.

INTRODUCTION

Chronic prostatitis (CP) is a prevalent issue of urology that contributes to 9% of the global disease burden [1]. This condition can affect men of all ages and ethnic backgrounds, but it is more prevalent among younger men, with an average onset age of 42 years [2]. Chronic prostatitis is characterized by pain, or discomfort in the pelvic area, accompanied by urinary symptoms and, or sexual dysfunction, persisting for > 3 months out of the past 6 months [3]. Chronic prostatitis consequences on the patient's quality of life (QOL) are significant [4]. It falls under Category IIIA and IIIB: Chronic Prostatitis/Chronic Pelvic Pain Syndrome (CP/CPPS) of NIH-CPSI (NIH-Chronic Prostatitis Symptom Index) by the National Institutes of Health (NIH) [5]. CP/CPPS impacts 2–16% of adult men, making it one of the most prevalent urological conditions with an incidence of 5% in Pakistan [6]. The symptoms of CP/CPPS profoundly impact patients' quality of life (QoL), manifesting as pelvic pain, discomfort, lower urinary tract symptoms (LUTS), and sexual dysfunction. Lower urinary tract symptoms such as hesitancy, reduced flow, and frequent urination frequently accompany CP/CPPS. Approximately 10% of CP/CPPS cases may exhibit

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urodynamic evidence of obstructive symptoms [7]. CP/CPPS could result from recurrent infections, inflammation of the prostate or surrounding nerves, or muscle spasms in the pelvic region [8]. The underlying mechanisms of CP/CPPS (NIH Category III) remain unclear. It is believed to involve abnormal immune responses triggered by previous bacterial infection, neural inflammation, and neurogenic damage following an adverse event [9]. Multiple theories suggest that numerous etiologies are accountable for chronic prostatitis and, therefore need a comprehensive approach to deal with the associated symptom complex because few therapies demonstrate significant efficacy in alleviating CP/CPPS-specific symptoms [10]. Management of CP/CPPS requires symptom-based intervention to deal with this debilitating illness [11]. Diagnosing CP/CPPS requires four key elements: a) symptoms that appear in the perineal and, or lower abdomen b) evidence of prostate infection and, or inflammation through lab results c) pain and discomfort associated with the prostate and lower UTI, and d) symptoms arising after a trigger with varying incubation periods. Each individual presents with a primary complaint and a combination of other symptoms, which typically fluctuate but persist for at least 3 months [12]. Despite its prevalence and clinical impact, effective treatment options remain limited, often necessitating a multimodal approach [12]. Medicinal treatment focuses on alleviating discomfort, pain, and urinary problems to enhance QOL [13]. The main medications prescribed include α-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, and 5-α reductase inhibitors. But, prolonged use of these drugs can lead to adverse events like low blood pressure and gastrointestinal issues [14]. Additionally, because of the absence of optimal treatment approaches, medical treatment costs are high [15]. Studies have demonstrated that α-blockers can successfully combat the symptoms in patients, particularly in reducing suffering and enhancing QOL, with strong anti-inflammatory and analgesic effects [16]. Silodosin selectively blocks α1A-adrenergic receptors in the lower urinary tract and central nervous system. This action reduces peripheral and central neuropathy, improves voiding function, and alleviates pain associated with CP/CPPS [17]. Understanding the precise mechanisms through which Silodosin exerts these effects will be crucial for optimizing its use in clinical practice [14]. Recently, there has been considerable advancement in the research of using α-blockers to treat chronic prostatitis.

This study aimed to evaluate the efficacy and safety of Silodosin (4mg) for men with chronic prostatitis.

METHODS

A quasi-experimental study was performed from July 2022 to June 2023 at Niazi Welfare Foundation Teaching Hospital, Sargodha with the following ethical clearance of research from IRB & Ethics Committee (NM&DC-IRB-43). Z2pq/d2 formula was employed to calculate sample size in open Epi software with a prevalence rate of 5% [6], and a margin of error = 0.05 at a confidence interval of 95%. The calculated size was 73. Considering a dropout rate of 10%, the adjusted sample size was 82 patients. A non-probability convenient sampling method was employed. The inclusion criteria for this study involved: (1) NIH-CPSI Category IIIA and IIIB CP/CPPS patients who have not previously received any treatment; (2) Patients aged 18 to 55 years; (3) Patients experienced chronic recurrent pelvic pain and discomfort with pain score of ≥ 4 points, from >3 month on NIH pain scale and had associated urinary symptoms and sexual problems. Exclusion criteria included patients with: (1) acute prostatitis; (2) those with other reproductive tract infectious diseases or serious liver and kidney diseases; (3) those who had used antibiotics or α-receptor blockers in the previous 2 weeks; (4) those with paratyphoid fever, seminal vesiculitis, varicocele, or tumors affecting the bladder, urethra, or prostate; (5) those who had undergone any prostate surgery; (6) those with cardiovascular, cerebrovascular or hematopoietic diseases. Written informed consents were obtained from all the study participants. Outcome variable of the study "efficacy" was the change in NIH-CPSI score on NIH-CPSI questionnaire [18] from baseline to week 12. The NIH-CPSI comprises 9 questions with a total possible score ranging from 0 to 43. It assesses three primary domains of the prostatitis experience: pain (ranging from 0 to 21), voiding disturbances (ranging from 0 to 10), and quality of life/impact (ranging from 0 to 12). Safety parameters were recorded on a specific predesigned performa that included blood pressure monitoring with mercury sphygmomanometer to detect hypotension, gastrointestinal evaluations to identify any discomfort or other gastrointestinal issues, general physical examinations to detect adverse reactions, and laboratory tests, including liver and kidney function tests, to monitor for any potential systemic effects at each follow-up visit. Blood samples were collected to estimate LFTs and RFTs. Demographic variables of participants (age and disease duration) were noted. The initial assessment involved completion of NIH-CPSI questionnaire and evaluation of safety parameters on specific performa. Patients were explained to take Silodosin at a dosage of 4 mg once daily with food at breakfast for a duration of 12 weeks. The medication was administered orally. Patients were advised for regular follow-ups at baseline week 0, week 4, week 8, and week 12. At week 4, first follow-up is done to monitor the initial response to treatment, any side effects, and treatment adjustment if required. At week 8, patients were assessed for ongoing efficacy, monitored for side effects, and ensured treatment adherence. Finally, 12th week follow-up was done to evaluate overall efficacy and safety

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of the study's intervention. If patients experienced side effects or complications, they were provided with appropriate medical intervention. Mild to moderate side effects were managed with supportive care, while severe side effects necessitated discontinuation of the study medication and provision of alternative treatments. Treatment failure was lack of significant improvement in NIH-CPSI scores (less than a 30% reduction from baseline) by week 12, or the occurrence of severe side effects leading to discontinuation of the medication. The drop-out rate and reasons for drop-out were recorded. Any patient who missed two consecutive follow-up visits was considered lost to follow-up. Data were processed using SPSS 25.0 software. Categorical data was presented as frequency and percentage while continuous data were reported as mean and standard deviation (SD). Paired t-test was used to compare intra-group differences at significance level, $p < 0.05$.

RESULTS

The demographic information included 75 patients with ages ranging from 18 to 55 years, having an average age of (41.57 ± 6.54) years. The average disease duration was (2.34 ± 1.03) years. Following treatment, there was a significant reduction in pain and, discomfort scores, urinary symptom scores, and QOL scores among patients with chronic prostatitis (Table 1).

Table 1: Comparison of NIH-CPSI Score

NIH-CPSI Score	Before Treatment Mean ± SD	After Treatment Mean + SD	p-value
Pain and Discomfort Domain	11.63 ± 2.13	5.63 ± 1.23	p<0.001
Urinary Symptom Domain	8.04 ± 0.45	4.36 ± 1.23	p<0.0001
Quality of Life Domain	9.65 ± 3.65	5.27 ± 1.27	p<0.001
Total Score	29.32 ± 2.20	15.26 ± 1.80	P<0.001

Regarding safety parameters, insignificant changes at baseline and week 12 ($p > 0.05$). Gastrointestinal evaluation revealed incidence of nausea and vomiting in 1 (1.2 %) participants. Incidence of headache and dizziness was found in 2 (2.4%), while skin itching in 1 (1.2 %). Lab values (LFT and RFT) show non-significant changes after 12 weeks of therapy ($p > 0.05$). No serious adverse effects or complications were noted during the 12-week period that required discontinuation of therapy (Table 2).

Table 2: Evaluation of Safety Parameter

Safety Parameter	Baseline Mean ± SD	Week 12 Mean ± SD	p-value
Blood Pressure (mm Hg)			
Systolic	120.4 ± 7.2	120.8 ± 6.9	0.432
Diastolic	80.6 ± 5.5	80.3 ± 5.2	0.508
Gastrointestinal Evaluations			
Nausea and Vomiting Incidence n (%)	0	1 (1.2%)	-
General Physical Examinations			
Headache and Dizziness Incidence n (%)	0	2 (2.4%)	-
Skin Itching Incidence n (%)	0	1 (1.2%)	-
Laboratory Tests			
Liver Function Tests (LFT)			
ALT (U/L)	25.3 ± 7.5	25.6 ± 7.2	0.687
AST (U/L)	22.8 ± 6.4	23.1 ± 6.1	0.582
Alkaline Phosphatase (ALP, U/L)	70 ± 15	72 ± 14	0.399
Gamma-Glutamyl Transferase (GGT, U/L)	25 ± 8	26 ± 70.7	0.416
Serum Bilirubin (mg/dL)	0.8 ± 0.2	8 ± 0.18	0.52
Prothrombin Time (PT, seconds)	12.5 ± 1	12.6 ± 0.9	0.520
International Normalized Ratio (INR)	1.0 ± 0.1	0.98 ± 0.08	0.178
Total Protein (g/dL)	7.0 ± 0.5	6.9 ± 0.6	0.269
Albumin (g/dL)	4.0 ± 0.31	4.1 ± 0.37	0.074
Kidney Function Tests (RFT)			
Creatinine (mg/Dl)	0.88 ± 0.16	0.89 ± 0.15	0.735
BUN (mg/Dl)	14.5 ± 3.2	14.6 ± 3.1	0.829
Glomerular Filtration Rate (GFR, mL/min/1.73 m^2)	90 ± 10	91 ± 10.1	0.543

In this study, there were 7 dropouts resulting in a dropout rate of 8.54%. The main reason for dropout was missing two consecutive visits. All the statistics were calculated after excluding dropouts.

DISCUSSION

This study aimed to evaluate the efficacy and safety of Silodosin (4 mg) in treating chronic prostatitis. Results showed a significant efficacy, indicating that the majority of patients experienced notable improvement in NIH-CPSI scores following the treatment. Silodosin proved a helpful regime in treating pain and discomfort caused due to CP. Results suggest significant differences in pain and discomfort scores ($p < 0.001$) that contribute to therapy. Along with pain score improvement, patients also experienced differences in urinary symptoms ($p < 0.0001$) and QOL score ($p < 0.001$). Significant differences gave fruitful information regarding the benefits of silodosin therapy. Silodosin accounts for the betterment of NIH-CPSI scores from baseline to week 12 periods, which is remarkable. These results are comparable with a study depicting the notion that silodosin provides a promising effect in combating CP-associated symptoms; its role in symptom score reduction is noteworthy. The therapeutic effects of silodosin on QOL offer evidence that it's a useful approach in clinical practice [19]. The finding of a study by Creta *et al.*, confirms the importance of silodosin in the treatment of CP/CPPS particularly in alleviating the associated symptoms and improving patient well-being [20]. The significant effect of silodosin in NIH-CPSI improvement is consistent with studies evaluating α1-adrenergic receptor antagonists' role in symptom alleviation in chronic prostatitis [21]. Moreover, the incidence of side effects with the use of 4 mg silodosin was 4.8% in our study viz. headache 2.4%, nausea and vomiting 1.2%, and skin itching 2.4% which were negotiable.

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Minimum side effects provide key evidence regarding safety parameters linked with the clinical use of silodosin for achieving therapeutic outcomes. The efficacy and safety of silodosin revealed I that treatment with α-blockers offers a safe option in clinical practice [21]. Similarly, studies showed that only a few side effects were reported with Alpha 1-blockers. Alpha 1 blockers offer a safe option for CP/CPPS patients with negligible side effects. Silodosin, a new selective α1A-adrenergic receptor inhibitor, has demonstrated effectiveness in improving symptom scores and is free from significant side effects [22]. Our study provides valuable data on the therapeutic outcomes of silodosin in clinical areas. The limitations of the study were the small sample size and the short follow-up duration of only 12 weeks. These limitations emphasize the further need for experimental studies with a control group to elaborate on the extensive role of silodosin for therapeutic outcomes.

CONCLUSIONS

Silodosin (4mg), a selective inhibitor of the α1A-adrenergic receptor, proved to be an effective approach that helps in improved symptom scores and is free of significant side effects. Silodosin could serve as a preferred choice in clinical practice for patients with CP/CPPS.

Authors Contribution

Conceptualization: ABN
Methodology: ABN, IA, SA
Formal analysis: MA, WA, SG
Writing-review and editing: SA, SG

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Importance of Mentors in Polishing the Professional Development and Decreasing the Burnout among Medical Students

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ABSTRACT

Burnout among medical students is a significant concern, affecting not only their academic performance but also their overall well-being and professional development. **Objective:** To determine the relationship between mentor behaviors and burnout among students of medicine and development of professional behavior in medical schools. **Methods:** This Cross-sectional study was held among 3rd, 4th and final year medical students (N=300) and convenient sampling technique was used. The questionnaire was completed voluntarily by the students via online surveys evaluating the Professional Self-Identity Survey and the Mentor Behavior Scale. Multivariate regression analyzes were conducted to examine the associations between mentor behaviors with student burnout and their influence on the development of professional attitude. **Results:** In this analysis, 23.3% of students of medicine experienced burnout. Several factors were found to be strongly related with medical students' burnout according to the multivariate analysis. Burnout was shown to be linked with participants who reported using medications (OR = 2.2, 95%CI: 1.2-3.95, p = 0.027). Burnout was also substantially correlated with medical students' poor GPAs (GPA< 3.00) (OR = 3.1, 95%CI: 1.4-6.7, p = 0.001). Furthermore, burnout in medical students was substantially correlated with low to moderate levels of competency support from mentors (OR = 1.98, 95%CI: 1.01-3.2, p = 0.014). **Conclusions:** The influence of mentors' behaviors on students of medicine is vital. Improving mentoring by denoting specific mentor behaviors can improve behavior of mentors.

INTRODUCTION

A qualified mentor helps a mentee achieve personal objectives, improve competence, and develop their professional identity through the crucial process of mentoring [1, 2]. Mentoring is essential to medical education because it helps students reach professional standards by providing helpful criticism and acting as an encouraging role model. Both the mentors and the mentees benefit from this practice, which enhances their leadership and teaching talents as well as their personal and professional growth [3, 4]. Effective mentorship has also been demonstrated to increase student recruitment and retention, which helps medical schools in selection process. Medical students are negatively impacted by the many pressures prevalent in the medical learning environment. According to earlier research, between 27 and 75 percent of medical students have experienced burnout [5]. The learning and work environments were found to be the main factors associated with burnout. There are many advantages of implementing a mentorship program, including reduced depression, stress and anxiety.

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In particular, medical students who took part in the mentorship program in the earlier burnout study reported significantly higher personal success scores on the burnout questionnaire [6]. Mentorship programs are essential for helping medical students advance professionally. Mentors can assist mentees in developing their professional identities by providing them with constructive criticism and role modeling. It is the first stage in assisting students for their professional careers. A mentorship program's effectiveness is contingent on various variables, the most significant of which is the quality relationship among mentor and mentee. A number of factors influence this relationship, one of which is the mentor's encouraging behavior. Nevertheless, limited studies have been done on the precise effects that mentors' encouraging actions have on medical students [7]. A key component of medical education is mentoring, where experienced mentors help mentees "in attaining their personal achievements, cultivating a robust professional identity and honing competence"[8, 9]. Therefore, successful mentoring programs have the potential to strengthen institutional retention and recruitment efforts as well as mold the future generation of healthcare professionals [10]. The milieu of medical education presents myriad stressors that profoundly impact students, often contributing to significant rates of burnout, which have been reported to affect as many as 75% of medical students [11]. These stressors are compounded by the rigorous demands of their learning and clinical environments, underscoring the critical need for supportive mechanisms such as mentorship [12]. Indeed, mentorship programs have demonstrated substantial benefits in reducing stress, anxiety, and depression among participants. Notably, studies have shown that such programs can enhance personal accomplishment scores, a pivotal factor in mitigating burnout and fostering the professional growth of medical students [13].

Despite the recognized benefits, there remains a notable gap in understanding how mentors' specific behaviors influence medical students' experiences, particularly in terms of mitigating burnout and shaping professional development. This study aimed to address this gap by examining the perceived impact of volunteer mentors' behaviors on medical students. By exploring these dynamics, it was aimed to illuminate the nuanced role of mentorship in medical education, thereby informing strategies to optimize mentorship programs for the benefit of both students and institutions.

METHODS

This Cross sectional study was conducted at the Medicine department of Rashid Latif Medical College from January 2023 to December 2023. Convenience sampling was used to administer online questionnaires to participants. Sample size of 300 students was estimated by using 95% confidence level, 10% absolute precision with expected percentage:

$n=(Z1-\alpha/2)2 \times P \times q / d2$

$Z1-\alpha 2$ = Confidence level 95% =

P = Prevalence 67.6%

q = 1-P

d = Absolute precision 10%

Inclusion Criteria

. Students of Third, Fourth and Final years MBBS

. Students who gave consent to participate

Exclusion Criteria

. Students with other Psychological disorders

. Students with previous history of burnout

. Students already taking any psychological treatment

300 total students were selected in this analysis. The two questionnaires were completed by third, fourth- and final-year medical students. Mentor Behavior Scale (MBS): The four dimensions of mentor behavior Autonomy Support, Competence Support, Engagement and Mentor Relationship Structure were measured by 15 Likert-scale items in this questionnaire.

For this study, the MBS has been modified and validated in order to assess the perceived efficacy of mentoring relationships. It gauges depersonalization, emotional weariness, and personal achievement and offers information on students' burnout levels. Professional Self-Identity Questionnaire (PSIQ): Given to third, fourth- and fifth-year students, the PSIQ comprised nine Likert scale items that evaluated various categories, including teaching skills, ethical awareness, teamwork, and communication. The purpose of this questionnaire was to assess how students who were exposed to actual work contexts developed their professional identities. Stata Version 20.0 was used for the statistical analysis. The percentage and frequencies were used to summarize "categorical data," whereas S.D, medians and means with ranges were applied for "continuous data," depending on the features of the distribution. For baseline comparisons, categorical variables were compared using Fisher's exact/chi-square, while T-tests/Mann-Whitney U tests were applied for continuous variables comparison. In univariate analysis, p-values less than 0.05 were taken into consideration for inclusion in subsequent models. To evaluate relationships between mentor behavior dimensions, burnout, and domains of professional self-identity construction, multiple logistic regression analysis was utilized. With a significance level of $p < 0.05$, odds ratios with 95% Confidence Intervals (CI) were computed. IRB letter was taken from Ethical review committee of Rashid Medical College, Lahore with the reference number (IRB) IRB00010673. Every subject gave consent of the study for their participation, and stringent measures were taken

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to guarantee the anonymity at all times. As a result, the possibility of selection bias was reduced because the researchers were unable to identify responders.

RESULTS

In Table 1, gender, medication use, underlying diseases, amount of sleep, Grade Point Average (GPA), extracurricular activities, amount of exercise and club activities were all gathered as baseline data. For convenience of interpretation, GPA was divided into 2 groups: high GPA group (GPA ≥ 3.00) and the low GPA group (GPA < 3.00). Table 1 displays the individuals' complete baseline information (Table 1).

Table 1: Baseline Characteristics of Patients (n=300)

Variables	N (%)
Gender	
Male	142 (47.3%)
Female	158 (52.6%)
Co-Morbidities	
(PCOS, Allergic Rhinitis, G6PD, Asthma, ADHD, Migraine, Diabetes Mellitus)	65 (21.7%)
No Comorbidities	235 (78.3%)
Medication Usage	
(Allopurinol, Antihistamine, OCP, Methylphenidate, Fluoxetine, Metformin, ICS)	45 (15%)
No Medicine Taking	255 (85%)
GPA	
2.00 - 2.49	8 (2.7%)
2.50 - 2.99	29 (9.6%)
3.00 - 3.49	141 (47%)
3.50 - 4.00	122 (40.7%)
Sleep Duration Per Hours at Night	
0 - <4	4 (1.3%)
4 - <6	110 (36.7%)
6 - <8	165 (55%)
≥8	21 (7%)
Extracurricular Activities	
No Extracurricular Activities	58 (19.3%)
Extracurricular Activities	242 (80.7%)
Duration of Exercise Per Week (Minutes)	
≥150	51 (17%)
100 - <150	43 (14.3%)
50 - <100	78 (26%)
0 < 50	128 (42.7%)
Club Activities	
No Activities	164 (54.7%)
Daily Activity	136 (45.3%)

Groups of five students were randomly allocated volunteer mentors, who began their mentoring relationship with the mentees in 3rd Year and continued it until final year. Essential mentoring skills such as goal-setting, feedback, active listening and effective communication were taught to all mentors. In addition to carrying out their mentorship responsibilities, program members met on a regular basis to offer guidance and support before each activity, as well as to enable evaluation and contemplation of their former mentoring experiences. Early clinical exposure, such as visiting operating rooms and patient wards, practicing communication skills with real patients, and performing physical examinations under mentor supervision, is part of pre-clinical initiatives that support Professional Identity Formation (PIF). Mentor-led retreat sessions include activities for personal growth and psychological support, which promote meaningful connections between mentors and mentees. These retreats foster an atmosphere where mentors actively listen, provide constructive criticism, and assist with goal-setting in a caring environment. The evaluation of the mentor program was done at the conclusion of each academic year to gauge its effectiveness. The cut-off points for the three categories high, moderate, and low that were taken from the scores were derived from an earlier study. From the perceptive of medical students, three of the four domains; engagement, competency support and mentor relationship structure had high overall mean scores (sum of scores) (Table 2).

Table 2: Perspectives of Medical Students on Mentor Behavior Scale (MBS) Scores

Domain	Minimum	Maximum	Sum Score (Mean ±SD)	Interpretation
Engagement (MBS Summation Score of 9-10) (Low <6, Moderate 6-7, High>7)	3	11	7 ± 1.4	High Score
Mentor Relationship Structure (MBS Summation Score of 1-8) (Low <24, Moderate 24-31, High>31)	7	39	33.1 ± 5.6	High Score
Competency Support (MBS Summation Score of 13-15) (Low <9, Moderate 9-11, High>11)	4	17	10.5 ± 2.1	High Score
Autonomy Support (MBS Summation Score of 11-12) (Low <6, Moderate 6-7, High>7)	3	9	6 ± 1.9	Moderate Score

The Maslach Burnout Inventory-Student Survey revealed that 70 (23.3%) of the 300 participants had experienced burnout. Several factors were found to be strongly related with medical students' burnout according to the multivariate analysis. Burnout was shown to be linked with participants who reported using medications (OR = 2.2, CI95%: 1.2-3.95, p = 0.027). Burnout was also substantially correlated with medical students' poor GPAs (GPA< 3.00) (OR = 3.1, CI95%: 1.4-6.7, p = 0.001). Additionally, there was a significant correlation found between medical students' burnout and low to moderate levels of competency support from mentors (OR = 1.98, CI95%: 1.01-3.2, p = 0.014). A subgroup analysis was performed, taking into account potential differences in curriculum and experiences among medical students, focusing on subjects from the preclinical year (third-year students) as well as among the clinical years (fourth to final-year students). Pre-clinical year medical students' low GPA (OR = 12.0, CI95%: 3.8-32.1,

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p < 0.001) and mentors' low-moderate degree competency support (OR = 2.1, CI95%: 1.01-4.75, p = 0.021) were found to be associated with burnout. In clinical year medical students, burnout was significantly correlated with the low-moderate degree of mentor relationship structure (OR = 2.77, CI95%: 1.20 to 6.89, p = 0.013)(Table 3).

Table 3: Related Factors with Burnout in Multivariate Subgroup Analysis among Clinical and Pre- Clinical Medicine Students

Factors	OR (95%CI)	p-Value
Pre-Clinical Year		
Competency Level		
High (Score>11)	1.01	0.021
Low-Moderate (Score <=11)	2.1 (1.01-4.75)	
Clinical Year		
Level of Mentor Relationship Structure		
High (score>31)	1.01	0.013
Low-Moderate (Score <=31)	2.77 (1.20-6.89)	
GPA		
3.00 - 4.00	1.01	<0.001
2.00 - 2.99	12 (3.8-32.1)	

High professional scores in the domains of communication, teamwork, record-keeping and ethical awareness were substantially correlated with a high degree of mentor relationship structure, according to the multivariate analysis (Table 4). Furthermore, a high professional score in the communication category was substantially correlated with a high degree of autonomy support (OR = 4.6, 95% CI: 1.4–18.1, p = 0.034). Additionally, a high professional score in the conducting assessment domain was significantly correlated with a high level of competency support (OR = 6.0, 95% CI: 1.9-17.6, p = 0.002). In contrast, no mentor behavior was discovered to be substantially associated (p > 0.05) with the high professional group in the domains of teaching, handling emergencies, cultural awareness, and introspection.

Table 4: Professional Self-Identity Formation and Mentor Behavior Scale Among Medicine Students

PSIQ Domain	MBS Domain	OR (95%CI)	p-Value
PSIQ 1. Teamwork	Mentor Relationship Structure (High Score)	4.3 (1.4-10.1)	0.005
PSIQ 2. Communication	Mentor Relationship Structure (High Score)	3.2 (1.3-7.2)	0.006
	Autonomy Support (High Score)	4.6 (1.4-18.1)	0.034
PSIQ 3. Conducting Assessment	Competency Support (High Score)	6.0 (1.9-17.6)	0.002
PSIQ 5. Ethical Awareness	Mentor Relationship Structure (High Score)	3.5 (1.5-7.8)	0.007
PSIQ 6. Using Records	Mentor Relationship Structure (High Score)	3.0 (1.4-6.9)	0.018

DISCUSSION

Mentorship programs have helped professionals in many disciplines, but little is known about what makes mentors effective in helping medical students establish their professional identities and minimize burnout [13]. This study used the MBS questionnaire to examine mentor behaviors in our mentorship program and identify which ones help medical students achieve their career goals [14]. Mentors showed moderating traits, which may have been influenced by cultural similarities, consistent with a Kupcewicz *et al* study [15]. Our research found that mentor relationship structure, engagement, and competency support were higher than autonomy support as described in the Asghar AA *et al* study in Karachi [16]. These findings emphasize the need for autonomous support for medical students and suggest curriculum improvements. Medical students often burn out due to challenging learning conditions, heavy workloads, and exam stress. This analysis shows 23.3% of medical students have burnout, consistent with other studies that found 28-76% [16]. It was observed that low GPAs caused burnout, supporting Saudi Arabian research. A low-moderate mentor competency support level was also substantially associated with student burnout. High competency support may predict decreased burnout. Subgroup study showed that third-year medical students still valued competency support, assuming they benefit from positive reinforcement regardless of success or failure. However, clinical year (4th and final year) students may need a strong mentor relationship to share their concerns and accept constructive feedback to avoid burnout [17, 18]. Medical students' professional identity is crucial to their success [19, 20]. Mentoring reduces burnout and helps medical students create a professional identity, according to our research. Strong mentor relationships were associated to professional self-identity traits like communication, record-keeping, teamwork, and ethics. High autonomy and competency support from mentors were linked to good exam performance and communication [21, 22]. Prior research have stressed the importance of mentorship, constructive feedback, and role models in building professional self-identity [23-25]. This study shows that mentorship programs help promote professional self-identity. This research also promotes mentorship by identifying mentor behaviors that help medical students establish strong professional self-identities. This study significantly advances our understanding of the connection between mentor behaviors as measured by the MBS questionnaire and how they affect medical students' mental health and development of their professional identitiesFinally, because this study used a cross-sectional methodology, the findings may only show correlations between the behaviors of mentors, burnout among medical students, and the development of professional identities. It is not possible to establish causation from this single-point

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data collection. To further explore these associations, future research should think about executing a long term prospective cohort analysis that includes uniform assessments of mentor qualities.

CONCLUSIONS

According to this study, medical students who have mentors who exhibit particular behaviors—like competency support and mentor relationship structure were less likely to experience burnout. Moreover, mentor behaviors that foster professional self-identity construction in medical students include autonomy support, competency support from mentors and mentor relationship structure. These results provide insightful information for improving the efficacy of mentoring programs and helpful advice for mentors looking to improve their mentoring abilities.

Authors Contribution

Conceptualization: SM

Methodology: MA, BH, SA[1], SA[2]

Formal analysis: SA[2]

Writing, review and editing: MA, BH, SA[1], SA[2], MI

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Validity of prothrombin-induced Vitamin K antagonist versus Alpha-Fetoprotein (Tumor Markers) in Diagnosis of Hepatocellular Carcinoma, Using Computed Tomography scan as Gold Standard

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ABSTRACT

Biomarkers like alpha-fetoprotein and prothrombin-induced Vitamin K deficiency/ antagonist are used in the early diagnosis and staging of hepatocellular carcinoma and are useful for better outcomes in the treatment and overall survival of the patient. **Objective:** To compare the diagnostic accuracy of alpha-fetoprotein and prothrombin-induced Vitamin K antagonist in the diagnosis of hepatocellular carcinoma using a computed tomography scan as a gold standard. **Methods:** A cross-sectional study was conducted in the Liver Transplant Unit of Shaikh Zayed Postgraduate Medical Complex, Lahore from July 2023 to January 2024. A total of 94 patients older than 12 years old with cirrhosis and CT scan suggestive of hepatocellular carcinoma were selected. Blood was collected to test for AFP and PIVKA-II. The samples were sent to the labs after labeling them properly and the results were collected and entered in the data sheet. Patients were advised to have a multiphase contrast-enhanced CT scan. Patients were followed up in the clinic after 7 days. **Results:** The diagnostic accuracy of AFP was 78% with a 74.7% sensitivity, 100% specificity, 100% positive predictive value, and 41.67% negative predictive value. The diagnostic accuracy of PIKVA-II was found to be 87.76% with 89% sensitivity, 80% specificity, 96.1% PPV, and 57.14% NPV. **Conclusions:** On comparing the tumor markers AFP with PIVKA-II against the gold standard multiphase CT scan it was found that PIVKA-II has better diagnostic accuracy than AFP.

INTRODUCTION

Liver cancer especially hepatocellular carcinoma is one of the most frequently occurring cancers in males and females [1]. Hepatocellular carcinoma (HCC) is common in cirrhotic patients in Asia and is the leading cause of death in Pakistan. HCC management has improved since last decade but prognostic outcomes are still not satisfactory. 75% of cases of HCC in Asia are due to a high incidence hepatitis B and C [2]. Timely detection of HCC is significant to ensure better treatment and eventually better outcomes. HCC is associated with cirrhotic liver disease regardless of the etiology in the majority of the patients but HCC also occurs in non-cirrhotic only in 10 percent of total HCC Cases [3]. Biomarkers are used in the early detection and staging of HCC and are useful for better outcomes in the treatment and overall survival of the patient. The most commonly used biomarker is AFP (Alpha-Fetoprotein) which is compared with PIVKA-II (prothrombin-induced Vitamin K deficiency/ antagonist). The diagnostic accuracy of AFP is unsatisfactory. The sensitivity ranges from 39-65 % and specificity for detection of HCC ranges from 76 -94

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%, which is not ideal [4]. PIVKA-II is tumor marker for hepatocellular carcinoma, it corresponds to HCC oncogenesis and disease progression. PIVKA-II is also utilized in discriminating neoplastic from regenerative nodules in cirrhotic patients. PIVKA-II has a higher diagnostic accuracy than AFP and shows enhanced results in combination of AFP for early detection of HCC [5, 6]. High levels of PIVKA-II have been seen in patients at risk of developing HCC within the first two years of cirrhosis [7]. PIVKA-II can also be used in combination with AFP and it is seen to increase the sensitivity and specificity of both biomarkers for HCC detection at a very early stage. The other modality used in the diagnosis of HCC is a contrast-enhanced multiphase CT scan. Recent guidelines recommend a CT scan as the first-line tool for the screening, diagnosis, staging, and surveillance of HCC [8]. The typical enhancement pattern which shows contrast uptake on the arterial phase and washout on the venous phase confirms the diagnosis of HCC. If this specific pattern is not seen on a CT scan, then the other modality used is Dynamic MRI scan. According to a recent meta-analysis, the sensitivity of contrast-enhanced multiphase CT scan ranges between 63-76% and the specificity ranges from 87-98 % [9]. On CT scan the diagnostic cutoff is 1cm in most of the guidelines. Due to the lack of evidence in the literature regarding early diagnosis of HCC in Pakistani patients with cirrhosis, it was mandatory to find a tumor marker that could give us better diagnostic and prognostic yield in these patients. Cancer treatment worldwide is very expensive, especially in Pakistan where people cannot bear the expenses of cancer treatment, by using the proposed tumor markers and imaging modalities which are sensitive to picking up the HCC at an early stage, we can significantly reduce the morbidity and mortality in our patients and they can avail better treatment options for an overall better survival in hepatocellular carcinoma.

This study was conducted to compare the diagnostic accuracy of alpha fetoprotein and prothrombin-induced Vitamin K antagonist in the diagnosis of hepatocellular carcinoma using a computed tomography scan as a gold standard.

METHODS

A cross-sectional study was conducted in the Liver Transplant Unit of Shaikh Zayed Postgraduate Medical Complex, Lahore from July 2023 to January 2024. A total of 94 patients older than 12 years old with cirrhosis and CT scans suggestive of hepatocellular carcinoma were selected by convenient sampling. The sample size was calculated by Epi Info software by keeping 0.69 expected sensitivity, 0.88 expected specificity, 0.89 expected prevalence, 0.10 desired precision and 95% confidence interval [10]. Patients with bi-lobar HCC with Childs Class C cirrhosis, any other malignancy except HCC, metastatic liver disease due to other malignancy, liver disease with known Vitamin K deficiency, and patients on warfarin or Vitamin K antagonist were excluded. All patients provided their informed consent for their data being used for research. The ethical board of the hospital approved the study Ref No. SZMC/TERC/371/23. Blood was collected for testing for AFP and PIVKA-II. The samples were sent to the labs after labeling them properly and the results were collected and entered in the datasheet. Patients were advised to have a multiphase contrast-enhanced CT scan. Patients were followed up in the clinic after 7 days and the proformas were filled. Data were entered and analyzed using SPSS version 24.0. Quantitative variables were presented in the form of mean ± SD whereas, qualitative data were presented in the form of frequency and percentages. Sensitivity, Specificity, positive predictive value, negative predictive value, and the diagnostic accuracy of PIVKA-II and AFP were calculated by taking contrast-enhanced multiphase CT as a gold standard. A 2x2 table was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy.

RESULTS

The demographic data collected in the current study shows the age groups mainly affected were ranging from late 40 to 70s (N = 87). On gender analysis the males were seventy (71.4%) out of 98 and the females were 28 (28.6%) out of 98. 86 (87.8%) patients had Hep-C infection and eight (8.2%) patients were Hep-B positive. Forty-two (42.9%) patients had international normalized ratio <1.3 and 56 (57.1%) patients had INR > 1.3. Ten (10.2%) participants had ascites. Thirty-eight (38.8%) patients had raised bilirubin. Thirty (30.6%) patients had low albumin. Seven (7.1%) patients had episodes of encephalopathy during their illness. The majority of patients in our study group had a short duration of illness and were not treated appropriately in their local health setting. A major subset of patients participating in our study group were from Child Pugh class A (77.5%)(Table 1).

Table 1: Patient's Baseline Characteristics

Variables	N (%)
Age	
15-30 Years	4 (4.1%)
31-45 Years	7 (7.1%)
46-60 Years	52 (53.1%)
61-75 Years	35 (35.7%)
Gender	
Male	70 (71.4%)
Female	28 (28.6%)
Viral Hepatitis	
HBV	8 (8.2%)
HCV	86 (87.8%)
Miscellaneous	1 (1%)

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B, C Negative	1 (1%)
B, C Positive	2 (2%)
INR	
<1.3	42 (42.9%)
>1.3	56 (57.1%)
Ascites	10 (10.2%)
Bilirubin	
Normal	60 (61.2%)
High	38 (38.8%)
Albumin	
Normal	68 (69.4%)
Abnormal	30 (30.6%)
Encephalopathy	7 (7.1%)
Previous Treatment	8 (8.2%)
Duration of Symptoms	
Less than 6 Months	68 (69.4%)
More 6 Months	25 (25.5%)
More than 1 Year	5 (5.1%)
Child-Pugh Score	
A	76 (77.5%)
B	18 (18.4%)
C	4 (4.1%)

Twenty-six (26.5%) patients were diabetic, 32 (32.7%) patients had a treatment history of hypertension, 8 (8.2%) patients had a history of ischemic heart disease, 11 (11.2%) patients had a previous history of tuberculosis, 16 (16.3%) patients had a previous history of asthma. Sixty-three (64.3%) patients had pain, 47 (48%) patients had a fever, 64 (65.3%) patients had some degree of loss of appetite, 74 (75.5%) patients developed generalized weakness, and 13 (13.3%) patients had a previous history of gastrointestinal (GI) bleed (Table 2).

Table 2: Co-Morbidities and Clinical Manifestations

Variables	N (%)
Comorbidities	
Diabetes	26 (26.5%)
Hypertension	32 (32.7%)
Ischemic Heart Disease	8 (8.2%)
Tuberculosis	11 (11.2%)
Asthma	16 (16.3%)
Clinical Manifestations	
Pain	63 (64.3%)
Fever	47 (48%)
Loss of Appetite	64 (65.3%)
Weakness	74 (75.5%)
GI Bleed	13 (13.3%)

Regarding the tumor, 36 (36.7%) patients had tumor sizes between 4-6 cm, 89 (90.8%) patients had single lesions, and 83 (84.7%) tumors were malignant (Table 3).

Table 3: Tumor Size, frequency and Type of Tumor Assessment

Variables	N (%)
Tumor Size	
1-3cm	25 (25.5%)
4-6cm	36 (36.7%)
7-10cm	24 (24.5%)
11-15cm	11 (11.2%)
More than 15cm	2 (2%)
Tumor Frequency	
Single Lesion	89 (90.8%)
Multifocal Lesion	9 (9.2%)
Tumor Type	
Benign	15 (15.3%)
Malignant	83 (84.7%)

The diagnostic accuracy of AFP was 78% with a sensitivity of 74.7%, specificity of 100%, positive predictive value of 100%, and a negative predictive value of 41.67%. The diagnostic accuracy of PIKVA-II was found to be 87.76% with a sensitivity of 89%, specificity of 80%, PPV of 96.1%, and NPV of 57.14% (Table 4).

Table 4: Validity of Alpha-Fetoprotein Test and PIVKA-II Taking CT Scan as the Gold Standard for Detection of HCC

Biomarkers	Gold Standard N (%)	
	Present	Absent
AFP		
Positive	62 (100%)	0
Negative	21 (58.3%)	15 (41.7%)
PIVKA-II		
Positive	74 (96.1%)	3 (3.9%)
Negative	9 (42.9%)	12 (57.1%)

AFP:.....PIVKA-II
Sensitivity: 74.7%.....Sensitivity: 89%
Specificity: 100%.....Specificity: 80%
PPV: 100%.....PPV: 96.1%
NPV: 41.67%.....NPV: 57.14%
Accuracy: 78%.....Accuracy: 87.76%

Regarding the presence of tumors on computer tomography, 83 (85%) cases had visible lesions on CT scan and 15% had no detectable lesions (Figure 1).

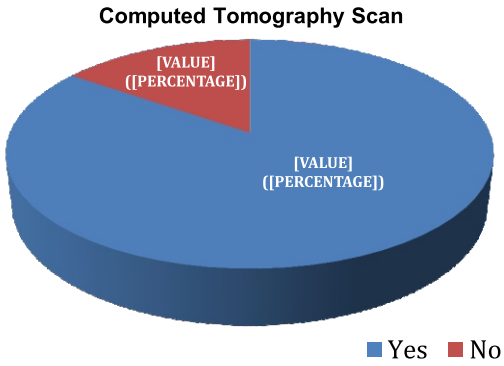

Figure 1: Presence of Tumor on Computer Tomography

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Seventy-seven (79%) patients had raised PIVKA-II and twenty-one (21%) had normal PIVKA-II levels indicating high sensitivity of this marker in diagnosis of HCC (Figure 2).

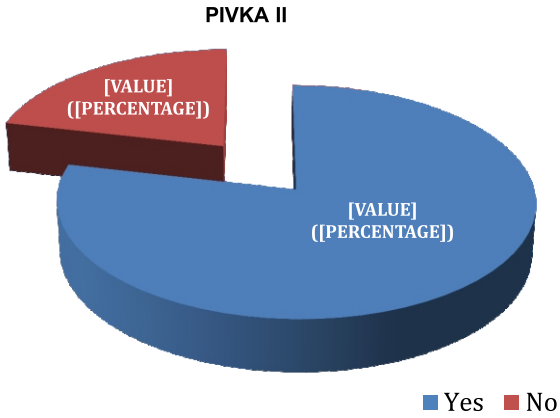

Figure 2: PIVKA-II is Highly Sensitive in the Diagnosis of HCC

DISCUSSION

Presently AFP is considered as the tumor marker that is used in the detection of HCC. However, it has been seen that in some patients even with very large tumor size the AFP remains normal so the diagnostic accuracy remains questionable [11]. Our study is aimed at identifying and validating the effective non-invasive tumor marker for HCC. We used a multiphase CT scan for confirmation of the diagnosis although the biopsy is taken as the gold standard in literature. It has been reported that due to the issue of tumor seedlings and the patient with cirrhosis patients having deranged coagulation, there was a lot of evidence favoring the usage of radiological investigation like multiphase CT scan for the diagnosis of HCC [12, 13]. In our study CT scan showed the presence of tumors in 83 (85%) patients and these parameters were comparable with the international values [14, 15]. In our study, PIVKA-II was seen as a promising biomarker for diagnosis of HCC with a sensitivity of 89%, specificity of 80%, PPV of 96.1%, NPV of 57.14% and diagnostic accuracy of 87.76% as compared to AFP with a diagnostic accuracy of 78%, sensitivity of 74.7%, specificity of 100%, positive predictive value of 100% and a negative predictive value of 41.67% and the same pattern is noticeable in the previous studies [16-18]. On comparison of the demographics, it was seen that males were predominantly more involved than females, this gender distribution was also reported by previous studies [19, 20]. Age distribution in our study showed a majority of patients in the age group of 40 to 70 years and older. A higher incidence of HCC in elder patients is also supported by the literature [21, 22]. 77.5% of the population had a Child Class A score, previous studies in HCC patients were also conducted in considerably healthier patients [23, 24]. In terms of the diagnosis, it was seen that sensitivity/ specificity/ PPV/ NPV along with the diagnostic accuracy of AFP was comparable with the previous studies which were 78% and 75.6% respectively [16-18]. For PIVKA-II the sensitivity/ specificity/ PPV/ NPV was also comparable along with the diagnostic accuracy which was 87.76% vs 86.1%. This was no statistical difference. There were some limitations of the present study. It is recommended that the sample size of the study be large, more studies should be conducted with the involvement of multiple centers and large sample size in order to find more biomarkers with better diagnostic accuracy to detect HCC at an early stage and provide relief to patient sufferings by providing them better curative treatment options.

CONCLUSIONS

On comparing the tumor markers AFP with PIVKA-II against the gold standard multiphase CT scan it was found that PIVKA-II has better diagnostic accuracy than AFP.

Authors Contribution

Conceptualization: AL
Methodology: AL, TAB, MKS, HA, UA
Formal analysis: RS
Writing, review and editing: AL, RS, TAB, MKS, HA, MAN

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

Peak Serum Creatinine as a Biomarker of Pancreatic Necrosis in Acute Pancreatitis: A Cross-Sectional Study

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ABSTRACT

Pancreatitis is the inflammation of the pancreas. Pancreatitis can result in pancreatic necrosis which may lead to significant morbidity and mortality. It is possible to predict pancreatic necrosis and organ dysfunction using many biochemical indicators and markers. Peak serum creatinine has been identified as one of such useful markers to predict pancreatic necrosis. **Objective:** To find the diagnostic accuracy of elevated peak serum creatinine as a predictor of pancreatic necrosis in patients with acute pancreatitis taking the contrast-enhanced computed tomogram scan (CECT) as the gold standard and to establish the degree of agreement between the two clinical tests. **Methods:** A cross-sectional, analytical study that was carried out at the Department of Surgery, Benazir Bhutto Hospital, Rawalpindi from January 2020 to January 2023. 150 patients diagnosed as having pancreatitis were enrolled in the study. Peak serum creatinine at 48 hours > 1.8 mg/dl was labeled as a predictor of pancreatic necrosis. Contrast-enhanced computed tomogram scan was done within 96 hours of admission. The pancreatic necrosis suggested by raised serum creatinine was confirmed by CECT. The diagnostic accuracy of peak serum creatinine and the degree of agreement between the two modalities was calculated. The Kappa coefficient was used to calculate the strength of agreement. **Results:** The results show that Peak serum creatinine has a sensitivity of 45.5%, specificity of 97.35%, PPV of 85.0 %, NPV of 93.8 %, and accuracy of 84.6%. This study found that the degree of agreement between raised peak serum creatinine levels and CECT to predict pancreatic necrosis was 84.7% with a "Kappa coefficient" of 0.51. Consequently, the null hypothesis was rejected in light of these findings. **Conclusions:** It was concluded that elevated serum creatinine (SCr >1.8 mg/dl) at 48 h of admission can be used as a predictor of pancreatic necrosis in patients with acute pancreatitis.

INTRODUCTION

Acute pancreatitis is a sterile inflammation of parenchyma of the pancreas. The annual global incidence of acute pancreatitis ranges from 5-50/100000 [1]. Acute Pancreatitis can be classified into mild, moderately severe, or severe acute pancreatitis based on the revised Atlanta classification [2, 3]. In severe pancreatitis, mortality varies from 20- 50 %. Severe pancreatitis may lead to a systemic inflammatory response (SIRS), multiple organ failure, pseudocyst, and pancreatic necrosis (PNec). A diffuse or focused area of non-viable tissue in the pancreas associated with peripancreatic fat necrosis is known as pancreatic necrosis [1]. On a contrast-enhanced computed tomography (CECT) scan, necrotic areas can be identified by the lack of contrast enhancement. The revised 'Atlanta classification' recommends a CECT scan as the preferred method for diagnosing pancreatitis complications. A study showed that the Contrast-enhanced computed tomography scan's sensitivity was 71.4%, specificity 87%, positive predictive value 83.33%, negative predictive value 76.99%, and overall diagnostic accuracy was 79.5% [2, 3]. Several grading schemes and predictors have been developed to help determine and predict the severity of pancreatitis [4]. Early diagnosis of the severity of the illness can help change the way patients are treated. Serum

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creatinine assessment has been identified as one of the predictors of the severity of pancreatitis. It has been found that high serum creatinine levels in the initial 48 hours are associated with the development of pancreatic necrosis [4,5]. Many other serum markers such as C reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin, albumin, serum creatinine, etc have been identified to be related to pancreatic necrosis [6]. Lipinski and colleagues found that elevated SCr and estimated glomerular filtration rate (EGFR) levels on admission in the initial 48 hours are associated with increased severity and PNec with a $p < 0.001$[4]. A study has found that the sensitivity, and specificity of SCr >1.8mg/dl within 48 hours to predict PNec was 41.2% and 98.9%, respectively with positive predictive value (PPV) of 93.3% and negative predictive value (NPV) of 82.1% [6]. But another study has shown that the sensitivity and specificity of SCr was 23% and 95%, respectively with PPV of 41% and NPV of 89% [7]. A study by Wiese *et al.*, demonstrated that a strong association with infected pancreatic necrosis was seen for creatinine (OR [95% CI] 1.019 [1.005–1.033], $p < 0.001$) [8]. Therefore, an elevated SCr concentration at any time during the first 48 hours of admission can be a marker for PNec in acute pancreatitis. To find the diagnostic accuracy of elevated peak serum creatinine as a predictor of pancreatic necrosis in patients with acute pancreatitis taking the CECT scan as the gold standard and to establish the degree of agreement between the two clinical tests. SCr is a very easily available and cost-effective test that can be of great help as a predictor of PNec[3,9].

This study aimed to gather local evidence to implement the use of Serum creatinine as a diagnostic tool for early prediction of pancreatic necrosis which may help in the prevention and management of pancreatic necrosis.

METHODS

A cross-sectional analytical study was undertaken at the Department of Surgery, Benazir Bhutto Hospital from January 2020 to January 2023, after receiving approval from the ethical review board of Rawalpindi Medical University (reference number: 13/55/RMU). The study was structured by the Standards for Reporting Diagnostic Accuracy Studies (STARD) checklist. The null hypothesis postulated that "Peak serum creatinine cannot accurately predict the PNec and there is no agreement between elevated peak serum creatinine and CECT for the prediction of pancreatic necrosis in acute pancreatitis". A sample size of 150 cases was calculated using the WHO calculator (95% confidence level), with a 6% margin of error and taking an expected percentage of the degree of agreement between serum creatinine > 1.8 mg/dl and CECT to be 83.5% in the prediction of pancreatic necrosis in acute pancreatitis [6]. Sampling was done using a non-probability consecutive sampling technique. Patients of the age group 20 years to 65 years presenting to surgical emergency with a diagnosis of acute pancreatitis as defined in the operational definition were included in the study. Patients with pancreatic malignancies and patients having previous renal compromise were excluded from the study. After informed consent, demographics (name, age, gender, address) were noted. Serum creatinine (SCr) levels were noted by obtaining blood samples on presentation and 48 hours after admission. Samples were sent to the Hematology lab of the Benazir Bhutto Hospital and reports were assessed. Patients having SCr > 1.8 mg/dl were labeled as positive. Then patients underwent a CECT scan from the hospital within 96 hours of admission to confirm the presence or absence of PNec. CECT scan was reported by consultant radiologists. All this information was collected with a specially designed proforma. Acute Pancreatitis was defined as upper abdominal pain often radiating to the back with serum amylase or lipase level >3 times than normal and inflammation of gland parenchyma of the pancreas on imaging [2]. For pancreatic necrosis (PNec), in terms of serum creatinine, if the value of SCr within 48 hours was > 1.8 mg/dl, PNec was labeled as positive but if the value was ≤ 1.8 mg/dl then PNec was labelled as negative. Confirmation of the PNec was done on a contrast-enhanced CT scan. A CECT scan was done within 96 hours of admission. The presence of a focal or diffuse area of non-viable parenchyma on CECT was labelled as PNec [6]. The diagnostic accuracy was defined as the ability of peak serum creatinine to correctly identify the patients of acute pancreatitis having pancreatic necrosis (PNec) as compared with the CECT scan as the gold standard test. Patients with PNec identified through elevated Peak Serum Creatinine (SCr) levels and subsequently confirmed by contrast-enhanced computed tomography (CECT) scan were categorized as true positive. Those labelled PNec solely based on elevated SCr levels but not detected on CECT scan were classified as false positive. Patients not demonstrating PNec on both peak SCr levels and CECT scan were designated as true negative, while those lacking elevated Peak Serum Creatinine levels but exhibiting PNec on the CECT scan were identified as false negative. Diagnostic accuracy was measured in terms of sensitivity (true positive rate), specificity (true negative rate), negative predictive value, positive predictive value, and accuracy. An agreement was labelled if both CECT and serum creatinine agreed upon the diagnosis of pancreatic necrosis, which can be either positive or negative. The strength of agreement was measured by Kappa statistics by Altman [10]. The data were entered and analyzed using SPSS version 22.0. Age and SCr level (quantitative variables) were calculated as mean and standard deviation. Gender, PNec (on SCr and CT) and agreement being qualitative variables were calculated as frequency and percentage. The normality of data was determined using the Q-Q plot analysis. Diagnostic accuracy in terms of sensitivity, specificity, positive predictive value, negative

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predictive value, and accuracy was calculated. The area under the curve (AUC) was calculated. This was done by constructing a contingency table between the PNec suggested by the peak serum creatinine and PNec confirmed by CECT. Kappa statistics (Altman, 1991) were calculated to determine the strength of agreement between serum creatinine > 1.8mg/dl and CECT findings for the absence or presence of pancreatic necrosis. Independent t-test was applied for discrete variables with a p-value ≤ 0.05 as significant.

RESULTS

There were a total of 150 patients with acute pancreatitis in this study. The mean age was found to be 43.27 ± 8.067yrs We found that the peak incidence of pancreatitis was in age group 40-49(Figure 1).

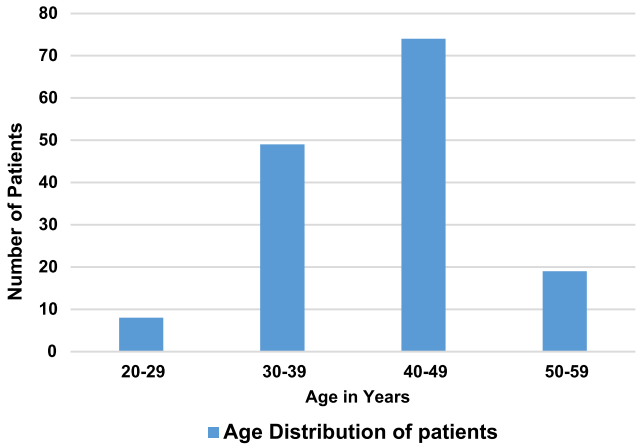

Figure 1: The Age Distribution of the Patients Presenting with Acute Pancreatitis

Total 66 patients were male while 84 patients were female with a male-to-female ratio of 1: 1.27(Figure 2).

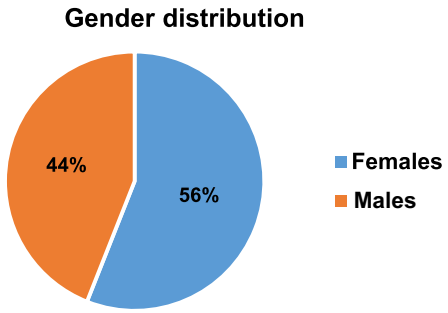

Figure 2: Gender Distribution of Patients(n=150)

Serum creatinine levels were assessed at admission and 48 hours' post-admission. The data exhibited a normal distribution based on Q-Q plot analysis. The mean creatinine level at 48 hours across the entire sample was 1.074 ± 0.64 mg/dl. A cohort of 20 patients was identified as potentially developing pancreatic necrosis, determined by a peak serum creatinine level exceeding 1.8 mg/dl. Calculation of the mean peak creatinine levels for patients diagnosed with pancreatic necrosis yielded 2.47 ± 0.68 mg/dl, while the corresponding value for patients without pancreatic necrosis stood at 0.85 ± 0.24 mg/dl (refer to Table 1). The resulting p-value of 0.001 signified a substantial disparity in peak creatinine levels between patients with and without pancreatic necrosis as determined by peak serum creatinine(Table 1).

Table 1: Mean Peak Creatinine in Patients with Pancreatic Necrosis on Creatinine(PNec on SCr)

Pancreatic Necrosis on Creatinine (Pnec on SCr)	Number of Patients n=150	Peak Creatinine at 48 Hours. Mean ± SD	*p value (95% CI)
Present	20	2.47± 0.68	0.001 (1.48-1.79)
Absent	130	0.85± 0.24	

CECT: Contrast Enhanced Computed Tomogram, SD: Standard Deviation, hours.: hours, CI: Confidence interval, *P value: independent samples T-test was applied

Among the 20 patients identified as having PNec based on SCr, 17 individuals were confirmed to have necrosis on CECT scan, categorizing them as true positive cases, while 3 patients did not exhibit any necrosis, constituting false positive results. Of the 110 patients anticipated to be free of pancreatic necrosis according to peak SCr levels, CECT scans corroborated the absence of necrosis, thus establishing them as true negative cases. Twenty patients initially not suspected to have PNec based on peak serum creatinine were subsequently found to have PNec upon undergoing a CECT scan 96 hours post-admission, representing false negative outcomes(Table 2).

Table 2: The number of patients having pancreatic necrosis on CECT scan and pancreatic necrosis on Peak Serum Creatinine (n:150)

Pancreatic Necrosis on Peak Serum Creatinine>1.8mg/dl	Pancreatic Necrosis on CECT Scan		Total
	Present	Absent	
Present	17	3	20
Absent	20	110	130
Total	37	113	150

The calculated sensitivity of serum creatinine as a predictor of pancreatic necrosis yielded 45.9%, with a specificity of 97.3%, a positive predictive value of 85.0%, and a negative predictive value of 93.8%. Notably, the overall accuracy of the method was ascertained to be 84.6%(Table 3).

Table 3: Measures of Diagnostic Accuracy for Pancreatic Necrosis on Peak Serum Creatinine

Variables	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)	AUC, p-value (95% CI)
PNec on Peak SCr	45.5% (29.9%-63.08%)	97.35% (92.4%-99.45%)	85.0% (63.5%-94.81%)	93.8% (80.3%-88.1%)	84.6% (77.6%-90.0%)	0.825,0.001 (0.733-0.916)

PPV: positive predictive value, NPV: Negative predictive value, CI: Confidence interval, AUC: Area under curve

The ROC curve analysis was done which showed an area under the curve (AUC) of 0.825 with a p-value of 0.001, 95%

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CI 0.733-0.916. This also shows that peak serum creatinine levels have a high diagnostic predictive value for pancreatic necrosis (Figure 3).

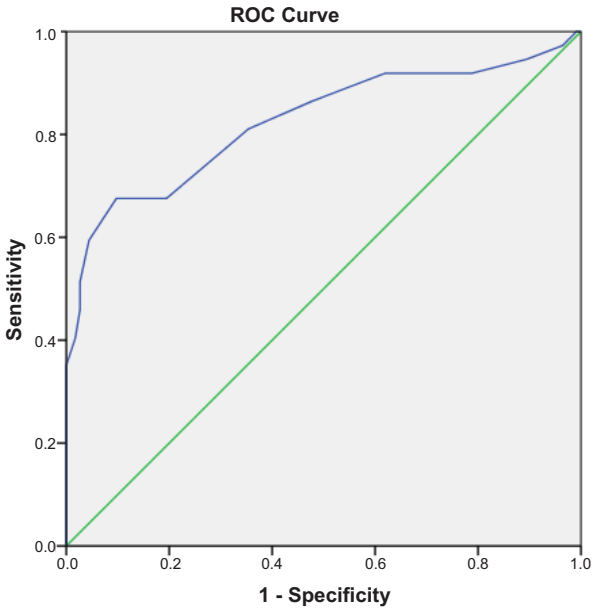

Figure 3: ROC Curve of Peak Serum Creatinine Levels by Pancreatic Necrosis

In the cohort of 150 patients, 127 exhibited concordant predictions for pancreatic necrosis (true positive and true negative) using both peak serum creatinine and CECT, while 23 patients displayed discordant predictions (false positive and false negative). The level of agreement between serum creatinine and CECT scan in predicting pancreatic necrosis was 84.7%. The computed kappa coefficient of 0.51 denotes a moderate level of agreement between the two modalities (Table 4).

Table 4: Degree of Agreement between Pancreatic Necrosis on Serum Creatinine and CECT scan (n:150)

Frequency (%)	Kappa Coefficient	p-value (95% CI)
127 (84.7)	0.51	0.001 (0.34-0.67)
23 (15.3)		

Kappa Coefficient: 0.51 means - strength of agreement (Altman, 1991)[10]

The overall results show that Peak serum creatinine has a specificity of 97.35%, PPV of 85.0 %, NPV of 93.8 %, and accuracy of 84.6%. and an agreement of 84.7% (kappa: 0.51). Consequently, the null hypothesis is rejected in light of these findings. Hence peak serum creatinine can be used as a predictor of pancreatic necrosis in patients with acute pancreatitis.

DISCUSSION

Acute pancreatitis is a disease with significant mortality and morbidity [1]. Pancreatic necrosis is associated with moderately severe and severe pancreatitis [2]. Early prediction and recognition of pancreatic necrosis and organ dysfunction can lead to a more tailored management which can improve the outcomes. Different biochemical markers such as are currently being investigated as predictors of pancreatic necrosis [11,12]. The mean age in current study was 43.27 ± 8.067yrs. One study found the mean age in acute pancreatitis patients to be 49.7 years [6]. However, another study found the mean age to be 52.5 years [13]. Yet another study has reported a mean age of 37 [14]. Hence the mean age of patients with acute pancreatitis in our study corresponds to that found in the international literature. Here 74 (49.3%) patients in the fourth decade of age that was age group 40-49 in present study. The mean ages in different international studies also show that acute pancreatitis is most common in the third and fourth decades of life. In our study, there are 66 (44%) males and 84 (56%) females with a male and female ratio of 1:1.27. Weis *et al.*, report that there was no significant gender difference in patients with acute pancreatitis developing pancreatic necrosis [8]. Walkowska *et al.*, also commented that gender distribution is dependent on etiology as alcoholic pancreatitis and gallstone pancreatitis are more common in male and female respectively [15]. In our study, acute pancreatitis was slightly more common in females and this can be because in our society alcohol intake is not as prevalent as in Western or other Asian societies and gallstones are the commonest etiology in our country. Serum creatinine was measured at admission and then at 48 hours. The highest value at 48 hours after admission was taken as peak creatinine. In current study mean peak creatinine at 48 hours in the whole sample was found to be 1.074 ± 0.64 mg/dl. This creatinine level is near the normal creatinine level of 1 mg/dl because only 37 (24.7%) out of 150 patients had pancreatic necrosis (confirmed on CT scan) and the rest had no necrosis and only mild acute pancreatitis. So mean creatinine levels in patients labelled as pancreatic necrosis on creatinine (Cr > 1.8 mg/dl) were calculated. It was found to be 2.47 ± 0.68 mg/dl (p-value = 0.001). In patients without pancreatic necrosis, it was 0.85 ± 0.24 mg/dl (p-value = 0.001). One study found the mean creatinine in patients with pancreatic necrosis to be 3.0 mg/dl [6]. In another study average concentrations of creatinine at baseline and 48 hours. after admission was 0.95 ± 0.75 mg/dl and 1.27 ± 0.81 mg/dl respectively (p-value = 0.001) [10]. This shows that serum creatinine is significantly raised in patients with pancreatic necrosis as compared to those without pancreatic necrosis. A peak serum creatinine level of > 1.8mg/dl at 48 hours was labelled pancreatic necrosis on creatinine (PNec on SCr). All the patients underwent a CT scan within 96 hours of admission to confirm the absence and presence of pancreatic necrosis being suggested on peak creatinine levels (PNec on CT scan). A total of 20 (13.3 %) patients had raised peak serum creatinine of more than 1.8 mg/dl and hence were predicted to have pancreatic necrosis. Among these 17 were confirmed to have PNec on CT scan. The sensitivity of

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serum creatinine as a predictor of pancreatic necrosis was calculated as 45.5%, specificity was 97.3%, positive predictive value was 85.0% and negative predictive value was 93.8%. The accuracy was 84.6%. The degree of agreement between PNec on SCr and PNec on CT scan was found to be 84.7 %. The AUC was 0.825. These results show that serum creatinine has a strong association with pancreatic necrosis and can be used as a predictor of pancreatic necrosis. Muddana *et al.*, studied the role of serum creatinine as a predictor of pancreatic necrosis. They studied a total of 129 patients. 15 patients had SCr > 1.8mg/dl predicting PNec and among these 14 were confirmed to have pancreatic necrosis on CT scan. 112 patients had SCr ≤1.8mg/dl suggesting the absence of PNec. On CT scan 92 patients were confirmed to have absence of necrosis. This showed that there was 83.5 % agreement between serum creatinine > 1.8mg/dl and CT scan on diagnosis of PNec. This study reported that SCr has a positive predictive value of 93%. Muddana *et al.*, concluded that an increase in SCr >1.8mg/dl within the first 48 h is strongly associated with the development of PNec [16]. One study has found that the sensitivity, and specificity of SCr in predicting pancreatic necrosis was 23% and 95%, respectively with PPV of 41% and NPV of 89%. According to this study, normal serum creatinine values at the time of presentation show that necrotizing pancreatitis is less likely and CECT is not needed unless complications occur [13]. A retrospective study of 2410 patients by Wiese *et al.*, demonstrated that a strong association with infected pancreatic necrosis was seen for creatinine (OR [95% CI] 1.019 [1.005–1.033], p < 0.001) [8]. The area under the curve (AUC) for serum creatinine in their study was 0.752. However, Wiese et showed that a predictive model has more diagnostic accuracy as compared to any of the serum markers alone. Another study by Papachristou *et al.*, concluded that early changes in serum creatinine can predict pancreatic necrosis and fatal outcomes [17]. Lipinski and colleagues found that elevated SCr and eGFR levels on admission in the initial 48 hours. are associated with increased severity and PNec with a p < 0.001 [18]. Hence this shows that findings in our study between PNec on SCr and CECT scan are comparable to that found in international literature. In our study Kappa statistics applied to determine the strength of agreement was found to be 0.51 with a p-value 0.001. Kappa coefficient of 0.51 shows a moderately strong degree of agreement [10]. A p-value of 0.001 shows that this agreement is highly significant statistically. Hence it shows that Peak serum creatinine >1.8 mg/l at 48 hours. is strongly correlated with pancreatic necrosis and may be used as a marker of pancreatic necrosis. The limitations of our study include that it was a single-center study. More such multicenter studies should be conducted to validate our results. In addition, in our study CECT scan was conducted within 96 hours. of admission, which could lead to missing the patients in whom pancreatic necrosis became evident after 96 hours. on CT scan. Also, we did not note the etiology and the severity of pancreatitis in this study and did not rule out their effect on the serum creatinine levels and pancreatic necrosis. Different scoring systems are used to estimate the severity of pancreatitis [19, 20] but the role individual biomarkers have not been studied yet. Also we did not differentiate infected pancreatic necrosis (IPN) from simple pancreatic necrosis in this study as some studies have shown association of biomarkers with IPN [5].

CONCLUSIONS

Severe acute pancreatitis (AP) presents a significant risk of mortality. Therefore, accurate prognostication of the disease's clinical trajectory at the time of admission is essential for formulating an effective treatment plan. Our study noted that elevated serum Cr >1.8 mg/dl within 48 h of admission can predict pancreatic necrosis with reasonable accuracy and hence can be used as a predictor of pancreatic necrosis.

Authors Contribution

Conceptualization: HSK

Methodology: HSK

Formal analysis: HSK

Writing-review and editing: HSK, MA, MH

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of Clinical Response to D-Mannose with Behavioral Modifications Versus Behavioral Modifications Alone in Asymptomatic Pyuria During Pregnancy

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ABSTRACT

The physiological and structural changes during pregnancy cause ureteral dilatation and urine stasis, which can lead to asymptomatic and symptomatic infections. **Objective:** To compare the clinical response between d-mannose with behavioral modifications versus behavioral modifications alone in asymptomatic pyuria during pregnancy. **Methods:** A quasi experimental study was conducted from April to September 2021, in the Department of Gynecology and Obstetrics Maternal and Child Health Center unit-1, PIMS, Islamabad. A total of 130 women with diagnoses of asymptomatic pyuria matching the inclusion criteria were recruited during study period and assigned to two groups by consecutive non-probability sampling method. Patients with urinary tract abnormalities, GDM, and antibiotic-treated symptomatic UTIs were excluded. Group A was instructed to take 1 g of D-mannose twice daily and follow the advises about behavioral changes.The group B was instrcucted to follow behavioral change only. pus cells in urine R.E.reports were used to evaluate response of treatments. **Results:** According to the study, the mean age of patients in group A was 27.69 ± 4.04 years, whereas group B had a mean age of 28.85 ± 4.12 years. The majority of patients (61.54%) were aged 15-30. Patients in group A had a mean gestational age of 23.72 ± 3.19 weeks, whereas group B had 24.26 ± 3.23 weeks. Patients had a mean BMI of 29.65 ± 3.55 kg/m^2. In group A; 23 (35.18%) and in group B 11 (16.92%) cases of asymptomatic pyuria achieved reolution. **Conclusions:** This study found that D-mannose with behavioral adjustments resolves asymptomatic pyuria during pregnancy better than behavioral modifications alone.

INTRODUCTION

During pregnancy, the physiological and anatomical changes are responsible for ureteral dilatation urinary stasis that facilitates the development of asymptomatic and symptomatic infections in women [1, 2]. The reported incidence of asymptomatic infection ranges from 2% to 12% in pregnant women. About 30-40% of the untreated pregnant women who have the asymptomatic urinary tract infection (bacteriuria /pyuria) will ultimately develop acute pyelonephritis, intrauterine growth retardation, and low birth weight, preterm labour [3-5]. Unfavorable maternal and perinatal outcomes are linked to untreated bacteriuria during pregnancy. Preterm birth, hypertensive problems, intrauterine growth restriction (IUGR), recurrent abortions, oligohydramnios and polyhydramnios, early rupture of the membranes, and labour induction are all independently linked to asymptomatic bacteriuria (ASB) [6]. Furthermore, throughout puberty, ASB raises the chance of pyelonephritis. Therefore, it has been recommended that all pregnant women attending an antenatal clinic, even in the absence of the symptoms, be regularly screened to avoid unfavorable problems in the baby and mother that may emerge owing to ASB [7]. Whether the infection is symptomatic or asymptomatic, pregnant women with UTIs are now treated with a brief course of antibiotics. An

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increase in antimicrobial resistance (AMR) is closely linked to the unnecessary or excessive use of antibiotics. Therefore, alternative therapies have been studied, such as cranberry juice and D-mannose. D-mannose is a sugar found in some fruits [8]. PIn human metabolism, D-mannose plays a role in the glycosylation of certain proteins. D-mannose is similar to the glycoprotein receptors on urothelial cells. Experiments have demonstrated that D-mannose binds to FimH adhesions present in fimbria of enteric bacteria and acts as a competitive inhibitor for bacterial adherence to urothelial receptors [9]. Therefore, if a sufficient amount of D-mannose is present in urine, then FimH adhesion will be saturated, so urothelial receptors are spared from bacterial adhesion. Ala-Jaakkola R *et al.*, compared the efficacy of D-mannose with trimethoprim/sulphametho xazole TMP/SMX in the prevention of urinary tract infection with results of mean time to recurrence 200 days in the D-mannose group, 52.7 days for the antibiotic group [10, 11]. Hayward *et al.*, compared D-mannose with nitrofurantoin [12]. Results favored the D-mannose group as an effective therapy for urinary tract infections. The recurrence rate of acute urinary tract infection in the D-mannose study group was 14.6%, while in the antibiotic group, it was 20.4%. Another study demonstrated the efficacy of D-mannose alone in managing acute urinary tract infections. This study displayed that the acute infection rate in the D-mannose group was 4.5%, while it was 33.3% in the placebo/no treatment group [12].

Studies have demonstrated the ability of D-mannose-like molecules to reduce bacterial load. So far, no study in Pakistan has been conducted to evaluate the efficacy of D-mannose in asymptomatic pyuria. Thus, the current study aimed to assess the role of D-mannose in resolving asymptomatic pyuria and recommend better treatment with less morbidity.

METHODS

A quasi experimental study was conducted from April to September 2021 in the Department of Gynecology and Obstetrics Maternal and Child Health Center unit-1, PIMS, Islamabad after the approval of the ethical review board (Ref No.F.1-1/2015/ERB/SZABMU/545). Patients with absence of any symptoms of urinary tract infections (UTI) with 15 or more white blood cells/µL on urine analysis report were included. Patients were excluded those with a history of urinary tract anomalies, pyelonephritis, history of antibiotics intake for symptomatic UTI, gestational diabetes, and systemic inflammatory urinary tract infections.Patients who fulfill the inclusion criteria were offered to participate in the study after informed verbal and written consent. A total of 130 women diagnosed with asymptomatic pyuria matching the inclusion criteria were recruited during study period and assigned to two groups by consecutive non-probability sampling method. The sample size was calculated using WHO sample size calculator with 5% level of significance and 80% power of test. With 65 subjects in each group, the total size was 130. Group A was instructed to take 1g twice daily of D-mannose (dietary supplement) for 5 days. Group B encountered no treatment and was the placebo group. Both groups were taught about behavioral modifications, i.e., drinking plenty of fluids (10-12 glasses a day), observing proper hygienic measures (washing front to back after the use of the toilet), frequency of urination, pre and post-coital voiding, complete bladder emptying before sleep). All patients were contacted by mobile phone to follow the advice and notified if any symptoms appeared. Urine Routine Examination (URE) was performed through laboratory after 5 days of therapy. Results of the study were assessed on the ability of either treatment plan to reduce white blood cells /pus cells on urine RE report i.e. <15 pus cells per µL. Resolution of pus cells ≥ 15 per µL of urine were regarded under asymptomatic pyuria. The collected data were analyzed by using the SPSS 23.0 version. Mean ± SD was calculated for age, BMI and gestational age. The outcome variable was calculated using frequency and percentages. A chi-square statistical significance test was applied to measure the frequency of pyuria between the two groups. p-value <0.05 was considered statistically significant.

RESULTS

This current enrolled 130 patients, with 65 patients in each group. The mean age of patients in group A was 27.69 ± 4.04 years, and in group B was 28.85 ± 4.12 years. The overall mean age of patients was 28.32 ± 4.09 years. Most of the patients in the current study were from the 15-30 age group, i.e., 61.54%. The mean gestational age of patients in group A was 23.72 ± 3.19 weeks, and in group B was 24.26 ± 3.23 weeks. The overall mean gestational age of patients was 23.89 ± 3.20 weeks. Most patients in the current study were from the >24 weeks gestational age group, i.e., 56.15%. The mean BMI of patients in group A was 30.03 ± 3.54 kg/m2 and 29.52 ± 3.58 kg/m^2 in group B. The overall mean BMI of patients was 29.65 ± 3.55 kg/m^2. Most patients in the current study were from the >30 BMI group, i.e., 53.85% (Table 1).

Table 1: Results of Age, Gestational and BMI in Study Groups (n=65)

Variables	Category	Study Groups		Total N (%) / (Mean ± SD
		Group A N (%) / (Mean ± SD)	Group B N (%) / (Mean ± SD)	
Age (Years)	15-30	44 (67.69%)	36 (55.0%)	80 (61.54%)
	31-45	21 (32.31%)	29 (45.0%)	50 (38.46%)
	Mean	27.69 ± 4.04	28.85 ± 4.12	28.32 ± 4.09
Gestational Age (Weeks)	13-24	30 (46.15%)	27 (41.54%)	57 (43.85%)
	>24	35 (53.85%)	38 (58.46%)	73 (56.15%)
	Mean	23.72 ± 3.19	24.26 ± 3.23	23.89 ± 3.20

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BMI (Kg/m^2)	≤30	27 (41.54%)	33 (50.77%)	60 (46.15%)
	>30	38 (58.46%)	32 (49.23%)	70 (53.85%)
	Mean	30.03 ± 3.54	29.52 ± 3.58	29.65 ± 3.55

This study found that the frequency for resolution of asymptomatic pyuria in group A was 23 (35.38%), and in group B, it was 11 (16.92%) with a significant p-value (p=0.017). These were detected by the presence of pus cells/WBCs ≥ 15 per µL of urine. Group A showed better results than Group B (Table 2).

Table 2: Results of Resolution of Asymptomatic Pyuria (n=65)

Resolution of Asymptomatic Pyuria	Study Groups		Total N (%)	p-value
	Group A N (%)	Group B N (%)		
Yes	23 (35.38%)	11 (16.92%)	34 (25.19%)	0.017*
No	42 (64.62%)	54 (83.08%)	96 (71.11%)	
Total	65 (100.0%)	65 (100.0%)	130 (100.0%)	

*Significance Level (p<0.05)

The stratification results of the resolution of asymptomatic pyuria with different variables were given in table 3.

Table 3: Stratification Results of Resolution of Asymptomatic Pyuria with Different Variables (n=65)

Variables	Category	Resolution of Asymptomatic Pyuria			
		Group A N (%)		Group B N (%)	
		Yes	No	Yes	No
Age of Patients (Years)	15-30	18 (40.91%)	26 (59.09%)	06 (16.67%)	30 (83.33%)
	31-45	05 (23.81%)	16 (76.19%)	05 (17.24%)	24 (82.76%)
GA (Weeks)	13-24	07 (23.33%)	23 (76.67%)	03 (11.11%)	24 (88.89%)
	>24	16 (45.71%)	19 (54.29%)	08 (21.05%)	30 (78.95%)
BMI (Kg/m^2)	≤30	08 (29.63%)	19 (70.37%)	05 (15.15%)	28 (84.85%)
	>30	15 (39.47%)	23 (60.53%)	06 (18.75%)	26 (81.25%)

DISCUSSION

One effective non-antibiotic preventive method is D-mannose. It is an inactive monosaccharide that prevents germs from adhering to the urothelium. It is broken down and eliminated in urine. D-mannose is a simple sugar crucial to human metabolism because it causes proteins to become glycosylated [13]. Specifically, D-mannose functions as a competitive inhibitor of bacterial adhesion to receptors of urothelial cells by binding to and blocking FimH adhesins on the tip of type 1 bacterial fimbriae. Type 1 pili have been seen on E. coli, Klebsiella pneumoniae, Enterobacter cloacae, Shigella flexneri, Serratia marcescens and Salmonella typhimurium, among other members of the Enterobacteriaceae family. As a result, D-mannose may stop many uropathogens connected to UTIs from adhering to the urothelium [14]. This study was conducted to compare D-mannose in combination with behavioral modifications to behavioral modifications alone for resolving the frequency of asymptomatic pyuria during pregnancy. The resolution of asymptomatic pyuria was found in 35.38% of women taking D-mannose in combination with behavioral modifications and 16.92% in women taking behavioral modifications only, p = 0.017. Results favored the D-mannose group as an effective therapy for urinary tract infections. The recurrence rate of acute urinary tract infection in the D-mannose study group was 14.6%, while in the antibiotic group, it was 20.4%. Another study demonstrated the efficacy of D-mannose alone in managing acute urinary tract infections. This study displayed that the acute infection rate in the D-mannose group was 4.5%, while it was 33.3% in the placebo/no treatment group [15]. Concentrated D-mannose pills or sachets were tested in human pilot trials at dosages ranging from 200 mg to 3 g, with potential benefits in lowering UTI symptoms or recurrence [16]. These findings support the findings of the current study. A prospective study, which included women with a history of UTIs, was conducted by Ala-Jaakkola R *et al* [10, 17]. An oral liquid nutritional supplement, including D-mannose, was given to women, and the safety, tolerability, and maximum tolerated dosage were checked. Efficacy regarding UTI and symptoms related to quality of life (QOL) were significantly reduced in women who use liquid nutritional supplements, including D-mannose. De Nunzio C *et al.*, evaluated the effectiveness of D-mannose alone in treating acute UTIs in 43 women and explored the drug's potential for managing recurrences [18]. The majority of symptoms in this prospective trial significantly improved 15 days after D-mannose was administered, according to the investigators. It's interesting to note that patients were randomized into two groups sequentially one month following diagnosis. In specifics, 21 women did not get treatment, while 22 women got prophylaxis with D-mannose. In the prophylactic group, the mean time to UTI start was 43 days (± 4.1 SD), but in the other group, it was 28 days (± 5.4 SD) (p = 0.0001). Marchiori D *et al.*, assessed the efficacy of D-mannose with antibiotic treatment to lessen the persistence of UTI in sixty women who had survived breast cancer [19]. The authors conducted a retrospective analysis of two groups of patients: 20 patients treated with antibiotics alone and 40 women treated with antibiotic treatment combined with D-mannose for six months. Compared to women treated only with antibiotics, patients treated with D-mannose showed a significant reduction in bacteria-positive urine cultures. A randomized three-arm parallel-group research with 72 women who had a history of recurrent cystitis and an acute UTI was reported by Genovese C *et al.* Oral D-mannose was administered to all three groups; in group A, it was linked to birch, arbutin, and berberine; in group B, it was linked to birch, arbutin, birch, and forskolin; and in group C, it was related to proanthocyanidins. There were twelve weeks in the trial. In contrast to patients recruited in group C, the authors noted that patients in groups A and B had a decreased incidence of bouts of recurrent cystitis throughout therapy and follow-up [20].

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CONCLUSIONS

This study concluded that D-mannose with behavioral modifications is better than behavioral modifications alone in resolving asymptomatic pyuria during pregnancy. So, this study recommends that D-mannose with behavioral changes be advised routinely to reduce the progression of asymptomatic pyuria during pregnancy as well as the complications of pyuria.

Authors Contribution

Conceptualization: IB

Methodology: IB, SS

Formal analysis: IB

Writing, review and editing: BB, IB, SD,SZ,ZA

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparative Evaluation of Effects of Propofol and Ketamine versus Dexmedetomidine and Ketamine on Blood Pressure, Heart Rate and Recovery of Patients undergoing Dilatation and Curettage

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ABSTRACT

Cardiovascular stability and fast recovery are fundamentals of anesthesia for day care surgery. Dilatation and curettage is a commonly performed minor surgery in obstetrics and gynecology. Propofol is well-studied agent in short surgical procedures. Dexmedetomidine, popular for conscious and cooperative sedation is being used for minor gynecological procedures nowadays. **Objective:** To compare the effects of propofol and ketamine combination with dexmedetomidine and ketamine combination on cardiovascular parameters and recovery of patients undergoing dilatation and curettage. **Methods:** In a quasi-experimental study from March 2021 to August 2021, 136 patients admitted for dilatation and curettage under anesthesia were enrolled. Patients were divided into two groups. Group P+K received intravenous propofol and ketamine and Group D+K received intravenous dexmedetomidine and ketamine. During the procedure, blood pressure, heart rate, oxygen saturation, and recovery time were noted in both groups. **Results:** The demographic data were comparable in both groups. Group P+K had significantly higher heart rate at 5, 10, 15 min, and at the ending of the procedure as compared to group D+K. Group D+K had significantly higher systolic and diastolic blood pressure at 2 min, 5 min, 10 min, 15 min and at procedure end in comparison with group P+K. Bradycardia was observed in 62 (91.2%) patients in D+K group whereas, in P+K group, hypotension was observed in 16 (23.5%) patients. The mean time to attain MAS (modified aldrete score) of 10 in group P+K was 32.0 ± 2.1 minutes whereas in group D+K was 41.3 ± 2.6 minutes. **Conclusions:** It was concluded that the use of dexmedetomidine and ketamine in dilatational and curettage provides cardiovascular stability without respiratory depression as compared to propofol and ketamine.

INTRODUCTION

Cardiovascular stability and early recovery are the mainstays of any type of Anesthesia. A combination of sedatives, analgesics, and hypnotics are used to achieve rapid onset, potent anesthesia, and fast recovery. It is also associated with minimum adverse effects due to reduced doses. Dilatation and curettage is a routine surgery that is frequently performed in obstetrics and gynaecology as a daycare procedure [1]. Day-care surgery is cost effective and removes economic burden from hospital resources. At present combination of sedatives, hypnotics and analgesics are used in anesthesia for minimally invasive procedures [2, 3]. Propofol is regarded as an effective anesthetic drug for short-duration procedures and ambulatory surgeries because of its quick onset and fast recovery [4, 5]. Due to minimal analgesic properties, propofol is often combined with opioids like fentanyl, morphine, or nalbuphine. Opioids are notorious for undesirable respiratory outcomes which are often related to depression of central nervous system [6]. Propofol may cause bradycardia and hypotension in addition to

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respiratory depression [7]. Propofol is a well-studied anesthetic agent in short surgical procedures but cannot be used as only an anesthetic agent. Ketamine has historical use in dilatation and curettage. It provides dissociative anesthesia with properties of fast onset, potent analgesia, sedation, and hypnosis. Propofol is strengthened with analgesic properties of ketamine instead of opioids due to the lack of respiratory compromise by ketamine. A combination of ketamine and propofol is a suitable option in gynecological procedures of short duration [8]. Dexmedetomidine is more selective alpha-2 receptor adrenergic agonist as compared to clonidine, with properties of analgesia, amnesia, sympatholysis and sedation [9]. It provides cardiovascular stability [10], without any significant respiratory depression [11]. Moreover, its sedative properties are unique due to mild cognitive impairment [12]. It can be used for conscious sedation [13, 14]. It is also useful in getting discharged earlier from post-anesthesia recovery unit [15]. The foremost advantage of dexmedetomidine on propofol is that it is not associated with suppression of spontaneous breathing and airway reflexes or fall of systolic blood pressures. Combination of dexmedetomidine with ketamine not only limits psychological side effects of ketamine like hallucinations but also avoids potential harmful effects of dexmedetomidine on heart rate like bradycardia So, the use of ketamine with dexmedetomidine appears to be a superior choice for dilatation and curettage [16, 17]. Though the efficacy of propofol, ketamine and dexmedetomidine are compared in many studies but use of a combination of dexmedetomidine in dilatation and curettage seems to be a better combination in terms of cardiovascular stability, effective sedation, potent analgesia, and minimum time of recovery.

The main aim of this research is to study the effects on cardiovascular parameters and recovery of patients undergoing dilatation and curettage using propofol-ketamine and dexmedetomidine-ketamine combinations. There is insufficient data for the use of these combinations of anesthetic drugs in dilatation and curettage. Results of different studies comparing cardiovascular parameters and recovery characteristics of propofol and dexmedetomidine are equivocal. There is a need for further studies to elaborate properties of dexmedetomidine and propofol when used in combination with ketamine.

METHODS

It was a quasi-experimental study conducted at Dr. Faisal Masood Teaching Hospital, Sargodha. Upon approval from our Hospital Ethical Committee (IRB NO.528) and after getting informed consent from participants, 136 patients undergoing dilatation and curettage (therapeutic or diagnostic) on elective list meeting the inclusion criteria were registered in a study from operation theatre, Department of Obstetrics and Gynecology, Dr. Faisal Masood Teaching Hospital Sargodha over a period of six months from March 2021 to August 2021. Patients were divided into 2 groups, Group (P+K) or Group (D+K), with 68 patients in each group by non-probability purposive sampling. Upon arrival in operating room, patients were infused with lactated Ringer (10ml/kg). Supplemental oxygen was provided to all (both groups) by nasal cannula @4 liters /min. Group (P+K) was injected with Ketamine 0.6mg/kg diluted slow IV then in Propofol 1mg/kg IV bolus slowly over 10 min followed by titrated intravenous infusion of 75- 100micro-gram/kg/min till end of procedure. Group (D+K) received Ketamine 0.6mg/kg slow IV then Dexmedetomidine at a loading dose 1micro- gram/kg IV over 10 min then a maintenance dose of 0.4 - 0.6 micro-gram/kg/hour infusion until achievement of RSS 4 (Ramsay sedation score). If the surgeon or patient was uncomfortable, the rate of infusion was increased and ketamine 20mg IV top up bolus was given as rescue sedation. The need for rescue sedation was noted and compared in both groups. During the procedure heart rate (HR), systolic BP, and diastolic BP were recorded at 0 min, 2 min, 5 min, 10 min, and 15 min afterwards every 5 min till completion of procedure. Any intraoperative adverse event like hypoxia, hypotension, hypertension, bradycardia, or tachycardia was noted and managed. cardiovascular characteristics were measured in terms of Heart rate, Systolic BP, and Diastolic BP. This study included Pregnant and non-pregnant females who undergoing elective dilatation and curettage. Diagnostic and therapeutic dilatation and curettage in whom dilatation of cervix is required before uterine curettage. And the age between 18-55 who are hemodynamically stable. And the patients with uncontrolled diabetes mellitus, hypertension, cardiac, renal, hepatic, and endocrine disorders. Patients with BMI <18 or >35, and who do not require dilatation of cervix for uterine curettage.

Operational Definitions

Bradycardia: Heart rate less than or equal to 50 bpm or Fall of Heart rate ≤ 20% from baseline value.

Tachycardia: Heart rate greater than or equal to 110 bpm or Rise in Heart rate ≥ 20% from baseline value.

Hypotension: Decrease in Systolic and Diastolic BP ≤ 20% from baseline.

Hypertension: Increase in Systolic and Diastolic BP ≥ 20% from baseline.

Recovery characteristics were measured in terms of time to reach Modified Alderete Score of 9.

Following formula was used for calculating sample size using perioperative hemodynamic variables, mean SBP (mmHg) of 120 in Group P and mean SBP (mmHg) of 117 in Group D, taken from the reference study [3].

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$$n = \frac{(Z_{1-\beta} + Z_{1-\alpha/2})^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)}$$

(Sample Size determination in health studies version 2.0.21 WHO)
Desired Power of study = 80%
Desired Level of Significance = 5%
Mean value of systolic BP in group 1 = 120
Mean value of systolic BP in group 2 = 127
Standard Deviation of systolic BP in group 1 = 15
Standard Deviation of systolic BP in Group 2 = 14
n = Minimum Sample size for each group= 68
All patients were shifted to Post Anesthesia Recovery Unit (PACU) after the accomplishment of procedure. Modified Aldrete Scoring System (MAS) and Ramsay Sedation Score (RSS) was used as a tool to evaluate post-anesthesia recovery every 5 minutes (Table 1&2).

Table 1: MAS Score among Patients

Characteristics	Score
Breathing	
Able to Breathe Deeply	2
Dyspnea	1
Apnea	0
Circulation	
Systemic BP not Equal to 20% of Preanesthesia Level	2
Systemic BP B/W 20% and 49% of Preanesthesia Level	1
Systemic BP not Equal to 50% of Preanesthesia Level	0
Oxygen Saturation	
Maintaining O_2 Saturation > 90% at Room Air	2
Needs Inhalation to Maintain O_2 Saturation > 90%	1
O_2 Saturation < 90% Despite Supplemental Oxygen	0
Consciousness	
Fully Awake	2
Arousable	1
Not Responding	0
Mobility	
Able to Move 4 Extremities on Command	2
Able to Move 2 Extremities on Command	1
Able to Move 0 Extremities on Command	0

Table 2: Ramsay Sedation Score among Patients

Sedation Level	Score
Anxious, agitated, restless.	1
Co-operative, oriented, tranquil.	2
Responds to commands only.	3
Brisk response to light glabellar tap or loud noise	4
Sluggish response to light glabellar tap or loud noise	5
No response.	6

Patients were discharged from PACU after gaining MAS ≥ 9. The time to reach MAS score of 9 was noted in PACUS and was compared in both Groups.

RESULTS

Data were compiled and analyzed using SPSS version 23.0. The mean age of patients in group (P+K) was 30.5 ± 5.4 years and mean age of patients in group (D+K) was 31.0 ± 5.9 years. The mean BMI of patients in group (P+K) was 24.4 ± 2.6 Kg/m^2 and mean BMI of patients in group (D+K) was 24.0 ± 2.3 Kg/m^2. The mean duration of procedure of patients in group (P+K) was 24.4 ± 2.6 min and mean duration of procedure of patient in group (D+K) was 24.0 ± 2.3 min. Independent sample t test showed that mean age, mean BMI and duration of procedure between the groups were not significant. Independent sample t test was used to compare the mean difference in heart rate between both groups at 0, 2, 5, 10, 15 min and at the end of the procedure. Results indicated that the mean heart rate was higher significantly in (P+K) group as compared to (D+K) group at 5 min, 10 min, and 15 min and at the end of the procedure (Table 3).

Table 3: Comparison of the Mean Heart Rate Between both Groups

Variables	Group (P+K) Mean ± SD	Group (D+K) Mean ± SD	p- value
0 Min	88.0 ± 3.3	86.8 ± 3.3	0.092
2 Min	82.7 ± 2.7	81.9 ± 3.3	0.197
5 Min	79.0 ± 3.1	69.7 ± 3.4	<0.001
10 Min	76.0 ± 3.6	62.4 ± 3.8	<0.001
15 Min	79.4 ± 3.9	67.6 ± 3.2	<0.001
At End of Procedure	81.6 ± 4.0	70.9 ± 3.4	<0.001

Independent sample t test was used to compare the mean difference in systolic blood pressure between both groups at 0, 2, 5, 10, 15 min and at the end of the procedure. Results indicated that the systolic blood pressure was significantly higher in (D+K) group as compared to (P+K) group at 2, 5, 10, 15 min and at the end of the procedure (Table 4).

Table 4: Comparison of the Mean Systolic Blood Pressure Between both Groups

Variables	Group (P+K) Mean ± SD	Group (D+K) Mean ± SD	p- value
0 Min	130.0 ± 8.1	129.4 ± 8.7	0.610
2 Min	118.7 ± 7.2	124.8 ± 8.0	<0.001
5 Min	111.0 ± 5.8	120.7 ± 7.5	<0.001
10 Min	106.1 ± 5.6	118.0 ± 7.2	<0.001
15 Min	111.4 ± 4.7	121.1 ± 7.3	<0.001
At End of Procedure	114.5 ± 5.6	123.2 ± 7.3	<0.001

Independent sample t-test was used to compare the mean difference in diastolic blood pressure between both groups at 0, 2, 5, 10, 15 min, and the end of the procedure. Results indicated that the mean diastolic blood pressure was significantly higher in (D+K) group as compared to the (P+K) group at 2, 5, 10, 15 min and the end of the procedure (Table 5).

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Table 5: Comparison of the Mean Diastolic Blood Pressure between both Groups

Variables	Group (P+K) Mean ± SD	Group (D+K) Mean ± SD	p- value
0 Min	85.3 ± 5.8	84.5 ± 5.3	0.441
2 Min	77.0 ± 5.5	81.2 ± 5.3	<0.001
5 Min	71.5 ± 5.1	78.5 ± 5.4	<0.001
10 Min	68.0 ± 4.7	76.2 ± 5.1	<0.001
15 Min	72.0 ± 4.5	78.9 ± 4.8	<0.001
At End of Procedure	74.0 ± 4.8	80.3 ± 5.0	<0.001

Mann Whitney U test was used to compare the mean difference in oxygen saturation between both groups at 0, 2, 5, 10, 15 min and at the procedure end. Results indicated that the mean oxygen saturation was significantly higher in (D+K) group as compared to the (P+K) group at 0, 2, 5, 10, 15 min and at the end of the procedure (Table 6).

Table 6: Comparison of the Mean Oxygen Saturation between both Groups

Variables	Group (P+K) Mean ± SD	Group (D+K) Mean ± SD	p- value
0 Min	98.0 ± 0.68	97.8 ± 0.72	0.037
2 Min	92.6 ± 1.36	97.2 ± 0.73	<0.001
5 Min	88.7 ± 1.45	96.3 ± 0.82	<0.001
10 Min	93.3 ± 1.36	96.7 ± 0.91	<0.001
15 Min	94.6 ± 1.03	97.3 ± 0.80	<0.001
At End of Procedure	95.6 ± 0.65	97.6 ± 0.66	<0.001

The mean time to achieve MAS of 9 of patients in group (P+K) was 32.0 ± 2.1 min and mean time to achieve MAS of 9 of patient in group (D+K) was 41.3 ± 2.6 min (Table 5). Normality of data were assessed by Shapiro Wilk test which revealed that the data were not normally distributed. Therefore, Mann Whitney U test was used to compare the mean time to achieve MAS of 9 between the groups. Result shows that mean time to achieve MAS of 9 was significantly more in group (D+K) as compared to group (P+K) (Table 7).

Table 7: Showing Comparison of Time to Achieve MAS of 9 between both Groups

Variables	Group (P+K)	Group (D+K)	p-value
Time to achieve MAS of 9 (in minutes)	32.0 ± 2.1	41.3 ± 2.6	<0.001

DISCUSSION

In this study, there was a significant fall in heart rate in group dexmedetomidine-ketamine as compared to group propofol-ketamine group at 5 min, 10 min, 15 min. Dexmedetomidine is well known for causing bradycardia due to its more selective affinity towards α2 adrenergic receptors and vagomimetic property. Heart rate at 2 min after loading dose was comparable in both groups probably due to cardiovascular effects of ketamine. A study comparing propofol-ketamine with dexmedetomidine-ketamine sedation in DCR (dacryocystorhinostomy) found that although there was significant reduction in mean arterial pressure and heart rate from baseline in two groups but the difference of heart rate and mean arterial pressure between two groups was not significant [18]. Research work done in pediatric patients undergoing minor cardiological procedures also commends our findings. Heart rate was significantly decreased in initial readings and kept on falling till twenty-five minutes in the dexmedetomidine and ketamine group as compared to propofol and ketamine [19]. A fall of heart rate of more than 20 percent of baseline was labelled as bradycardia. 62 patients out of 68, in dexmedetomidine-ketamine group had more than twenty percent fall of heart rate from baseline while none in propofol-ketamine group experienced bradycardia. Bradycardia in dexmedeto midine-ketamine group neither caused cardiovascular instability in any patient nor demanded atropine administration. A statistically significant difference of systolic and diastolic blood pressure was found in two groups. A decrease in trend of systolic and diastolic blood pressures was found at 2 min, 5 min, 10 min, and 15 min in propofol and ketamine group. This finding of our study is contradictory to findings of that of Farrukh *et al.*, in which difference between mean arterial pressures of two groups was not significant [20]. This decrease in blood pressure was due to peripheral vasodilation caused by propofol. In propofol-ketamine group, 16 out of 68 patients had fall in systolic and diastolic blood pressure of more than 20 percent of baseline values. While in dexmedetomidine-ketamine group, none experienced hypotension. Hypotension in patients was managed with rapid administration of crystalloids and colloids in most of patients. Vasopressor bolus (phenylephrine 50-100 micro gram) was administered only in two patients. Relatively stable blood pressure readings were observed in dexmedetomidine-ketamine group throughout procedure. Study of Sethi *et al.*, showed similar results when comparing propofol and dexmedetomidine in dilatation and curettage. They reported a higher number of episodes of hypotension (52%) with propofol as compared to dexmedetomidine (8%) [3]. Patients given propofol had significantly less values of systolic BP and diastolic BP at 2 min, 5 min, 10 min and 15 min of procedure as compared to dexmedetomidine. A study conducted in hemodynamically stable ICU patients with sepsis by Benken *et al.*,. also mentioned that hypotension was pronounced with propofol as compared to dexmedetomidine (a fall of 47 mmHg versus 34 mmHg) [21]. In our study reduction in non-invasive blood pressure was not as higher because of addition of ketamine and non-critical, relatively healthy patients. However, our results differed from published work of Canopolat *et al.*, which reported that propofol-ketamine had similar hemodynamic profile (heart rate, non-invasive BP) as dexmedetomidine-ketamine in pediatric population undergoing dental procedures under

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sedation [22]. Difference in oxygen saturation recorded by pulse oximeter was found to be significant at 2 min, 5 min, 10 min, 15 min and at end of procedure. A fall in oxygen saturation was noted in propofol and ketamine group at 2 and 5 minutes which was managed by increasing flow of oxygen. None of patient went into apnea. Oxygen saturation gradually started increasing at 10, 15, and 20 minutes and till end of procedure. In comparison, dexmedetomidine-ketamine group-maintained oxygen saturation throughout procedure. Kandil and his coworkers also found that the use of ketamine and dexmedetomidine combination resulted in less fall of oxygen saturation (less than 85%) as compared to propofol group during drug induced sleep endoscopy [23]. Difference in time to attain MAS (Modified Aldrete score) of 9 was found significant between dexmedetomidine-ketamine and propofol-ketamine group (41.31 ± 2.57 vs 32 ± 2.13 min respectively). This is consistent with findings of a research that compared dexmedetomidine- ketamine and propofol-ketamine procedural sedation in gastrointestinal endoscopy for patients with hepatic disease (9 ± 1.41 min in KP group versus 19 ± 1.53 min in the KD group). The shorter mean recovery time in comparison with our study is probably due to use of different drug dosing regimens and a different criterion for recovery [24].

CONCLUSIONS

Dexmedetomidine and ketamine is an effectual substitute to propofol and ketamine in dilatation and curettage. Combination of dexmedetomidine with ketamine provides cardiovascular stability without any respiratory depression but at the cost of delayed recovery and more need for rescue sedation in comparison with propofol and ketamine combination in obstetrics and gynaecology procedures of short duration.

Authors Contribution

Conceptualization: RF, MM

Methodology: FO

Formal analysis: AR

Writing-review and editing: FQ, SA

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

Conflicts of Interest

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Original Article

Comparative Study of the Combined Antibacterial Effects of Grape Seed and Cranberry Fruit Extracts on Extended-Spectrum Beta-Lactamase (ESBL)-Producing *Escherichia coli*

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ABSTRACT

Antimicrobial resistance is a threat to global healthcare system. Therefore, there has been growing interest towards the natural plants which possess antimicrobial properties. **Objective:** The key goal of the current research is to find out the combined effect of cranberry fruit and grape seed extracts against Extended-Spectrum Beta-Lactamase (ESBL) *Escherichia coli* strains. **Methods:** *E.coli* bacteria with ESBL resistance were collected from the patient's samples having bacterial infection. The extracts, grape seeds and cranberry fruits extract were prepared in different concentrations. Antibiotic susceptibility testing was done with different concentrations of the extracts, using agar dilution methods to assess their antibacterial efficacy against Meropenem and Linezolid. SPSS version 21.0 was used for data analysis. **Results:** The combined effect of cranberry fruit and grape seed extracts demonstrated significant antibacterial influence in counter to decrease ESBL *E.coli* strains. There were 40 specimens, with 45% female and 55% male, with an age range between 10 to 80 years old. Both the plant extract revealed high sensitivity against ESBL *E.coli*, with 95% sensitivity at the highest concentrations. The combination of CFE and GSE (50mg+60mg) showed more than 90% sensitivity, more than commonly used antibiotics like Meropenem and Linezolid. **Conclusions:** The combined effect of cranberry fruit and grape seed extracts showed excellent effect against antimicrobial resistance, particularly in ESBL-producing *E.coli* strains. The finding suggested the increase potential of natural products as alternative antimicrobial agents.

INTRODUCTION

Antibiotics, often referred to as "magic bullets," transformed 20th-century medicine by saving millions of individuals from bacterial infections [1]. The addition of antibiotic brought a positive change in the healthcare system, saving people from life threatening consequences. This plays a vital role in contemporary medicine [2]. However, the increased and excessive and inappropriate use of the antibiotics has directed to the development of the drug resistance. Thus, this inclination has developed the resistance of the antibiotics and also reduced the possibilities for treating bacterial infections. In the 21st century, the prevalence of antimicrobial-resistance have reached to alarming levels, leading towards a silent and profound threat to worldwide healthcare system similar to a pandemic [3]. Antimicrobial resistance is the capability of bacteria to continue to multiply regardless of the drug

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that was used to eradicate them. [4]. Antibiotic resistance presents a healthcare pandemic, after the appearance of ESBL-producing strains of (*E.coli*). The increase of ESBL has increases the rates of death, longer hospital stays, and increased expenses for treatment [5]. ESBLs are enzymes found in Gram-negative bacteria from the Enterobacteria ceae family, where they are encoded on plasmids or chromosomes. These enzymes degrade β-lactam antibiotics, making them ineffective. The World Health Organization (WHO) has recognized ESBL-producing Enterobacteriaceae (ESBL-E) as dangerous infectious agents which present major therapeutic problems [6]. Penicillin, Aztreonam, and first, second, and third generation Cephalosporins are among the antibiotics to which ESBL-E strains are resistant; however, they are still susceptible to cephamycin and carbapenems [7]. Natural products have received significant interest recently as possible sources of antimicrobial compounds because of their different chemical profiles and apparent reduced tendency to cause resistance when compared to conventional antibiotics [8]. These natural sources, cranberries and grape seeds have gained quite attention because of their well-established health benefits and high polyphenol content [9].

Therefore, the purpose of this study was to compare the antibacterial efficacy of grape seed and cranberry fruit extracts to ESBL *E.coli*.

METHODS

The *in vitro* research was done at a Tertiary care hospital from February to August 2023 to investigate the anti-bacterial efficacy of grape seed extract and cranberry fruit extract against ESBL *E.coli*. The participant involved in this study have an age range of 15 to 70 years old, showing symptoms of microbial infections. Samples of discharge, urine, body fluid, and tracheal aspirates were obtained for analysis at Clinical Microbiology Laboratory. Both were purchased from the marketplace in Karachi. The authentication of the grape seeds was conducted by the Botanical Department, GSE and CFE were extracted at the Department of Pharmacognosy, University of Karachi, and stored at room temperature for experiment. Patient of all ages and sample of blood, pus or urine in which ESBL E.coli were included whereas sample showing double growth or contamination on agar plates were excluded. Fresh grapes and cranberries purchased from Karachi markets underwent similar extraction processes. The grapes were crushed to separate the seeds, which were then carefully rinsed with fresh water and consequently dried-out at 60°C in an oven while cranberries were kept at 35°C in oven. The dried fruits were then powdered using an electric grinder.20-gram powder of the grape seed and cranberry fruit extract was mixed with 100 ml of ethanol in a conical flask separately. The mixtures were agitated for 48 hours; for grape seed extract, this was done by stirring, while for cranberry fruit extract, a rotary shaker was used. After the incubation period, the mixtures were filtered using Whatman filter paper (Whatman no. 1) to remove solid particles. The filtrates were then concentrated by evaporating the ethanol at 50°C in an oven. Finally, the concentrated extracts were mixed with 25% dimethyl sulfoxide (DMSO) to prepare solutions with concentrations ranging from 20 to 60 mg/ml. These solutions were stored in sealed vessels at 4°C for future analysis and use. Patient samples cultured on Mueller-Hinton agar plates were used to identify microorganisms using standard laboratory methods. Agar dilution techniques assessed the antibacterial effectiveness of GSE + CFE against Extended-Spectrum Beta-Lactamase-producing *Escherichia coli* (ESBL *E. coli*) isolated from patient specimens (urine, blood, pus). Test bacteria cultures grown in Nutrient broth for 24 hours were spread evenly on sterile Nutrient agar plates. Wells (8 mm diameter) created with a sterile cork borer in inoculated plates contained GSE (20 mg/ml in 25% Dimethyl sulfoxide), CFE (20 mg/ml in 25% Dimethyl sulfoxide), and positive controls Linezolid (10 µg) and Meropenem (30 µg) and plates were incubated for 24-48 hours at 37°C. Zones of inhibition was measured using a ruler to assess bacterial growth inhibition by extracts and antibiotics. The cranberry fruit and grape seed extracts were combined in equal ratios to maintain the desired concentrations. The concentrated extracts were diluted with final concentrations of 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, and 60 mg/ml. The susceptibility testing was performed using combined extract of both fruits against E. coli taken from patient samples. Agar dilution techniques were used for testing, where the bacteria cultured in nutrient broth were uniformly spread onto agar plates. Wells were prepared in the agar, and into these wells, various concentrations of GSE and CFE extracts were added, along with standard antibiotics Linezolid and Meropenem for comparison. Following incubation, the plates were examined to measure the zones of inhibition around the wells, indicating the extent to which the extracts and antibiotics inhibited bacterial growth. Data investigation was conducted using SPSS version 21.0. Frequencies and Percentages were calculated for categorical variables such as gender distribution (women vs. men). Mean and Standard Deviation were reported for continuous variables like participant age. Chi-square test was applied to determine whether there were significant differences in susceptibility rates between the combined CFE + GSE extract and the conventional antibiotics (Meropenem and Linezolid) against ESBL-producing *E. coli*. ($p < 0.05$).

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RESULTS

The demographics of the studied partakers are brief in Table 1. Total 40 specimens were processed in the investigation. Amongst the partakers, there were 18 women, comprising 45% of the total, and 22 men, constituting 55% of the total cohort. The age range of the participants varied from 10 to 80 years. The average age of the partaker was 40.34 ± 11.45 years.

Table 1: Profile of the Investigation Participants

Variables	N (%) / Mean ± SD
Samples Analyzed	40
Gender	
Women	18 (45%)
Men	22 (55%)
Age	
Age Distribution (Years)	10 to 80
Age	40.34 ± 11.45 Years

Table 2 showed the sensitivity of *Escherichia coli* to the extract across various concentrations. At the highest concentrations of 60 mg/ml, both CFE and GSE demonstrated 95% sensitivity. As the concentration levels decreased to 50mg/ml, sensitivity remained notably high, with 82.5% sensitivity observed at 40 mg/ml and 87.5% at 30 mg/ml. At the minimal dose tried, 20 mg/ml, a considerable sensitivity of 80% was still observed

Table 2: Evaluation of Efficacy of Cranberry Fruit and Grape Seed Extracts against ESBL *Escherichia coli*

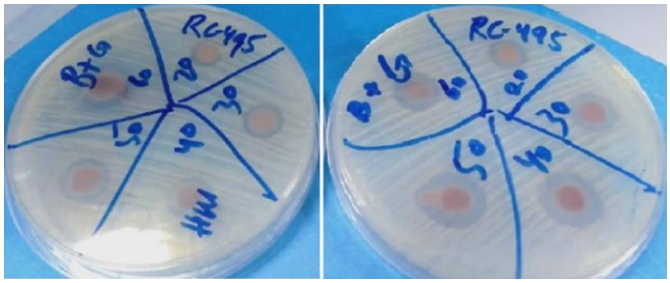
Escherichia coli	Cranberry Fruit and Grapes Seeds Extract Dose N (%)				
	20 mg /mL	30 mg /mL	40 mg /mL	50 mg /mL	60 mg /mL
Resistance	5 (12.5%)	4 (10%)	4 (10%)	3 (17.5%)	2 (5%)
Sensitivity	35 (87.5%)	36 (90%)	36 (90%)	37 (92.5%)	38 (95%)
Total	40 (100%)	40 (100%)	40 (100%)	40 (100%)	40 (100%)

At a concentration of 60 mg/ml, significant efficacy was observed, demonstrating a 95% sensitivity in inhibiting ESBL-producing *E.Coli.* Comparing the sensitivity rates, the combination of CFE + GSE 90% sensitivity was compared that exhibited a sensitivity of Meropenem at 75% (p-value <0.05) and Linezolid on the other hand, demonstrated a sensitivity of 0% (p-value = <0.05), as indicated in table 3.

Table 3: Assessment of Efficacy: CFE+GSE Blend versus Conventional Antibiotics against ESBL Producing *Escherichia coli*

Bacteria	Combined Extract	Antibiotic	Susceptibility Rate (%)	p-value
Extended-Spectrum Beta-Lactamase *E.Coli*	CFE and GSE (60mg/mL)	Meropenem	75%	0.032
	CFE and GSE (60mg/mL)	Linezolid	0%	0.001

The figure 1 illustrated that higher concentrations of combined extracts generally result in greater antibacterial activity, as indicated by larger inhibition zones or lower bacterial counts of ESBL producing *E.Coli.*



(a) MH Ager plate (b) MH Ager plate

Figure 1: Antibacterial Activities of Different Concentration of Cranberry Fruit and Grapes Seed Extract against Pathogenic Bacteria

DISCUSSION

The rising incidence of anti-microbial resistance, coupled with recurring outbursts and worldwide epidemics, underscores the urgent necessity for ongoing investigation [10]. As concerns about antibiotic resistance continue to mount, there has been a surge in efforts to investigate natural alternatives to antibiotics. Cranberry fruit and grape seeds, commonly utilized in herbal drug and nutritional aid, have bring in attention for their possible anti-microbial, antioxidant, and health-enhancing properties [11, 12]. The current study used a combination of grape seed and cranberry fruit extracts to kill ESBL-producing Escherichia coli to validate their antibacterial properties. The study mentioned the positive antibacterial effect against *E.Coli* strains. The results obtained are consistent with previous research that demonstrated the antibacterial efficacy of both cranberry and grape seed extracts individually against a range of pathogens. [13, 14]. Grape seed extract has also earlier been recognized for its antibacterial activity against many pathogens, including ESBL-producing organisms [15]. Likewise, cranberry fruit extract has also shown antibacterial effects, particularly against *Escherichia coli* strains [16]. Therefore, it is predicted that the combination of these two extracts likely stated on their complementary mechanisms of action, subsequent in greater antibacterial efficacy. The increase in the dosage activity observed specifically against E.coli strains in our study mentioned the important role of concentration in determining the efficacy of the combination of cranberry and grape seed extract. The steady increase in Zone of Inhibition (ZOI) with increase concentrations of the extract proposes a concentration-response relationship, where higher concentrations lead to greater antimicrobial activity [12, 17]. Kandasamy M *et al.*, conducted a study revealing that grape seed extract displayed bactericidal properties, yielding moderate zones of inhibition against common clinical isolates. Furthermore, it exhibited efficacy against drug-resistant strains, with inhibition zones ranging from 2 to 4 mm at extract concentrations between 2 mg/ml to 20 mg/ml. Notably, the extract demonstrated a more potent

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bactericidal effect against *Escherichia coli* in comparison to other selected gram +ve and gram -ve bacteria [11]. Several investigations have suggested that Grape Seed Extract (GSE) harbors the most substantial levels of antioxidant and antimicrobial elements, including polyphenols [14, 18]. The finding of a study on cranberry fruit extract found that active compound successfully reduced the antibiotic resistance of the ESBL-producing *E.Coli* strain. The strain exhibited resistance to multiple drugs [19]. The other study similarly mentioned that cranberry juice decreased *E.Coli* colonization in the experimental mice in the bladder reducing urinary tract infection, with organic acids determined as the active agents. This demonstrated the possible benefit of cranberry products, especially their organic acid content, in avoiding and handling urinary tract infections caused by *E.Coli* [20]. As per the data researched and our knowledge, this is the first study to explore the combined effect of cranberry and grape seed extract against ESBL-producing Escherichia coli. There are, however, different studies that mentioned the synergistic potential of natural extracts against antibiotic-resistant bacteria [21, 22].

CONCLUSIONS

It was concluded that combination of grape seed and cranberry fruit extract showed promising results against ESBL-producing *Escherichia coli,* mentioning it a possible alternative against antibiotic resistance. The dosage adjustment emphasizes on the better efficacy and long term effectiveness. It also highlighted the growing synergistic interaction against antimicrobial resistance but also serve as safer option with minimal or no adverse effects.

Authors Contribution

Conceptualization: ANB

Methodology: ANB

Formal analysis: US

Writing, review and editing: US, NI, NN, SI, MKA

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Association of Previous Surgical Miscarriage with Risk of Preterm Subsequent Pregnancy in Females Presenting in a Tertiary Care Hospital

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ABSTRACT

Surgical miscarriages are a common obstetric issue with potential long-term effects on subsequent pregnancies. **Objective:** To evaluate the association between previous surgical miscarriages and the risk of preterm birth in later pregnancies. **Methods:** This descriptive cross-sectional study was conducted at the Department of Obstetrics & Gynaecology, Mekran Medical College (MMC), Turbat, from November 2023 to April 2024. Data collected included age at second pregnancy, BMI, socioeconomic status, smoking status, and medical conditions such as hypertension and diabetes. Collected data were processed and analyzed using IBM SPSS, version 27.0. **Results:** The study included 230 patients with a history of miscarriage. Participants with ≥ 3 previous miscarriages had significantly higher odds of all-cause preterm birth (OR = 8.19, p = 0.050), spontaneous preterm birth (OR = 6.38, p = 0.005), and induced preterm birth (OR = 4.64, p < 0.001) compared to those with 1 previous miscarriage. After adjustment, those with ≥ 3 previous miscarriages had higher odds of all-cause (OR = 4.92, p < 0.001) and spontaneous preterm birth (OR = 5.79, p = 0.005), but not induced preterm birth (OR = 5.63, p = 0.050). **Conclusions:** Our study results revealed a significant association between a history of previous surgical miscarriages and the probability of preterm births in subsequent pregnancies. These findings underscore the need for clinical monitoring and interventions for women with a history of surgical miscarriages.

INTRODUCTION

Abortion is a common and emotionally distressing event that affects various females in the global society as it refers to the spontaneous pregnancy failure before the foetus is capable of standing on its own without the additional support offered by the womb. Surgical miscarriage, particularly accomplished through procedures including dilatation and curettage (D and C), is employed to remove foetal tissue from the uterus once miscarriage has occurred [1, 2]. Surgeries are sometimes necessary for various clinical reasons, but their impact on future pregnancies has raised concern and controversy. The association between prior surgical miscarriage and the risk of later preterm birth remains a significant area of focus for concern and research among clinicians [3]. Preterm birth, defined as delivery before 37 weeks of pregnancy, is associated with significant infant morbidity, mortality, and long-term health complications. It also puts lots of pressure on families and health organizations making it a big financial burden [4]. It is understood that preterm birth has polyetiologic factor with a genetic and environmental as well as medical aspect. Out of these factors, the past history of obstetric events, namely miscarriages, and the

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ways that have been used to treat them, have been deemed the most important predictors for timing of birth in any subsequent pregnancy [5]. The idea of the usage of prior surgical miscarriage as an influential factor in increasing the risk factor for preterm delivery is anchored on several biology and mechanics of a pregnant woman's body. Hysterectomy can lead to surgery complications, for example, Dilation and Curettage (D and C) may cause injury to the endometrium and cervical tissue [6]. This traumatic event can sometimes make the cervical structure weak, which translates to mean that the lady is at high risk of having preterm labour. However, it may lead to other complications such as the creation of intrauterine adhesions typically termed Asherman's syndrome. These can result in various complications such as placenta abruption that undermines the ability of the organ to stick to the lining of the uterus hence leading to premature delivery. The obvious risks associated with such complications may vary depending on how often surgeries are performed, the skills of the surgeon, and the body's ability to handle the presence of the injured uterus [7, 8]. An underlying mechanism that could elucidate the correlation between prior miscarriage and the likelihood of preterm birth is the probable debilitation of the cervix due to surgical interventions performed during miscarriage care. This mechanism has been hypothesised to elucidate the correlation between prior therapeutic pregnancy termination and heightened susceptibility to premature birth. Notably, there have been modifications in the techniques utilised for therapeutic pregnancy termination during the past 30-40 years. These changes have coincided with a decrease in the relationship between previous pregnancy termination and the likelihood of giving birth prematurely [9, 10].

In order to develop evidence-based procedures for future professionals and offer the best recommendations when addressing patients, it is crucial to form a clear understanding of the possible risks connected with surgical miscarriage. Women who have an abnormality that requires surgical intervention to evacuate the uterus are well informed about the implications of such an occurrence on future pregnancies. Possessing this information also enable people to exercise their rights by deciding on ways to regulate their fertility in case they are willing to. Furthermore, the group of women who might be in high risk of delivering preterm after surgical miscarriage might help with close follow up and monitoring in the subsequent pregnancies to eliminate adverse outcomes.

METHODS

This descriptive cross-sectional study was conducted at Department of Obstetrics and Gynaecology Mekran Medical College (MMC), Turbat from November 2023 to April 2024. The study was approved by the Institutional Review Board (MMC/ERC/107/2023) of the hospital and informed consent was obtained from all participants. The sample size for this study was calculated using the WHO calculator (available at www.openepi.com, version 3). A total of 230 patients were determined to be necessary based on a 95% confidence level, a 5% margin of error, and an assumed miscarriage rate of 54.3% in females [11]. The study used a convenience sampling technique. Demographic data involved the age at the time of the second pregnancy, BMI, smoking status, and medical issues including hypertension, and diabetes. The obsteric history included the number and type of prior miscarriages, whether surgical or medical; the gestational age when miscarriages occurred; number of full-term pregnancies; and the number of preterm births. The present pregnancy issues include number of pregnancies/ gestational weeks at delivery, mode of delivery; whether vaginal or caesarean section, presence of pregnancy complications like gestational diabetes, preeclampsia, neonatal result in terms of birth weight and Apgar scores. The main variable was a previous history of surgical miscarriage which was self-reported at the first antenatal visit and defined as the spontaneous loss of a non-registerable foetus (defined as <28 weeks and <24 weeks thereafter). Preterm birth which was classified as delivery before 37 completed weeks of pregnancy. The questionnaire used for data collection was developed based on a comprehensive review of the literature and validated through expert review to ensure clarity and reliability. Bias was controlled through exclusion criteria. The collected data were processed and analyzed using IBM SPSS, version 27.0. Descriptive statistics were computed, presenting means and standard deviations for continuous variables such as age and height, and frequencies and percentages for categorical variables including smoking status, alcohol status, marital status, socio-economic deprivation (insufficient financial and material resources), therapeutic pregnancy termination history, and preterm birth outcomes. Unadjusted odds ratios assessed the association between previous miscarriages and the likelihood of preterm delivery. The significance level was set at $p < 0.05$.

RESULTS

A total of 230 patients with a previous history of miscarriage were included in the study. Table 1 presented the descriptive characteristics and outcomes of the study participants. The majority of participants (n=181, 78.7%) belonged to the age group of 20-29 years, followed by 30-39 years (n=46, 20%). The mean age of the participants was 26.83 ± 5.16 years, with a mean height of 162.08 ± 7.09 cm. Most participants were non-smokers (n=132, 57.4%), non-alcoholic (n=217, 94.3%), and married (n=201, 87.4%). The

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socio-economic deprivation status varied among the participants, with the majority falling into categories 4 (n=57, 24.8%) and 5 (n=36, 15.7%). Additionally, 36 (15.7%) participants had a history of therapeutic pregnancy termination. Regarding preterm birth outcomes, 34 (14.8%) participants experienced preterm birth, 22 (9.6%) had spontaneous preterm birth, and 12 (5.2%) had induced preterm birth.

Table 1: Descriptive Characteristics and Outcomes of Study Participants

Variables	N (%) / Mean ± SD
Age Groups (Years)	
20-29	181 (78.7%)
30-39	46 (20.05)
More than 40	3 (1.3%)
Age (Years)	26.83 ± 5.16
Height (cm)	162.08 ± 7.09
Smoking Status	
Smoker	73 (31.7%)
Non-Smoker	132 (57.4%)
Ex-Smoker	25 (10.9%)
Alcohol Status	
Alcoholic	13 (5.7%)
Non-Alcoholic	217 (94.3%)
Marital Status	
Married	201 (87.4%)
Divorced	29 (12.6%)
Socio-Economic Deprivation Status	
Least Deprived, 1	14 (6.1%)
2	31 (13.5%)
3	46 (20.0%)
4	57 (24.8%)
5	36 (15.7%)
6	26 (11.3%)
Most Deprived, 7	20 (8.7%)
Therapeutic Pregnancy Termination	
History of Therapeutic Termination	36 (15.7%)
None	194 (84.3%)
Preterm Birth (PTB) Outcomes	
All-Cause PTB	34 (14.8%)
Spontaneous PTB	22 (9.6%)
Induced PTB	12 (5.2%)

The maternal characteristics and outcomes were tabulated by number of previous miscarriages Participants were categorized based on the number of previous miscarriages (1, 2, or ≥ 3). Significant differences were observed in the mean age of participants across the three categories (p = 0.003), with those in the ≥ 3 miscarriages group having a higher mean age (33.66 years). No significant differences were found in height, smoking status, alcohol status, marital status, or socio-economic deprivation status across the three categories (p > 0.05). However, a significant association was observed between the number of previous miscarriages and the history of therapeutic pregnancy termination (p = 0.001) and preterm birth outcomes (all-cause PTB, p < 0.001; spontaneous PTB, p = 0.011; induced PTB, p = 0.038)(Table 2).

Table 2: Descriptive Characteristics and Outcomes In Relation To Number of Previous Miscarriages

Variables	Number of Previous Miscarriages			p-Value
	1	2	≥ 3	
	N (%) / Mean ± SD	N (%) / Mean ± SD	N (%) / Mean ± SD	
Number of Patients	189 (82.2%)	30 (13.0%)	11 (4.8%)	-
Age (Years)	26.24 ± 4.43	28.17 ± 7.00	33.66 ± 6.28	0.003
Height (cm)	162.19 ± 7.10	161.23 ± 7.44	162.45 ± 6.23	0.778
Smoking Status				
Smoker	59 (31.2%)	10 (33.3%)	4 (36.4%)	0.988
Non-Smoker	109 (57.7%)	17 (56.7%)	6 (54.5%)	
Ex-Smoker	21 (11.1%)	3 (10.0%)	1 (9.1%)	
Alcohol Status				
Alcoholic	10 (5.3%)	2 (6.7%)	1 (9.1%)	0.568
Non-Alcoholic	179 (94.7%)	28 (93.3%)	10 (90.9%)	
Marital Status				
Married	169 (89.4%)	24 (0.0%)	(72.7%)	0.216
Divorced	20 (10.6%)	6 (20.0%)	(27.3%)	
Socio-Economic Deprivation Status				
Least Deprived, 1	10 (5.3%)	1 (3.3%)	3 (27.3%)	0.791
2	26 (13.8%)	4 (13.3%)	1 (9.1%)	
3	38 (20.1%)	6 (20.0%)	2 (18.2%)	
4	47 (24.9%)	7 (23.3%)	3 (27.3%)	
5	29 (15.3%)	5 (16.7%)	2 (18.2%)	
6	22 (11.6%)	4 (13.3%)	0 (0.0%)	
Most Deprived, 7	17 (9.0%)	3 (10.0%)	0 (0.0%)	
Therapeutic Pregnancy Termination				
History of Therapeutic Termination	23 (12.2%)	12 (40.0%)	1 (9.1%)	0.001
None	166 (87.8%)	18 (60.0%)	10 (90.9%)	
Preterm Birth (PTB) Outcomes				
All-Cause PTB	21 (11.1%)	7 (23.3%)	6 (54.5%)	<0.001
Spontaneous PTB	14 (7.4%)	4 (13.35)	4 (36.4%)	0.011
Induced PTB	7 (3.7%)	3 (10.0%)	2 (18.2%)	0.038

Table 3 presented the unadjusted Odds Ratios (ORs) for the association between previous miscarriages and the risk of preterm birth outcomes. Participants with ≥ 3 previous miscarriages had significantly higher odds of experiencing all-cause preterm birth (OR = 8.19, p = 0.050), spontaneous preterm birth (OR = 6.38, p = 0.005) and induced preterm birth (OR = 4.64, p < 0.001) compared to those with 1 previous miscarriage.

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Table 3: Unadjusted Odds Ratios Were Calculated To Assess the Association between Previous Miscarriages and the Likelihood of Experiencing Preterm Delivery

Outcome	Unadjusted Odd Ratio (95% CI)			p-Value
	Number of Previous Miscarriages			
	1	2	≥ 3	
All-Cause PTB	0.27 (0.12-0.60)	1.95 (0.76-4.98)	8.19 (2.34-28.61)	0.050
Spontaneous PTB	0.33 (0.13-0.85)	1.56 (0.49-4.96)	6.38 (1.70-23.88)	0.005
Induced PTB	0.28 (0.08-0.92)	2.36 (0.60-9.26)	4.64 (0.8824.39)	<0.001

The associations persisted after controlling for potential confounding factors, including maternal age, maternal height, smoking Status, alcohol status, marital status, deprivation status and history of pregnancy termination. After adjustment, participants with ≥ 3 previous miscarriages remained at significantly higher odds of experiencing all-cause preterm birth (OR = 4.92, p < 0.001) and spontaneous preterm birth (OR = 5.79, p = 0.005), but not induced preterm birth (OR = 5.63, p = 0.050), compared to those with 1 previous miscarriage (Table 4).

Table 4: Adjusted Odd Ratios for Past Miscarriages and All-Cause and Subtype Preterm Birth Risk

Outcome	Adjusted odd ratio (95% CI) *			p-Value
	Number of Previous Miscarriages			
	1	2	≥ 3	
All-Cause PTB	0.16 (0.04-0.60)	5.01 (1.04-24.05)	4.92 (0.77-31.31)	<0.001
Spontaneous PTB	0.19 (0.05-0.72)	6.24 (1.01-38.64)	5.79 (0.75-44.79)	0.005
Induced PTB	0.18 (0.02-1.58)	3.07 (0.39-24.43)	5.63 (0.10-29.33)	0.050

*Adjusted for maternal age, maternal height, smoking Status, alcohol status, marital status, deprivation status and history of pregnancy termination.

DISCUSSION

Miscarriage, the loss of pregnancy before viability, often necessitates surgical intervention such as Dilation and Curettage (D and C) or Dilation and Evacuation (D and E), especially for complications in the second trimester. Although these procedures are generally safe and effective, concerns exist about their impact on future pregnancies, with increased risks of preterm delivery and higher neonatal morbidity and mortality rates reported [12, 13]. The mean age of the patients was 26. 83 ± 5. 16 years. Mitrogiannis I *et al.*, Mitrogiannis I *et al.*, reported an umbrella review of meta-analyses identifying risk factors for preterm birth, highlighting multiple observational study findings. [14]. In our study, 78.7% of participants were aged 20-29 years, with approximately 17% having a history of previous miscarriages. We observed a statistically significant positive association between previous miscarriages and preterm birth (p < 0.001). Conversely, Iqbal Z *et al.*, in 2021 found a mean age of 31.08 ± 5.10 years among women and reported that a history of miscarriage was significantly associated with an increased risk of subsequent miscarriages (AOR = 2.91; p = 0.003) [15]. Our study's findings align with Brown JS *et al.*, in 2008, which also identified a significant association between previous miscarriages and preterm birth (p < 0.001), they noted that each subsequent abortion increased the risk of low birth weight and preterm birth, with odds ratios ranging from 2.93 to 3.67 [16]. Parker W *et al.*, reported a revised Markov model assessing the benefits of oophorectomy during hysterectomy for benign conditions, particularly revisiting the age threshold of 65 years [17]. According to our research conclusions, level of three or more previous miscarriages increased all-cause preterm birth: OR 4.92 (95% CI, p < 0. 001, and spontaneous preterm birth: OR 5.79 (95% CI), p = 0. 005 as compared to the level of one previous miscarriage. Rush SK and Rose SL addressed considerations for patients aged 65 years and older. [18]. Another study examined the long-term reproductive outcomes in women who had experienced multiple miscarriages and reported a significantly higher risk of preterm birth in subsequent pregnancies. Their study found that women with a history of multiple miscarriages had an increased odds ratio for preterm delivery, similar to our finding that multiple previous miscarriages are associated with a higher risk of preterm birth. Wen T *et al.*, analyzed trends and outcomes related to deliveries with hypertensive disorders of pregnancy from 2000 to 2018, while Gascoigne EL *et al.*, investigated accelerated epigenetic clock aging in maternal peripheral blood and its association with preterm birth. [19, 20]. This study is limited by its single-center design, which may not be generalizable to broader populations. The cross-sectional nature of the study restricts causal inferences and temporal relationships between surgical miscarriage and preterm birth. Lastly, the study does not account for variations in surgical procedures or healthcare access, which might affect the generalizability of the results.

CONCLUSIONS

Our study results revealed a significant association between a history of previous surgical miscarriages and the probability of preterm births in subsequent pregnancies. Therefore, women with surgical miscarriages should be closely monitored and have management plans developed to reduce risks in future pregnancies.

Authors Contribution

Conceptualization: YG
Methodology: AY, RA, RB, BS
Formal analysis: SK
Writing, review and editing: RB, SK, BS

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

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Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Metabolic Disruptions in Serum Calcium and Phosphate Levels Among Pre-Diabetic and Type 2 Diabetic Patients

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ABSTRACT

Diabetes mellitus is a metabolic disorder classified by persistently raised blood sugar levels. **Objective:** To identify diabetes mellitus disturbances in serum calcium and phosphate levels. However, the exact mechanisms underlying this association were not fully understood. **Methods:** It was a cross sectional study. It was conducted at Isra University Hospital, Hyderabad from March 2023 to August 2023. 170 patients were selected with 85 patients in each group. Group A included patients with diabetes and Group B included patients with prediabetes with fasting blood glucose levels of 101-125 mg/dl or HbA1c levels of 5.7-6.4%. Fasting blood glucose levels, HbA1c levels, total serum calcium levels and serum phosphate levels were compared. Data were assessed by using SPSS version 24.0. P-values of ≤0.05 will be statistically significant. **Results:** This study has shown that in both in Group A and Group B, the mean age was 47.2 ± 8.4 years and 48.5 ± 7.6 respectively (p value=0.62). Group A exhibited a mean fasting plasma glucose level of 109.34 mg/dl ± 17.92 and Group B 140.59 mg/dl ± 31.03. Group A displayed a mean serum phosphate level of 3.79 mg/dl ± 1.31, while Group B exhibited mean level of 4.43 mg/dl ± 1.04 (p=0.03). Group A demonstrated a mean serum calcium level of 8.41 mg/dl ± 1.03, whereas Group B had serum calcium level of 8.01 mg/dl ± 0.98 (p=0.02). **Conclusions:** The findings underscore the intricate relationship between metabolic disorders and mineral homeostasis, highlighting the potential implications for clinical management and risk stratification in diabetic patients.

INTRODUCTION

Diabetes mellitus is a persistent endocrine disorder that is identified by high blood sugar. The inadequate insulin secretion causes type II diabetes as well as tissues that are insensitive to insulin are playing a crucial role in disease causation [1]. The International Diabetes Association (IDF) has revealed that during 2019 more than 460 million people aged between 21 and 80 years were suffering diabetes mellitus globally especially the Type 2 type [2]. In the years between 1990 and 2017, there was 102.9% rise in new cases of diabetes mellitus occurring across all countries, such that number increased from 11,303,084 cases registered during the year 1990 to 22,935,630 incidences seen by the end of 2017 while Age Standardized Incidence Rates advanced by 234-285/100000 person-years [3]. Physical inactivity, BMI, blood pressure, age & sex are all highly correlated with Diabetes Mellitus. Hence, it has been established that owing to the escalating obesity levels worldwide, cases of diabetics will be more numerous in the next few years as per projections [4]. Diabetes mellitus can also affect the serum levels of calcium and phosphate. Calcium homeostasis is regulated by insulin because it brings in calcium into cells including bone cells and keeps it

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out of the bone. Insulin resistance and impaired insulin secretion in DM can interfere with this equilibrium and result in changes in calcium metabolism [5]. Some studies suggest that individuals with DM2 may have lower serum calcium levels compared to non-diabetic individuals. However, the exact mechanisms underlying this association are not fully understood. In addition, Insulin resistance and hyperglycemia in DM2 can affect phosphate levels indirectly through their impact on insulin signaling pathways [6]. Studies have reported conflicting findings regarding serum phosphate levels in individuals with DM2. A study aimed to evaluate the serum levels of calcium and phosphatein diabetics, pre-diabetics, and non-diabetics has revealed that Calcium and Phosphorus Levels in diabetic patients were around 1.97 ± 0.16 mmol/l and 0.76 ± 0.07 mmol/l respectively. While in pre-diabetics the Serum Calcium (Ca) levels were 2.15 ± 0.18 mmol/l and Serum Phosphate (PO_4) levels were 0.93 ± 0.06 mmol/l. In non-diabetic group Serum Calcium (Ca) levels were 2.33 ± 0.10 mmol/l and Serum Phosphate (PO_4) levels were 1.19 ± 0.20 mmol/l highlighting that as glycemic control deteriorates; blood calcium and phosphate levels tend to fall [7]. While some studies have shown higher serum phosphate levels in DM2 patients, others have found no significant difference compared to non-diabetic individuals. Several factors contributes towards the disturbances in calcium and phosphate levels in blood in diabetes mellitus, particularly type 2 diabetes (DM2), can be influenced by. Persistent high blood sugar levels may lead to increased urinary excretion of calcium and phosphate, resulting in lower serum levels. It can also disrupt insulin signaling pathways involved in calcium and phosphate homeostasis [8]. The kidneys have an important contribution in maintaining calcium and phosphate balance through filtration, reabsorption, and excretion processes. Disruption of these mechanisms can alter calcium and phosphate quantities in blood. Examples of drugs used in the management of diabetes which affect calcium and phosphate concentrations include Thiazolidinedione's (TZDs) [9]. The literature has notable omissions. There are few longitudinal studies that look at how disturbances in serum calcium and phosphate levels develop over time [10]. The pathophysiology of prediabetes and DM2 is still not well understood as far as the underlying mechanisms connecting disruptions of calcium and phosphate metabolism to it are concerned. However, chronic inflammation and oxidative stress contribute significantly to the pathogenesis of prediabetes as well as DM2 [11, 12]. It is not well-understood what happens specifically when conditions such as inflammation and oxidative stress interact with serum calcium or phosphate production though there are findings implying that these things may influence them in some way. Minimal data have examined contrasting groups of drugs used for diabetes prevention regarding their influence over these two parameters.

This research aimed to assess serum calcium and phosphate levels in individuals with prediabetes and DM2. By comparing these parameters across different stages of glucose metabolism impairment, from prediabetes to established DM2, the study seeks to identify potential trends or patterns in disturbances of calcium and phosphate homeostasis along the continuum of diabetes development.

METHODS

It was a cross-sectional study. It was conducted from March 2023 to August 2023 at Isra university hospital Hyderabad after the authorization of Institutional ethics committee, Isra University, Hyderabad (IU/DM&DR/2023/5266). A specific criterion of inclusion and exclusion was designed. All individuals more than 21 years of age suffering from with T2DM and pre-diabetes were included in this study. Patients with chronic kidney and liver diseases, cancer, bone and mineral disorders, and drug use that interfered with the metabolism of Ca and PO4 were excluded. The sample size was calculated by using population proportion 26.3%. The confidence interval of 95% and error margin of 6.5%. 170 patients were selected with 85 patients in each group. Group A included patients with diabetes mellitus presented in outdoor patients' department of admitted in emergency ward of Isra university hospital. Group B included patients with prediabetes with fasting blood glucose levels of 101-125 mg/dl or HbA1c levels of 5.7-6.4%. Random distribution was done in groups named as Group A (diabetes patients) and Group B (pre- diabetics). Written informed consent was taken from the participants and structured study Performa was designed to collect the data. Blood was withdrawn to measure fasting blood glucose levels, HbA1c levels, total serum calcium levels and serum phosphate levels. HbA1c was compared in both groups to establish the baseline glycemic control status of each group and to confirm the classification criteria for diabetes and prediabetes. The demographic data like age, gender and BMI was also calculated. To compare the mean values of two independent groups (Group A: patients with diabetes and Group B: patients with prediabetes), the study used an independent t-test for continuous variables such as fasting blood glucose levels, HbA1c levels, serum calcium levels, and serum phosphate levels. The results were presented as means and standard deviations. The analysis was performed using SPSS version 24.0. Demographic data are presented as percentages, calculated in Excel. A p-value of ≤ 0.05 was considered statistically significant. The findings were interpreted in the context of the study objectives and existing literature.

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RESULTS

This study has shown that in Group A, the mean age was 47.2 ± 8.4 years while Group B had a slightly higher mean age of 48.5 ± 7.6 (p value=0.62). The distribution of gender within the groups was fairly balanced, with Group A consisting of 39 males (45.88%) and 46 females (54.11%), while Group B had 44 males (51.76%) and 41 females (48.23%). Group A had a mean BMI of 27.5 ± 7.6, whereas Group B had a slightly lower mean BMI of 26.3 ± 6.4. In Group A 31 individuals (36.47%) were diagnosed with hypertension , while in Group B had 26 individuals (30.59%) with the condition, as shown in table 1.

Table 1: Demographic Features of the Study Sample (n=170)

Variables	Group A (Mean ± SD) / N (%)	Group B (Mean ± SD) / N (%)
Age (Years)	47.2 ± 8.4	48.5 ± 7.6
Male	39 (45.88%)	44 (51.76%)
Female	46 (54.11%)	41 (48.23%)
Body Mass Index	27.5 ± 7.6	26.3 ± 6.4
Hypertension	31 (36.47%)	26 (30.59%)

In this study, fasting plasma glucose levels and HbA1c percentages were measured in both Group A and Group B to assess glycemic control and potential differences between the groups. Group A exhibited a mean fasting plasma glucose level of 109.34 ± 17.92 mg/dl. In contrast, Group B showed a significantly higher mean fasting plasma glucose level of 140.59 ± 31.04 mg/dl suggesting poorer glycemic control compared to Group A. Similarly, when examining HbA1c percentages, Group A displayed a mean value of 5.73% ± 0.39, indicative of well-controlled blood glucose levels over time. Conversely, Group B presented a substantially higher mean HbA1c percentage of 9.41% ± 1.73, suggesting poorer long-term glycemic control compared to Group A (p=0.03)(table 2).

Table 2: Assessment of Blood Glucose Levels and HbA1c Levels

Variables	Group A (Mean ± SD)	Group B (Mean ± SD)
Fasting Plasma Glucose Levels (mg/dL)	109.34 ± 17.92	140.59 ± 31.04
HBA1C (%)	5.73 ± 0.39	9.41 ± 1.73

In this investigation, serum phosphate and serum calcium levels were assessed in both Group A and Group B to explore potential variations in mineral metabolism between the two cohorts. Group A displayed a mean serum phosphate level of 3.79 ± 1.31 mg/dl, while Group B exhibited a slightly higher mean level of 4.43 ± 1.04 mg/dl (p=0.03). This suggests that individuals in Group B had elevated serum phosphate levels compared to those in Group A. Furthermore, when examining serum calcium levels, Group A demonstrated a mean level of 8.41 ± 1.03 mg/dl, whereas Group B had a slightly lower mean level of 8.01 ± 0.98 mg/dl (p=0.02). This indicates a trend towards lower serum calcium levels in Group B compared to Group A as shown in table 3.

Table 3: Comparison of Serum Calcium and Serum Phosphate in Group A and Group B

Variables	Group A (Mean ± SD)	Group B (Mean ± SD)
Serum Phosphate (mg/dL)	3.79 ± 1.31	4.43 ± 1.04
Serum Calcium (mg/dL)	8.41 ± 1.03	8.01 ± 0.98

DISCUSSION

Diabetes is a disorder characterized by deranged levels of glucose in the blood. This can be due to either insulin deficiency or resistance of the action of insulin and often both of them. It is an important health problem that affects many people across the global especially in the management of healthcare including patients themselves [13]. Insights concerning metabolic profiles and demographic features of Group A and Group B can be deduced from findings of the aforementioned research, revealing the possible variation in health parameters between them. About demographic characteristics, these two groups were similar in that they had the same levels when it came to age and sex distribution, without any major disparities being noticed. This means that demographic factors are not likely to affect health differences between the two groups. In terms of metabolic parameters, Group B (type II diabetes patients) showed significantly increased levels of fasting plasma glucose as well as HbA1c than in Group A (pre diabetes patients). Thus, depriving them might be worsening the glycemic controls as well increasing numbers suffering from this condition in comparison with those from Group A. The results of this study show that people belonging to Group B may suffer from diabetes more often and to a larger extent. According to the data, the high values of fasting plasma glucose and HbA1c in Group B have underlined the significance of efficient management of diabetes and measures aimed at improving glycemic control among these people [14]. Additionally, there was a noticeable distinction when it came to levels of phosphate and calcium in the blood serum of the two groups. Talking about the serum test results, group B showed higher amounts of serum phosphate while having slightly decreased serum calcium levels in contrast with group A. These disparities could also reflect any potential variations that exist within our bodies' way of processing substances like minerals based on their own contexts. Further investigation is warranted to elucidate the factors contributing to these differences and their implications for overall health and disease risk in the respective populations [15]. Moreover, blood calcium levels in type 2 diabetes mellitus patients significantly reduce, with an inverse correlation between duration and age of diabetes mellitus [16]. The findings of this study are also comparable with the findings of a study conducted in Bangladesh. It has revealed that in Type 2 diabetes mellitus patients have considerably lower serum calcium levels (8.46 ± 0.63 vs 8.86 ± 0.64mg/dl) than healthy controls [17].

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The deranged calcium and phosphate levels in type II diabetes mellitus can lead to diabetic osteopathy. Studies have shown that those with Type II Diabetes mellitus had impaired bone remodeling processes [18]. Various factors are involved in alteration in serum mineral levels. Gut microbiota alterations can affect the absorption of serum calcium and it can play a role in both diabetes mellitus and osteopathogenesis, potentially contributing to bone health and diabetic osteopathy [19]. Another study has highlighted that the hypocalcemia (serum calcium level less 2.15 mmol/L) was detected in 73.6% of patients with type 2 diabetes mellitus. The prevalence of electrolyte abnormality entails that thorough investigation must be exerted to find out the causative factors behind these derangements [20]. This study employs a cross-sectional design, it only provides an assessment of calcium and phosphate levels at a single point in time. This limits the ability to establish causal relationships between disturbances in serum calcium and phosphate levels. There may be confounding variables, such as diet, physical activity levels, medication use, or comorbidities. Moreover, the small sample size can affect the generalizability of the outcomes of this study. Detection of abnormal levels of calcium and phosphate in the serum can be an early warning for the onset of metabolic dysfunction among individuals who are at risk for diabetes. With this information, medical professionals (doctors, nurses, etc.) can prevent this from happening by making changes in lifestyles like diet or drugs that prevent or control diabetes [21]. The study may stimulate further research into the mechanisms underlying disturbances in serum calcium and phosphate levels in diabetes. This could lead to the development of novel therapeutic interventions aimed at restoring metabolic balance and improving outcomes for diabetic patients.

CONCLUSIONS

In conclusion, the findings underscore the intricate relationship between metabolic disorders and mineral homeostasis, highlighting the potential implications for clinical management and risk stratification in diabetic patients. Further research is warranted to elucidate the underlying mechanisms driving these disturbances and to explore their prognostic significance in the context of diabetes-related complications.

Authors Contribution

Conceptualization: AFQ
Methodology: NUR
Formal analysis: SM, RA
Writing, review and editing: MP, MM

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Forensic Age Estimation by Maxillary and Mandibular Canines Pulp-Tooth Ratio Using Cone-Beam Computed Tomography in Adult Population of Peshawar, Pakistan

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ABSTRACT

Age estimation is a vital aspect of forensic sciences and numerous age estimation methods are suggested in dentistry, emphasizing the need for easy and quick technique appropriate for adults. Forensic age estimation can be performed using physical, biochemical, histological, and radiological methods. However, Cone-Beam Computed Tomography (CBCT) offers a promising approach in this regard. **Objective:** To estimate the age on the basis of maxillary and mandibular canines' Pulp-Tooth Ratio (PTR) using CBCT in adults and developing age estimation standards for local population based on PTR. **Methods:** A cross-sectional study was performed at Prime Teaching Hospital, Operative Dentistry and Oral Surgery department of Peshawar Dental College, and Khyber Teaching Hospital for Dentistry, Peshawar, from October 2019 to April 2020. CBCT images of maxillary and mandibular canines of 222 individuals were taken using consecutive sampling technique. PTR was estimated and correlation between age and PTR was determined using linear regression. **Results:** The mean documented age of patients was 36.31 ± 13.44 years. When linear regression was run on individual parameters, only upper left maxillary tooth area (mm^2) was found significant with $p < 0.01$ and $R = 0.132$, with regression model as Age = 26.64 + 0.072 (x). The overall model was found as, Age (years) = 35.519 -0.165 (Upper right maxillary tooth area (mm^2)) + 0.298 (Upper right maxillary pulp area (mm^2)) + 0.316 (Upper left maxillary tooth area (mm^2)) + 0.090 (Upper left maxillary pulp area (mm^2)) -0.102 (Lower left mandibular tooth area (mm^2)) -0.211 (Lower left mandibular pulp area (mm^2)) -0.087(lower right mandibular tooth area (mm^2)) + 0.082 (lower right mandibular pulp area (mm^2)). **Conclusions:** Age can be estimated by maxillary and mandibular canines' PTR using CBCT. Using the obtained regression model, age estimation for the adult population can be performed using CBCT scans.

INTRODUCTION

Forensic Age Estimation (FAE) is of crucial importance in forensic science as well as medical and legal conditions like diagnosis, management, prognosis, criminal proceedings, and identification [1]. Understanding of chronological age is essential when official documentation lacks real age. Usually court of law and other civil agencies need this type of expert opinion [2]. FAE is performed using multiple techniques and these techniques are commonly used in combination to find out the accurate age. Determination of secondary sexual, psychological, skeletal, and dental development are a few common methods [3]. As teeth are less impacted by environmental, hereditary, nutritional, hormonal, and pathological factors, these are commonly used structures for age estimation in both deceased and alive individuals [4]. Physical, biochemical, histological, and radiological methods may be used to estimate age from dentine. However, biochemical and histological techniques have limited advantages due to increased time, complex laboratory procedures, and extensive operator experience required for FAE [5]. Radiological method is

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preferred by odontologists due to its time efficiency, cost-effectiveness and the noninvasive nature. Odontometric estimation can be performed using two dimensional (panoramic and periapical radiograph) and three dimensional [Computed Tomography (CT), or Cone-Beam CT (CBCT)] radiographs for age estimation using dental structures. 2D radiographs have limited visualization of dental structures due to distortion and superposition [6]. On the other hand, three dimensional radiographs provide more consistent ant accurate results. But, exposure to ionizing radiation is a debatable matter in both clinical and forensic settings, so there should be careful evaluation of radiation dose in each individual [7]. CBCT provides precise structural evidence on sagittal, axial, coronal, and multi-planar sections for identification and management planning for healthcare providers. Resultantly, CBCT has been used in multiple studies to identify the relationship between age and secondary dentine growth like Pulp Tooth Area Ratio (PTR), pulp volume, and pulp tooth volume ratio [8-10]. Adult age estimation is challenging task. However, Kvaal method provides accurate PTR estimates in adults using radiographs of maxillary and mandibular canines [11]. Numerous studies have been conducted using this method in different populations to make standards for their respective age estimations [11-13]. However, there is a scarcity of literature on forensic odontology in Pakistan.

This study aimed to estimate the age on the basis of maxillary and mandibular canines' PTR with CBCT in adults and to develop age estimation standards for local population based on PTR.

METHODS

It was a cross-sectional study. It was conducted from March 2023 to August 2023 at Isra university hospital Hyderabad after the authorization of Institutional ethics committee, Isra University, Hyderabad (IU/DM&DR/2023/5266). A specific criterion of inclusion and exclusion was designed. All individuals more than 21 years of age suffering from with T2DM and pre-diabetes were included in this study. Patients with chronic kidney and liver diseases, cancer, bone and mineral disorders, and drug use that interfered with the metabolism of Ca and PO4 were excluded. The sample size was calculated by using population proportion 26.3%. The confidence interval of 95% and error margin of 6.5%. 170 patients were selected with 85 patients in each group. Group A included patients with diabetes mellitus presented in outdoor patients' department of admitted in emergency ward of Isra university hospital. Group B included patients with prediabetes with fasting blood glucose levels of 101-125 mg/dl or HbA1c levels of 5.7-6.4%. Random distribution was done in groups named as Group A (diabetes patients) and Group B (pre- diabetics). Written informed consent was taken from the participants and structured study Performa was designed to collect the data. Blood was withdrawn to measure fasting blood glucose levels, HbA1c levels, total serum calcium levels and serum phosphate levels. HbA1c was compared in both groups to establish the baseline glycemic control status of each group and to confirm the classification criteria for diabetes and prediabetes. The demographic data like age, gender and BMI was also calculated. To compare the mean values of two independent groups (Group A: patients with diabetes and Group B: patients with prediabetes), the study used an independent t-test for continuous variables such as fasting blood glucose levels, HbA1c levels, serum calcium levels, and serum phosphate levels. The results were presented as means and standard deviations. The analysis was performed using SPSS version 24.0. Demographic data are presented as percentages, calculated in Excel. A p-value of ≤ 0.05 was considered statistically significant. The findings were interpreted in the context of the study objectives and existing literature.

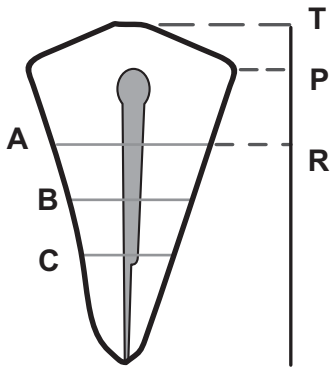

Figure 1: Dental Measurements in Kvaal's PTR Method [15]

RESULTS

The study comprised of 222 individuals. There were 145 (65.32%) male and 77 (34.68%) female cases. The mean documented age of patients was 36.31 ± 13.44 years with minimum and maximum age as 18 and 60 years. Descriptive statistics of maxillary and mandibular tooth and pulp area is shown in table 1. In this study, the mean upper right and upper left maxillary tooth area was 138.44 ± 20.54 mm2 and 134.64 ± 24.71 mm2, respectively. The mean lower left and lower right mandibular tooth area was 129.74 ± 26.86 mm2 and 129.28 ± 24.12 mm2, respectively. The mean upper right and upper left maxillary pulp area was 21.50 ± 14.36 mm2 and 21.03 ± 14.57 mm2, respectively. The mean lower left and lower right mandibular pulp area was 20.48 ± 17.50 mm2 and 18.48 ± 13.46 mm2, respectively (Table 1).

Table 1: Descriptive Statistics of Maxillary and Mandibular Tooth and Pulp Area

Maxillary and Mandibular Tooth and Pulp Area			Mean ± SD
Tooth Area (mm^2)	Maxillary	Upper right	138.44 ± 20.54
		Upper left	134.64 ± 24.71
	Mandibular	Lower right	129.28 ± 24.12
		Lower left	129.74 ± 26.86

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Pulp Area (mm^2)	Maxillary	Upper right	21.50 ± 14.36
		Upper left	21.03 ± 14.57
	Mandibular	Lower right	18.48 ± 13.46
		Lower left	20.48 ± 17.50

Table 1: mm^2 = millimeter square

Real-time images of mandibular and maxillary canines in the studied planes are shown in figures 2-9. Figure 2 presented the 3D sagittal section view of Cone-Beam Computed Tomography (CBCT) images, illustrating the precise measurements of the periodontal tissue remodeling(PTR)in the mandibular canines.

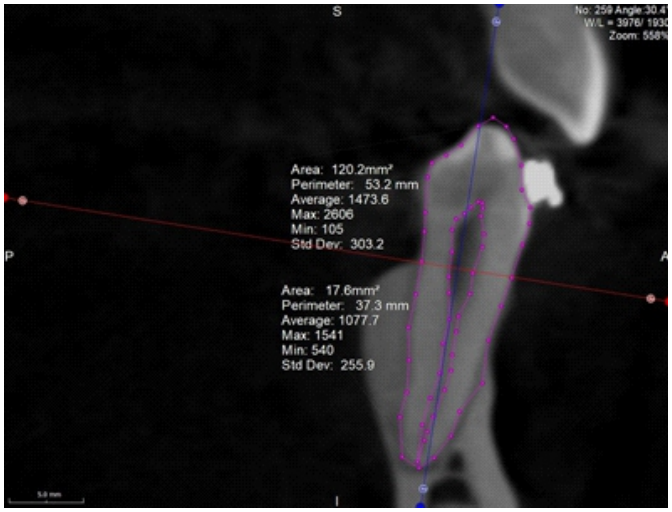

Figure 2: Measurements of PTR in the Mandibular Canines in 3D View from CBCT Images(Sagittal Section)

Figure 3 depicted the 3D sagittal section view from CBCT images, highlighting the measurements of periodontal tissue remodeling(PTR)in the mandibular canines.

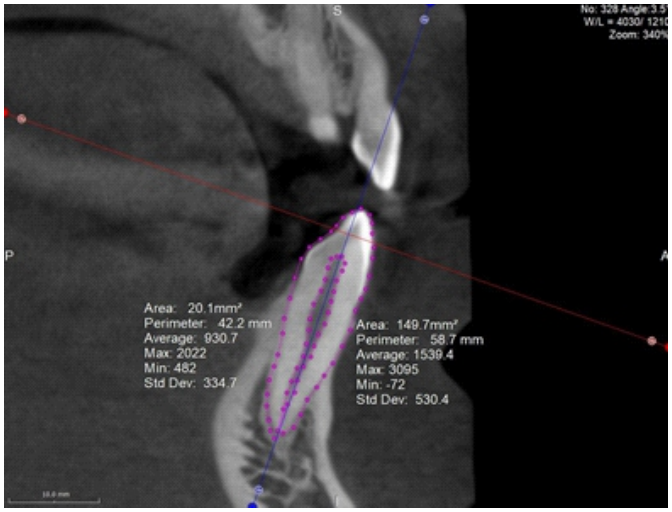

Figure 3: Measurements of PTR in the Mandibular Canines in 3D View from CBCT Images(Sagittal Section)

Figure 4 illustrated the 3D coronal section view from CBCT images, showcasing the measurements of periodontal tissue remodeling(PTR)in the maxillary canines.

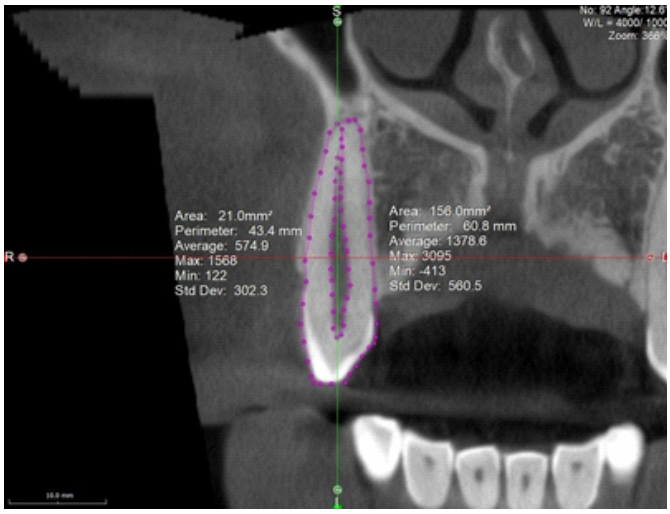

Figure 4: Measurements of PTR in the Maxillary Canines in 3D View from CBCT Images(Coronal Section)

Figure 5 depicted the 3D coronal section view from CBCT images, emphasizing the measurements of periodontal tissue remodeling(PTR)in the maxillary canines.

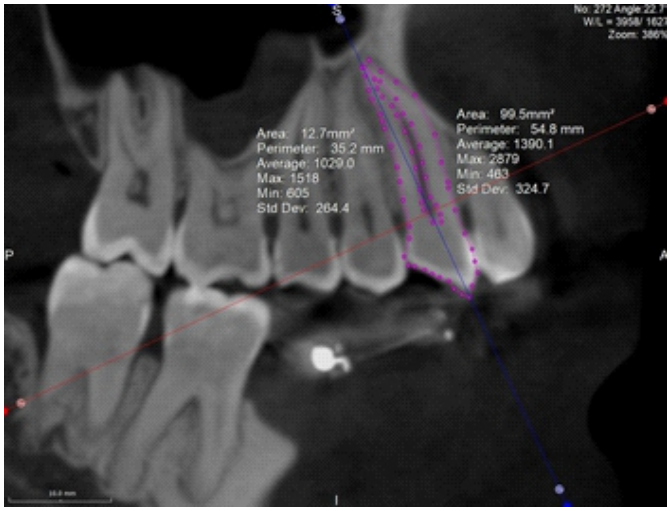

Figure 5: Measurements of PTR in the Maxillary Canines in 3D View from CBCT Images(Coronal Section)

Figure 6 displayed the 3D coronal section view from CBCT images, focusing on the measurements of periodontal tissue remodeling(PTR)in the maxillary canines.

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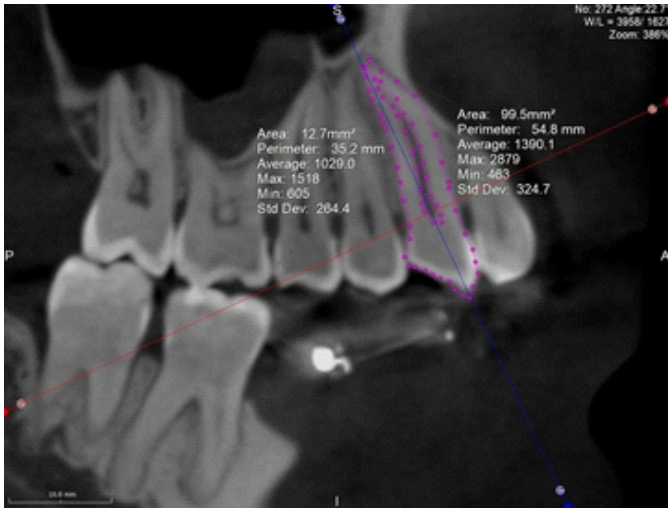

Figure 6: Measurements of PTR in the Maxillary Canines in 3D View from CBCT Images (Coronal Section)

Figure 7 presented the 3D coronal section view from CBCT images, detailing the measurements of periodontal tissue remodeling (PTR) in the maxillary canines.

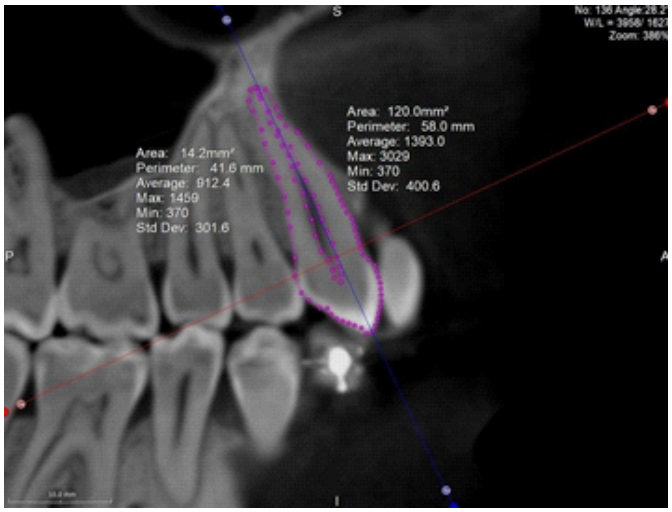

Figure 7: Measurements of PTR in the Maxillary Canines in 3D View from CBCT Images (Coronal Section)

Figure 8 illustrated the 3D coronal section view from CBCT images, capturing the measurements of periodontal tissue remodeling (PTR) in the mandibular canines.

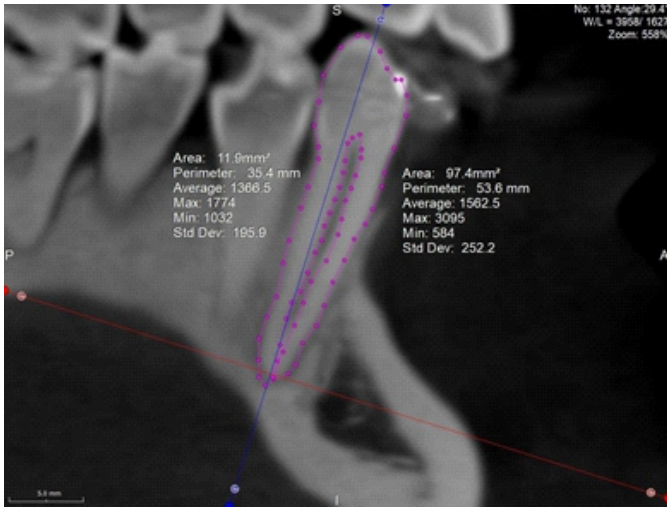

Figure 8: Measurements of PTR in the Mandibular Canines in 3D View from CBCT Images (Coronal Section)

Figure 9 displayed the 3D sagittal view from CBCT images, highlighting the measurements of periodontal tissue remodeling (PTR) in the mandibular canines.

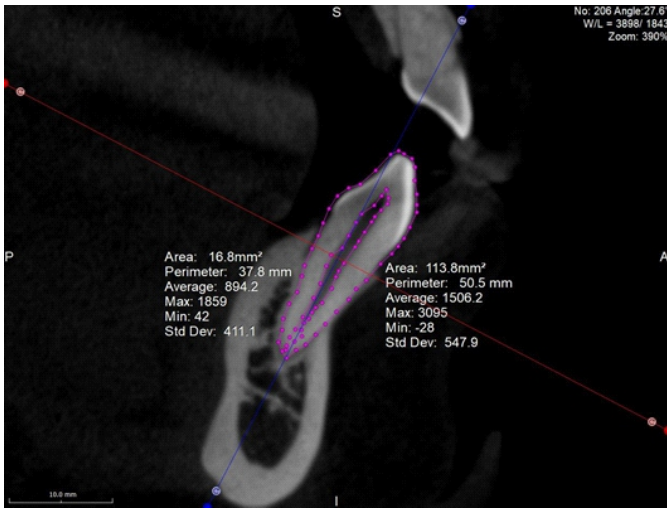

Figure 9: Measurements of PTR in the Mandibular Canines in 3D View from CBCT Images (Sagittal View)

When regression was run on individual parameters, only upper left maxillary tooth area (mm) was found significant with $p < 0.01$ and $R = 0.132$, with regression model as Age = 26.64 + 0.072 (x), as described in table 2. Here any possible value of upper left maxillary tooth area (mm) can be entered to estimate the age (Table 2).

Table 2: Regression Model for Maxillary and Mandibular Tooth and Pulp Area

Independent Variables (x)				R	R^2	B	S.E	p-Value	Model
Tooth area (mm)	Maxillary	UR	x1	0.040	0.002	0.026	0.004	0.553	Age = 32.69 + 0.026 (x)
		UL	x2	0.132	0.017	0.072	0.036	0.049*	Age = 26.64 + 0.072 (x)

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Pulp area (mm)	Mandibular	LL	x3	0.030	0.001	-0.15	0.034	0.659	Age = 38.24 – 0.150 (x)
		RL	x4	0.057	0.003	-0.32	0.038	0.398	Age = 40.42 – 0.320 (x)
	Maxillary	UR	x5	0.059	0.004	0.055	0.063	0.379	Age = 35.12 + 0.055 (x)
		UL	x6	0.087	0.008	0.08	0.062	0.918	Age = 34.63 + 0.08 (x)
	Mandibular	LL	x7	0.058	0.003	-0.44	0.052	0.392	Age = 37.22 – 0.44 (x)
		RL	x8	0.042	0.002	0.042	0.067	0.533	Age = 35.53 + 0.042 (x)

*Table 2: R = correlation coefficient; R^2 = coefficient of determination; β = regression coefficient; S.E = standard error; x = pulp/tooth area ratio; * = p≤0.05 was significant; UR = upper right; UL = upper left; LL = lower left; RL = lower right.*

In overall model, only two parameters that is upper left maxillary tooth area (mm) was found positively significant and lower left mandibular pulp area (mm) was found negatively significant, p-value < 0.05, as shown in Table 3. Hence, the overall model was found as,

Age = 35.519 -0.165 (x1) + 0.298 (x2) + 0.316 (x3) + 0.090 (x4) - 0.102 (x5) -0.211 (x6) -0.087 (x7) + 0.082 (x8)

Table 3: Overall Regression Model for Individual Parameters

Independent Variables			Maxillary UR Tooth Area (mm)	β	S.E	p-Value*	Significance
(Constant)			-	35.519	6.096	<0.001	Significant
Maxillary	UR	Tooth Area (mm)	x1	-0.165	0.096	0.089	Negative Insignificant
		Pulp Area (mm)	x2	0.298	0.211	0.159	Positive Insignificant
	UL	Tooth Area (mm)	x3	0.316	0.075	<0.001	Positive Significant
		Pulp Area (mm)	x4	0.090	0.179	0.617	Positive Insignificant
Mandibular	LL	Tooth Area (mm)	x5	-0.102	0.053	0.058	Negative Insignificant
		Pulp Area (mm)	x6	-0.211	0.076	0.006	Negative Significant
	RL	Tooth Area (mm)	x7	-0.087	0.056	0.124	Negative Insignificant
		Pulp Area (mm)	x8	0.082	0.081	0.309	Positive Insignificant

*Table 3: β = regression coefficient; S.E = standard error; * = p<0.05 was significant; UR = Upper right; UL = upper left; LL= left lower; RL = Right lower; mm = millimeter*

DISCUSSION

Adult age estimation is a challenging task in forensic medicine. Evaluation of morphological variations needs tooth sectioning, which is not possible in alive individuals. Therefore, radiographic approach is mainly employed in estimating age in living adults [16]. In 1995, Kvaal *et al.*, designed a radiographic technique to estimate age based on the deposition of secondary dentine by evaluating the pulp dimensions. It was regarded that pulp width was substantially correlated with age of the individuals [17]. Any tooth can be used for this purpose. However, canines are preferred because they mostly remain in the oral cavity until old age, have one root and pulp chamber, and pose a lower risk of caries [18]. At present, CBCT scans offer useful 3D evidence about teeth and is more frequently employed in forensic dentistry than traditional CT because of high resolution and low radiation exposure [19]. Additionally, CBCT allows determining the areas of tooth and pulp in both mesiodistal and buccolingual dimensions as well as calculating the precise volume of teeth and pulp [20]. So this study was carried out to estimate the age on the basis of maxillary and mandibular canines PTR using CBCT in adults and to get age estimation standards for Pakistani population based on PTR. A number of studies have been conducted for forensic age estimation employing CBCT [6, 20-23]. In an Indonesian study, it was found out that PTR of lower canine had a higher reliability in estimating age, p<0.05 [24]. Another study stated that the ages of the people of Iranian descent can be dependably calculated by subjecting the canines of the upper jaw to CBCT and analyzing their PTR (R^2 = 0.392) [6]. The findings of the previous literature also showed that there is an inverse relationship between pulp area and age [20]. This finding was relatable to the findings of the current study where lower left mandibular pulp area was found negatively correlated with age. A few more studies validated the results of the current study. Afify *et al.*, concluded that with r=.919, the sagittal CBCT images of the maxillary canines were more accurate and correlation of PTR and age was high [25]. Another study also used regression model and reported that the CBCT of maxillary canines provides high correlation between PTR and age (r = 0.532) [26]. Salemi *et al.*, reported that there was a strong correlation between PTR and estimated age (r = 0.88) using CBCT [19]. However, Molina *et al.*, reported that measuring canines PTR was not a reliable approach for FAE. Instead, upper incisors had the highest coefficient of determination (R^2 = 0.366), contrary to the findings of the current study [5].

CONCLUSIONS

Through the findings of this study, it is concluded that age can be estimated by using CBCT of maxillary and mandibular permanent canines PTR. Specifically, two parameters such as upper left maxillary tooth area was found positively correlated and lower left mandibular pulp area was found negatively correlated for age estimation. Using the obtained regression model, age estimation for the adult population can be performed using CBCT scans.

Authors Contribution

Conceptualization: MZ

Methodology: MZ, OK

Formal analysis: AH

Writing, review and editing: SS^1, SS^2, YK, AH, RUH

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

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Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Effectiveness of Intramuscular Ketamine as an Adjunct to Standard Care for Reducing Emergence Agitation in Nasal Surgery Patients

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ABSTRACT

As patients awaken from general anesthesia, they experience restlessness and bewilderment known as emergence agitation. Contributory factors for Emergence agitation include smoking, inhalational anesthetic usage, particular surgical procedures, being young, and being a member of the male population. **Objective:** To examine the frequency and severity of anxiety attacks in patients having nasal surgery and to assess how well intraoperative ketamine and placebo reduced the incidence of EA. **Methods:** This study was conducted at Bacha Khan Medical Complex in Swabi. Seventy patients undergoing nasal surgery were divided into two groups in a double-blind trial. One group received intramuscular ketamine, while the other group received saline. A standardized agitation scale measured the incidence and severity of postoperative agitation. The statistical software SPSS for Windows (version 28.0; IBM Corporation) was used to conduct the analysis. **Results:** Just 5% of patients in the ketamine group experienced EA, compared to 56.3% in the saline group ($p \leq 0.001$). The risk of getting EA was 96.7% lower in those on ketamine. Also had much less discomfort following surgery ($p < 0.001$). Additionally, they reported much less discomfort following surgery ($p < 0.001$). There were no significant differences in postoperative nausea and vomiting across the groups. **Conclusions:** After nasal operations, intramuscular ketamine administered after the procedure was quite successful in avoiding EA. Although total prevention of EA is difficult, risk factors can greatly lower the incidence of EA. Longer procedures, OSRP surgeries, and ASA II physical condition were the primary risk elements for EA.

INTRODUCTION

Emergence agitation is a post-anesthetic condition that appears early in the recovery from general anesthesia [1]. It is more common in children but can occur in adults affecting 4.7% to 21.3% of them [2, 3]. Restlessness, excitement, and perplexity are characteristics of Emergence Agitation (EA). It makes managing agitated patients challenging and its precise origin is unclear. Risk factors include young age, male gender, inhalational anesthesia, postoperative pain, postoperative nausea and vomiting, oral and ENT surgeries, smoking, and tracheal tube usage. While EA usually resolves on its own, it can lead to complications such as bleeding, self-extubation, prolonged hospital stays, patient traumas, and hazards for medical personnel [4]. EA can be avoided by lowering these risk factors and offering effective postoperative pain management. Research has indicated that EA is more frequent in adults and children following ENT procedures [5, 6]. Numerous drugs including opioids and alpha-2 receptor agonists like ketamine and dexmedetomidine have been investigated for their potential to prevent EA [7]. Rapid-acting anesthetic ketamine primarily blocks the NMDA receptor while it also affects other receptors. It can be administered orally, intramuscularly or by a variety of other routes. Ketamine administered intramuscularly is

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especially notable because of its adaptability and quick start of action peak plasma concentrations happen in a matter of minutes [8]. Ketamine has additional adverse effects as well such as liver damage, elevated intracranial pressure, respiratory depression, cognitive problems and changes in blood pressure or heart rate. It can also raise the risk of PONV. Additionally, it increases salivary secretions which may lead to laryngospasms however a tiny amount of atropine may be used to treat this. Those with schizophrenia, uncontrolled blood pressure and those who are pregnant or breastfeeding should not use ketamine [6]. In a recent study the effects of sub anesthetic dosages of intramuscular ketamine on emergence agitation during nasal surgery were investigated. It was found that ketamine significantly reduced the incidence of agitation compared to the control group. Additionally, administering Nefopam after the induction of anesthesia was also found to reduce the occurrence and severity of emergence agitation in adult patients undergoing nasal surgery [2, 6]. A case series study involving 15 patients suggested that acute agitation might benefit from a reduced intramuscular ketamine dosage. This study also shows that otorhinolaryngological procedures and EA are correlated. Numerous studies have shown a higher prevalence of EA in pediatric patients with tonsillectomy and strabismus surgery [9, 10]. However, a number of further studies connected the kind of surgery to EA [4, 11]. Adult patients with procedures related to the spine, musculoskeletal system, oral cavity, otolaryngology, breast or abdomen have a higher chance of acquiring EA [12]. A prospective cohort research including 521 kids between the ages of 3 and 7 discovered a relationship between EA and procedures related to ophthalmology and otorhinolaryngology. In particular surgeries linked to otorhinolaryngology were separate risk factors for EA [13]. Inhalational anesthetics with low blood gas solubility such as desflurane and sevoflurane are more frequently associated with EA than halothane, isoflurane, desflurane and sevoflurane [14]. This study is significant since nose surgeries are associated with a greater prevalence of endodontic and treating this disease well may improve patient outcomes significantly.

This study aimed to investigate the efficacy and safety of intraoperative ketamine in minimizing postoperative agitation with the goal of offering practical insights into enhancing postoperative care and increasing recovery for patients undergoing nose surgery. The aim of this study was to compare the incidence of allergic responses in patients undergoing nose surgery between intramuscular ketamine and placebo.

METHODS

In this study, patients scheduled for nose surgery participated in a double-blind randomized control experiment at Bacha Khan Medical Complex/MTI, Swabi. The study began on June 15, 2023, and ran four months after the Gajju Khan Medical College's ethical committee accepted the research request with reference number 2245/Ethical Board/GKMC. Non-probability sampling, which is convenient, was used. A sample size of 70, a 5% margin of error, 4.75% were taken from study with a 95% confidence level were required by the WHO calculation [15]. Informed consent was obtained from each participant. Participants in the research ranged in age from 15 to 70. Individuals who fulfil the qualifying criteria must possess an American Society of Anesthesiologists classification of I or II. Age extremes, a Body Mass Index (BMI) of more than 30 kg/m2, a known ketamine allergy and the patient unwillingness to participate were among the exclusion criteria for the study. Patients having a history of head and neck radiation therapy, cardiac, neurological, or behavioral disorders, or glaucoma diagnosis will not be included in the trial. Following clearance from the ethics committee patients who met the inclusion criteria were informed about the study and asked for their agreement to participate. We obtained each person informed permission. Data on patients and hospital management was kept confidential and used only for this study. Data were collected through the designed questionnaire. Seventy individuals were randomly assigned to receive either an intravenous ketamine or a placebo. In Group A, the intervention group received IM ketamine (0.7 mg/kg body weight) diluted in the same medium whereas in Group B the control group received 3 ml of normal saline. Both groups received the treatment five minutes before they were extubated. Patients without previous medication were brought to the surgery room. Standard anesthetic monitors were employed. Anesthesia was induced with 2 mg/kg of propofol and 0.5 mg/kg of atracurium and the patient was kept unconscious with 2.5 L/min of a 50% oxygen and 1.2% isoflurane mixture. Nalbuphine at a dose of 0.1 mg/kg was used to relieve discomfort. To avoid postoperative nausea and vomiting all patients received 8 mg of dexamethasone and 8 mg of ondansetron after being intubated. By modifying the ventilator settings end-tidal CO2 levels were maintained between 30 and 35 mmHg. After the procedure 2 ml of normal saline was administered to Group B, and 2 ml of normal saline + 0.7 mg/kg of intramuscular ketamine was given to Group A. Every group received an injection in the lateral thigh. Every patient had nasal packs. After satisfying the extubation criteria patients were extubated and ventilated with 100% oxygen at a rate of 7 L/min. The patient's levels of agitation were measured before their transfer to the postanesthesia care unit using the. The patient in which agitation occurred, then rescue medication Midazalom (Dormicum) after proper follow-up. Richmond Agitation Score (RAS) used for agitation measurement. A RASS score of +2 or above

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indicated the presence of emergent agitation (EA). The pain was measured using a Numerical Rating Scale (NRS) of 0–10 where 0 represents no discomfort and 10 represents the highest level of pain. Patients receiving intravenous injections of one gram of paracetamol were those who scored five or higher on the pain scale. While frequency and percentages were provided for the categorical data mean ± standard deviation was used to illustrate the continuous variables. The chi-square of independence was used to look at the bivariate relationship between the category data. Continuous variables (Age, BMI, Pain Score) were compared using the independent t-test. A value was considered statistically significant if it was less than 0.05. The statistical analysis was performed using SPSS for Windows (version 28.0) from IBM Corporation.

RESULTS

Seventy people with BMIs ranging from 21.10 to 29.00 with an average of 24.15 were enrolled in the research. Participants ages ranged from 16 to 66 years old with a mean age of 31.29. The average pain score was 3.60, with reported pain levels ranging from 2 to 7. With a mean score of 1.61 the agitation levels varied from 1 to 2. Every measurement applied to all seventy individuals. A t-test was used to compare the Group and ASA variables, and the results were displayed in the table. The Group variable has 69 degrees of freedom a two-tailed significance level of 0.000 and a t-value of 24.920. The mean difference was 1.500 with a 95% confidence interval that ranges from 1.38 to 1.62. The ASA variable's two-tailed significance level was 0.000 and its t-value was 24.076 with 69 degrees of freedom. The mean difference with a 95% confidence range between 1.14 and 1.35 is 1.243. This table compares a number of characteristics between people who were classified as agitated and non-agitated. Using a test value of 37.683 and a p-value of ≤0.000, the ketamine group (A) had a substantially larger proportion of non-agitated people (34) compared to the saline group (B) where more participants were agitated (26). With regard to gender there were 19 agitated and 19 non-agitated people among the male population and 24 agitated and 8 agitated people among the female population. This indicates a significant variance with a test value of 4.582 and a p-value of 0.032. With a test value of 0.0641 and a p-value of 0.800, the analysis based on ASA status showed no significant difference in agitation between ASA I and ASA II subjects. Likewise, there was no significant difference in age and BMI between the non-agitated and agitated groups (test values of 0.874 and 0.788, and p-values of 0.385 and 0.434, respectively), indicating that the kind of surgery did not affect agitation. With a test value of 3.704 and a p-value of 0.000, the two groups mean pain scores differed significantly with agitated individuals reporting a mean score of 4.33 ± 1.359 and non-agitated persons having a mean score of 3.14 ± 1.283 (Table 1).

Table 1: Comparison of Variables between Non-Agitated and Agitated Groups

Variables	Category	Non-Agitated N (%)/(Mean ± SD)	Agitated N (%) /(Mean ± SD)	Test Value	p-Value
Study Group	A-Ketamine	34 (79.1%)	1 (3.7%)	37.683	0.001
	B-Saline	9 (20.9%)	26 (96.3%)		
Gender	Male	19 (44.2%)	19 (70.4%)	4.582	0.032
	Female	24 (55.8%)	8 (29.6%)		
ASA	ASA I	33 (76.7%)	20 (74.1%)	0.064	0.800
	ASA II	10 (23.3%)	7 (25.9%)		
Type of Surgery	FESS	20 (46.5%)	15 (55.6%)	0.764	0.858
	Septoplasty	20 (46.5%)	10 (37.0%)		
	Rhinoplasty	2 (4.7%)	1 (3.7%)		
	Septorhino-plasty	1 (2.3%)	1 (3.7%)		
Age	Mean ± SD	30.09 ± 14.1	33.11 ± 13.968	0.874	0.385
BMI	Mean ± SD	24.30 ± 2.1182	23.9185 ± 2.1182	0.788	0.434
Pain Score	Mean ± SD	3.14 ± 1.283	4.33 ± 1.359	3.704	0.001

The research looked at two groups non-agitated and agitated and several kinds of nasal procedures such as Functional Endoscopic Sinus Surgery (FESS), Septoplasty, Rhinoplasty, and Sept rhinoplasty. FESS and Septoplasty were performed 20 times apiece in the non-agitated group, whereas Rhinoplasty and Sept rhinoplasty were performed 2 and 1 times apiece. FESS was done fifteen times Septoplasty ten times and Rhinoplasty and Sept rhinoplasty one each in the agitated group. With a p-value of.858a and a test value of.764 for these surgeries the statistical analysis of these frequencies. The gender distribution in both the agitated and non-agitated groups was examined in the study. Nineteen men and twenty-four women made comprised the non-agitated group. In contrast there were exactly the same number of men (19) but far fewer women (only 8) in the agitated group. There was a statistically significant difference in the gender distribution between the two groups as indicated by the test value of 4.582 and the p-value of.032a for this gender distribution (Figure 1).

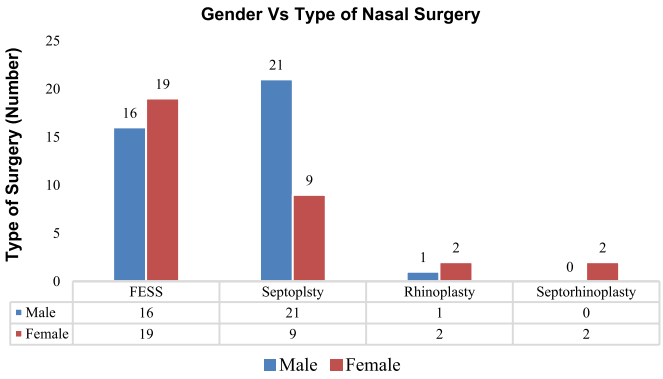

Figure 1: Gender-Wise Distribution of Nasal Surgical Patients

DISCUSSION

The study findings show how effectively intramuscular ketamine at a lower dosage after surgery lowers the

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incidence of emergence agitation in patients who have had septoplasty or open sept rhinoplasty. Notably this intervention resulted in lower pain scores for the treatment group (Group B). These results were consistent with other research that highlights the hypnotic and analgesic properties of ketamine which increase its efficacy in lowering EA [14, 15]. Unlike some earlier studies that identified postoperative pain, male gender and youth to be substantial risk factors for EA our investigation did not find any significant differences in the incidence of EA between males and females [10, 16-17]. This divergence may be attributed to the fact that our study was carried out across various centres and encompassed a diversity of surgical teams, surgical methods and patient treatment practices. Despite this variability intramuscular ketamine injection remained a consistently effective approach across several centers suggesting the resilience of this intervention [10, 18]. Previous research has linked the use of tracheal tubes and urinary catheters, smoking, inhalational anesthesia, postoperative nausea and vomiting and these conditions to an increased risk of endodontic [19-20]. Our research yielded similar results showing that ASA II physical status and lengthier surgical periods were significant predictors of early anesthesia. Moreover, the kind and length of nose surgery were discovered to be significant risk factors defying previous studies that had not found these variables to be significant. This discrepancy may be explained and the risk of EA increased by include OSRP operations which often involve more extensive manipulation and longer operating times than simpler nasal procedures [19]. This study provides compelling evidence in favor of intramuscular ketamine administration at a lower dosage to successfully reduce the incidence of EA and pain ratings in individuals undergoing septoplasty or OSRP [2]. These findings emphasize the need for tailored anesthetic strategies to lower EA particularly in patients with established risk factors such as ASA II status and longer recovery periods. The findings demonstrate that EA and pain following surgery were two different clinical occurrences. However, distinguishing between EA and post-operative pain-induced behavioral changes may prove difficult. Adults with a greater prevalence of EA were found to be those who scored five on a numerical rating scale for postoperative pain. However, EA has the potential to exacerbate post-operative discomfort. Consequently, appropriate postoperative pain treatment may have an impact on when EA develops [10]. The limitations of the study should be considered when assessing the results. The multicenter design of the study introduces diversity in surgical methods patient management practices and anesthesia protocols which might affect the consistency of the results. Also the sample size and specific patient attributes may limit the data generalizability to broader populations. Moreover, the study did not completely account for known risk factors for EA such as the use of catheters and tubes smoking and PONV. In conclusion distinguishing between EA and postoperative pain can be challenging which may lead to an inaccurate interpretation of the data. Further research should focus on conducting larger-scale multicenter studies using established methods to improve the validity and generalizability of findings on the efficacy of intramuscular ketamine in reducing pain and anxiety. To further understand the influence of possible confounders on EA results thorough evaluations of patient characteristics including smoking status and the presence of tubes and catheters should be included.

CONCLUSIONS

When ketamine was injected intramuscularly at a dosage of Comprehensive assessments of patient characteristics including smoking status and the presence of tubes and catheters should be included to better understand the impact of potential confounders on EA outcomes 7 mg/kg at the conclusion of the procedure it was highly effective in stopping EA following OSRP and septoplasty. Although complete prevention of EA was not possible it can be lessened when appropriate risk factors were changed. Even though injectable ketamine was a preventive treatment the three most risk factors for the development of EA were longer surgical durations OSRP surgery and ASA II physical status.

Authors Contribution

Conceptualization: AT
Methodology: SN
Formal analysis: WK, KJ, BK
Writing, review and editing: KJ, BK, AR

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

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Exploring Undergraduate Medical Students Perspectives on PowerPoint Presentation In Medical Evaluation: A Qualitative Study

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ABSTRACT

PowerPoint lectures are a growing way of improving topic understanding for students. Its use in teaching has increased in every field of education. **Objective:** To access different perceptions of students towards PowerPoint lectures at public sector medical college. **Methods:** Phenomenological survey was performed in Physiology Department, Sahiwal Medical College, Sahiwal. Questionnaire was spoken in front of participants one-by-one and responses were collected in voice notes. These responses were converted into text later. Six undergraduate students of 1st, 2nd, and 3rd year each were included in study. **Results:** Under the Development section the participants said "Yes, PowerPoint teaching helps in better collection of subject matter because it allows one to dive into the excellent presentation of PowerPoint." After that, we discussed the Spectacles part "Yes, PowerPoint teaching increases attention span to the lecture session when it is being made in a versatile pattern." When discussion moved towards Multimedia "Yes the major difference between PowerPoint teaching and traditional board teaching style is that you cannot deliver your expressive thoughts in board teaching styles." When discussion moved towards teaching. One of them said, "Educators can improve the integration of PowerPoint in teaching by using it as a support tool, not a replacement for teaching." **Conclusions:** Our study concluded that there was difference of opinion among students regarding PowerPoint in terms of its uses and better integration in lectures. Still, further studies are required to find out more beneficial ways of using PowerPoint in educational system.

INTRODUCTION

PowerPoint is a popular presentation software developed by Microsoft, allowing users to create engaging and interactive slideshows, presentations, and reports [1]. A PowerPoint lecture usually consists of a series of slides, each containing text, images, diagrams, charts, or multimedia elements that support the speaker's message. The slides can be designed to be interactive, with features like animations, transitions, and hyperlinks. With its user-friendly interface and versatile features, PowerPoint enables users to design and customize slides with text, images, charts, graphs, and other multimedia elements, making it an essential tool for professionals, educators, and students alike. Whether you're creating a business pitch, academic project, or personal photo album, PowerPoint provides a powerful platform to communicate ideas, showcase creativity, and leave a lasting impression on your audience [2]. The software also provides collaboration features, allowing multiple users to work together on a presentation in real time. PowerPoint is commonly used in business, education, and personal projects, making it an essential tool for effective communication, persuasion, and information sharing. Whether you're creating a sales pitch, training module, or personal photo album, PowerPoint provides a powerful platform to engage and inform your audience [3]. It is used worldwide because of its benefits. It is used in different fields because of its advantages, it becomes part of the educational system. PowerPoint lectures offer several benefits. They help to illustrate complex concepts and make the information more engaging and memorable. They

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provide a structured format for presenting information, making it easier to follow and understand. They allow speakers to convey a large amount of information in a short amount of time. They can be easily edited, updated, and shared with others. Around the world before its proper implementation, the first studies were done to get responses and analyse its benefits. Still, studies are being done to get more beneficial outcomes from PowerPoint. It is found helpful to both teachers and students. For teachers, it is a time saviour to present lectures and for students, it brings visual help in understanding [4]. To create effective PowerPoint lectures, it's essential to keep the design clean and simple, use clear and concise language, and practice the presentation to ensure a smooth delivery. PowerPoint is widely used in education for various purposes. Instructors create PowerPoint presentations to deliver lectures, illustrate key concepts, and provide visual aids. Students use PowerPoint to create presentations for assignments, projects, and research papers. Teachers create interactive PowerPoint lessons with quizzes, games, and activities to engage students. PowerPoint is used in online courses and virtual classrooms to deliver instruction and facilitate discussion. Students use PowerPoint to create study guides, flashcards, and concept maps. PowerPoint is used for student presentations, such as book reports, science fairs, and history projects. Teachers create PowerPoint videos for students to watch at home, and then use class time for discussion and activities. PowerPoint's accessibility features help students with disabilities, such as text-to-speech functionality and closed captions. PowerPoint's collaboration tools enable students to work together on group projects and presentations. Teachers use PowerPoint to create quizzes, tests, and assessments, making it easier to track student progress. In SLMC, Sahiwal PowerPoint is part of lectures. After getting good reports from international researchers, it also becomes part of our college lectures. There is less research work on it in public-sector medical colleges. The objective of this research is to check difference of opinion of SLMC students from other students worldwide.

METHODS

This Phenomenological Qualitative Study was conducted at the Physiology Department of Sahiwal Medical College Sahiwal from 8th May 2024 to 1st June 2024 after obtaining Institution Review Board Approval (104/IRB/SLMC/SWL). Non-probability purposive sampling technique was used for data collection. Undergraduate students of MBBS were included in the study while those with graduate or post-graduate status were excluded. Informed consent was taken from all the participants of the study beforehand. 3 focus groups from the 1st year, 2nd year, 3rd year were made. The reason for not including 4th year and final year was that the PowerPoint is majorly used in 1st 2nd and 3rd year whereas 4th year and final year classes are more of clinical based in wards so there is non-significant use of PowerPoint in their lectures. In each focus group, there were 3 girls and 3 boys, and these were randomly selected. Focus group discussions were conducted and a validated questionnaire was put in front of them after taking their informed consent. All their data were recorded on 2 separate mobile phones. Two mobiles were used so if unfortunately, one device is lost then the other can be used for this purpose. This data were translated into the text manually and then the thematic analysis was done by using the software NVivo (Non-Versioned Information, Versatile Outcomes). Sample size is calculated by saturation of data. After 18 responses we got repetition in responses so we concluded that saturation of data are achieved.

RESULTS

Development: In this section, the participants of the focus group discussion talked about the developmental role of PowerPoint in the study. Different participants had different views about the developmental benefits of PowerPoint. It was evident from their discussion that they had benefits in subject matter recollection and in understanding concepts and complex topics. "Yes, PowerPoint teaching helps in better collection of subject matter because it allows one to dive into the excellent presentation of PowerPoint writing style and visual animation with slides" Another participant thought that it gives memory clues "Yes it can because visual aid provided by the PowerPoint site can serve as a memory clue helping students recall information more easier and more quickly" One of them rise importance of animation in it "Yes, it helps a lot, but just theory is not always attractive. One should add more and more pictorial views and animations for better recollection of the subject." Concept development also became part of the discussion. One of them said "The PowerPoint teaching emphasizes the visual information, and this helps one to widen their parameter of thinking" Another participant added that "PowerPoint teaching helps in grasping the concepts more efficiently because it allows the one to understand the topics by returning to its visual memory." Complex topic understanding also became part of the discussion, one of them said "Yes. PowerPoint usually helps in well-organized slide making, and this can break down complex topics into digestible chunks." Another participant used word digestible chunks "Yes. PowerPoint usually helps in well-organized slide making, and this can break down complex topics into digestible chunks." Spectacles: After a discussion of the developmental role, we discussed the Spectacles part of PowerPoint. We got supportive responses "Yes, PowerPoint teaching increases attention span to the lecture session when it is being made in a versatile pattern, including pictures, animations, videos or its excellent writing." One of them said about

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normal brain behaviour "Yes. The idea of PowerPoint teaching increases the attention span of the lecture session. It is because, for a human brain, it is very convenient to like get the information in a digital pattern, to assess that information, and also to memorize it and get the better meaning of it." Another participant raised the importance of Spectacles in it "Yes, PowerPoint teaching increases attention span to the lecture session when it is being made in a versatile pattern, including pictures, animations, videos or its excellent writing." One of the participants found a colourful portion of PowerPoint impactful "The PowerPoint teaching increases the attention paths because the colourful pictures, colourful picture related to topic help divide our attention towards that, towards the lecture rather than from the warning whiteboard." Some thought that quiz in it is also eye-catching "Interactive elements also include in this in which teachers arrange like polls, quizzes, hyperlinks, which can increase the engagement between the students and teachers." The spectacles portion of PowerPoint was considered a major useful part of it. Visual memory became part of the discussion and in most of the discussion importance of pictures was discussed "Yes, it boosts attention by displaying pictures and breaking down text, which makes learning more engaging. "Multimedia: When our discussion moved towards Multimedia, participants of the different focal groups started comparing it with board teaching "Yes the major difference between PowerPoint teaching and traditional board teaching style is that you cannot deliver your expressive thoughts to the board teaching styles to the students but you can create an image of your expressive thoughts through the PowerPoint." One of them said "Yes. With PowerPoint, instructors can create consistent and well-developed presentations, and all these things will ensure that the students receive the content in a uniform format, and these things promote clarity and build the comprehension of the topic." Multimedia used in engaging students also became part of the discussion "PowerPoint presentations enhance engagement and comprehension through visual aids, while the board teaching may allow for more spontaneous interactions." Multimedia is a vast thing that includes a lot of things but due to more use of PowerPoint in lectures, students mostly use PowerPoint in discussion "The main thing that is different in PowerPoint teaching is animation and pictures, while both teaching lacks this one. So when you see the things happening in actuality through animation, I think this method will be a favorite one for anyone."While discussing Multimedia, participants also talked about its educational role "Yes. Preparing PowerPoint presentations can save instructors time and also the students. And they also allow them to create reusable and standardized material." One of them emphasized its use in the education system "Yes, obviously, there is no doubt it plays an effective role in education. We are living in a digital era and are blessed to use technology for educational purposes. Students stay focused and time is also saved." Participants of focal groups were convinced of its importance in education "Arguments for a larger role includes engagement. It helps a better engagement between the teacher and the students. Organization in which teachers present the lecture in an organized way and complex information. "Teaching: when the discussion among participants moved toward teaching there two main things became topics of discussion one was Student- Tutor relationship and the other one was improving PowerPoint integration. One of them said "It can enhance the student-tutor relationship by providing a structured and engaging platform for communication. Again, the visual aids and interactive features like videos, audio, and animations, promote clarity, understanding, and collaborations between student and tutor as well." Some thought that it depended mostly on tutors "We listen to the lectures of teachers who use excellent PowerPoint illustrations in their lectures." Another participant thought that it shows teachers' efforts "Yes. PowerPoint helps the teacher-student relationship in such a way that by looking at the PowerPoint lectures, by looking into the effort the teacher made, by making the lectures easier for the students and more convenient to understand, we understand, how well the teachers are working for our better learning." We also got responses on how PowerPoint integration can be improved "Educators can improve the integration of PowerPoint in teaching by using it as a support tool, not a replacement for teaching, by keeping the slides concise, clear, and visually emerging" One of the participants talked about active learning "I think instead of just using PowerPoint for lectures, educators can encourage students to create their presentations, and this will promote their active learning." One participant discussed psychological calmness "I think this is the main thing a professor must care about. He should put lesser theory in his slides to make students psychologically calm down about the content"(Table 1).

Table 1: Themes Identified Along with Their Categories and Codes

S.No.	Themes	Categories	Codes
1	Development	Improvement	Increase
			Enhance
			Better
		Aid	Help
			Use
2	Spectacles	Immersive	Interactive
			Engaging
			Attention
			Discuss
			Group
		Imagery	Pictures
			Visuals
		Impression	Influence
			Remember

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			Learning
3	Multimedia	Resources	Information
			Content
		Display	Slide
			Presentation
4	Teaching	Teaching	Teaching

DISCUSSION

PowerPoint is a software widely used by presenters in business, marketing conferences, and education. Advanced use of PowerPoint in teaching and lectures has revolutionized the education system [5, 6]. The impact of PowerPoint lectures was already established and known among the researchers but we emphasized more on the Pakistani undergraduate medical students' perspectives on PowerPoint lectures. The perceptions are mostly in line with already published studies related to PowerPoint lectures [7]. Whatever the likely impact of these viewpoints will be, the purpose of this approach was that the use of PowerPoint can be optimized and improvement in teaching methods can be achieved. The sample of students interviewed was self-selected and very small and the findings were essentially the perceptions of this small group of students about the PowerPoint lectures [8]. The validity of this study to generalize with those of other Pakistani university students was therefore limited. However, the study provided important validation for some subjective evidence both about the perception of students about PowerPoint lectures and the reasons for that viewpoints [9]. We argued that students of all the focus groups had almost correct conceptions of PowerPoint lectures. Delivering content by creating slideshows using text, pictures, and videos, engaging students by using interactive elements, discussions, or application activities based on the slides, and lectures that are displayed on the screen with the help of a projector were the main concepts of PowerPoint lectures shared by the students [10]. As far as the perceptions of PowerPoint lectures were concerned, students considered that PowerPoint lectures were used to increase attention span, build concepts, understand complex topics, build healthy student-tutor relationships, and better content recollection. Moreover, better student collaboration was highlighted by many students, and a comparison of PowerPoint lectures with board teaching was also discussed [11]. Students perceived that PowerPoint presentations can increase attention span to lecture sessions if used skilfully by making visually appealing slides and interactive elements like animations [12]. It can make lectures engaging for a longer duration, decreasing distractions and keeping focused. However, the demonstrator should be skilful to avoid poor design and well equipped to reinforce students' attention rather than surpassing slides in a monotonous manner which makes students bored [13]. While comparing and contrasting PowerPoint lectures with board teaching mixed opinions were submitted. Students were in favour of PowerPoint teaching because of visual-based learning, delivering expressive thoughts in a more organized and easy manner to follow [14]. Some were of the viewpoint that board teaching encouraged discussion and participation creating an interactive and dynamic environment promoting problem-solving and brainstorming but at the same time limiting space and visibility. A striking response of weakening eyesight was also received with PowerPoint lectures [15]. Students identified that PowerPoint lectures harm student-tutor relationships because of an impersonal learning environment leading to disconnection between tutor and student reducing face-to-face interaction making it harder to build a personal connection and trust [16]. Therefore, tutors needed to strike a balance between technology and human interaction by engaging students rather than just making lecture notes and cramming slides [17]. Regarding student collaboration positive feedback was achieved. Students were of the favour that PowerPoint presentations enhanced collaboration by developing communication skills in students, and promote socialization by organizing group presentations [18]. This encourages teamwork. The quiz should be arranged on PowerPoint. Students can share ideas and gather maximum knowledge about their topics. Hence teachers can utilize PowerPoint for group activities and discussions [19]. The subject material recollection was also a highlighting feature of the research. Opinions of students in this matter showed that PowerPoint lectures help in organizing information and retaining key concepts via summarizations, mnemonics, and repetition through slides in a short time. Visual aids such as graphs and diagrams served as memory clues for recalling information more easily and quickly. In short, it should be combined with other teaching tools for optimal resilience. The role of PowerPoint in education had a considerable debate among our respondents. Students argued its role in enhancing engagement and understanding with the help of visuals, interactive features, and structures which make it effective in the digital age to learn and understand concepts [20]. This can also facilitate organized delivery and can help in standardization, but its usage can hinder critical thinking reduce student-teacher interaction and limit hands-on experience. Poorly designed slides can distract or oversimplify important concepts. Thus, a hybrid approach The data revealed mixed perceptions of students regarding the use of PowerPoint. Students in favour of the use of multimedia and PowerPoint appreciated how visual animations and dividing topics into digestible segments aid in comprehension and retention. Conversely, some students had concerns regarding the oversimplification of material, lack of depth, and reduction in teacher-student interaction due to the use of it which is crucial for grasping intricate subjects. The effectiveness of PowerPoint,

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therefore, depended upon its design and use. This dichotomy underscores the need to employ PowerPoint in such a way that it supplements rather than supplants traditional teaching methods.

CONCLUSIONS

Our study concluded that there was a difference of opinion among students regarding PowerPoint in terms of its idea, uses, and better integration in lectures. Still, further studies are required to find out more beneficial ways of using PowerPoint in the educational system. In our study, while comparing, the majority of students were having almost the same opinions.

Authors Contribution

Conceptualization: SZ

Methodology: MAN

Formal analysis: SZ

Writing, review and editing: ASS, NS

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

Conflicts of Interest

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Original Article

Evaluation of Variables Impacting the Onset of Hypocalcemia After Thyroid Surgery: A Postoperative Perspective

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ABSTRACT

All across the globe, thyroidectomy is a common surgical procedure. After thyroid surgery, hypocalcaemia, which can be caused by either temporary or permanent hypoparathyroidism, is the most prevalent side effect. **Objective:** To quantify the frequency of hypocalcemia in individuals treated with thyroid surgery. **Methods:** In this descriptive study/ cross-sectional study, sixty-three cases were considered. The ages of the patients ranged from 18-60 years. Researchers checked patients' blood calcium levels both before surgery and on day one after the procedure. Those who underwent a complete thyroidectomy were checked for symptoms of low calcium levels. Utilizing SPSS version 24.0, the analysis was carried out. **Results:** There were more females than males among the 63 patients. In terms of tumour kind, papillary cancer, follicular cancer, and Hurthle cell carcinoma were the most prevalent. Hypocalcemia was detected in 18 instances (28.6% of the total). Thirteen females and five males constituted up the eighteen patients with hypocalcemia. In seven cases (38.9%), the retrosternal extension of goiter was detected, while in eleven cases (61.1%), no such extension was detected. Additionally, in every case, postoperative complications such as seroma, transient hoarseness of voice, or a hematoma in the neck were noted. **Conclusions:** Hypocalcemia was more common in 28.6% of patients following thyroid surgery, according to this research. Without retrosternal extension, the majority of the cases were female. All patients also experienced seroma, temporary hoarseness of voice, and neck hematoma in addition to hypocalcemia.

INTRODUCTION

Total thyroidectomy is associated with a high risk of hypocalcaemia, which may be temporary or long-lasting. Temporary hypocalcaemia has an incidence of 1% to 68% and chronic hypocalcaemia of 0% to 13% according to the reports [1, 2]. In addition, bilateral central neck dissection increases the risk of transitory hypocalcaemia from 20% with complete thyroidectomy alone to 50% to 60% [3]. A longer hospital stay is associated with patients experiencing symptomatic hypocalcemia, which is awful. Muscle spasms, cramps, paresthesia, tingling, seizures, tetanic contractions and an ECG showing a prolonged QT interval are all symptoms [4]. The parathyroid gland is the most prevalent site of post thyroidectomy complications. This could be because of unintentional removal of tissue, blockage of veins and arteries, or parathyroid devascularization. In addition to intraoperative hemodilution and postoperative thyrotoxicosis, other possible causes of hypocalcaemia after a thyroidectomy include hungry bone syndrome and the quick transfer of calcium into bones [5]. Postoperative blood calcium levels

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should be thoroughly monitored in patients with high-risk goiters, such as toxic, retrosternal, or recurring goiters. It is critical to lay the groundwork for a safe outpatient thyroidectomy [6]. The most common side effect of thyroid surgery is hypocalcemia, which affects between 3% and 52% of people who have the procedure done, and 0.4% to 13.2% of those people [7, 8]. Hypocalcemia can be identified in a variety of ways after surgery. The conventional two-day hospitalization and serum calcium monitoring approach is still used by many medical facilities worldwide since the lowest amount of hypocalcemia often occurs within 48 hours after surgery [9]. While it is important to keep an eye out for signs of bleeding or airway blockage in the first twenty-four hours following surgery, calcium monitoring is usually not needed unless there are obvious complications during the procedure. This is because most patients only have mild pain after surgery and are able to get back to their regular routines rather fast. As several surgeons have mentioned, this could help reduce the likelihood of hypocalcemia and minimize the duration of hospitalization after surgery. In outpatient or short-stay settings, regular usage is expected when hypocalcemia is detected. If hypocalcemia is detected, patients may be sent home with a prescription for elemental calcium supplements [10, 11]. New research suggests that the rapid detection of hypocalcemia may be possible due to the shorter half-life of parathyroid hormone (IPTH) than was previously believed. the eleventh Predicting the likelihood of postoperative hypocalcemia by routinely evaluating IPTH is still not considered standard practice. Dissimilarities in assays, measurement times, and cutoff values make direct comparisons among studies difficult [12]. The diagnosis and management of hypocalcaemia following thyroidectomy have been approached from many angles. In an effort to identify patients at risk of post-thyroidectomy hypocalcaemia, intact parathyroid hormone testing has been used more recently following complete thyroidectomy [13].

It was set out to learn more about hypoparathyroidism after thyroid surgery and how PTH readings can help find those who could be at danger of hypocalcemia.

METHODS

This cross-sectional/descriptive study was conducted at Department of Surgery, Bakhtawar Amin Trust Teaching Hospital, Multan. Duration was 14 months from Jan 2023 to Dec 2023 after getting approval with reference no 2642/MD/BATTH and comprised of 63 patients. Patient demographics information including age, sex, Body Mass Index (BMI), and tumor type were collected once written consent was obtained. To calculate the sample size of the study, using the prevalence of hypocalcemia as 0.03, d = 0.075 and N = 63 in the following formula's= $(Z_1- \alpha/2)^2 * p(1-p)$ d^2 [35]. This study did not include individuals who had hyperparathyroidism, hypocalcemia, hyperparathyroidism after parathyroid auto transplantation, or who were already taking calcium supplements. The patients' ages varied from eighteen to sixty. No patient has ever had parathyroid surgery or neck dissection done before. All of the patients were in good health going into the operation. Neither patient was on any medication that could alter their serum calcium metabolism, including antiresorptive agents, oral calcium/vitamin D supplements, antiepileptic drugs, anabolic agents, thiazide type diuretics, or hormone replacement therapy for postmenopausal women. Neither patient also displayed any symptoms of metabolic bone disease. Donated blood was tested for a whole range of diseases and conditions, including thyroid function, calcium and parathyroid hormone levels, coagulation profile, kidney and liver function, and fasting blood sugar. The patients underwent a CT scan of the neck with contrast, a plain chest X-ray with a P-A view, and a thyroid scan. Hypocalcemia occurred at a certain frequency. An analysis was conducted with the help of SPSS version 24.0. Frequency and percentage was used to represent qualitative variables, while mean and Standard Deviation (SD) are used to describe continuous variables. Descriptive analysis was conducted.

RESULTS

Included cases had age 40.7 ± 20.38years and BMI 23.8 ± 5.73 kg/m^2. There were more females than males among the 63 patients. In terms of tumor kind, papillary cancer, follicular cancer, and hurthle cell carcinoma were the most prevalent (Table 1).

Table 1: Demographics of the Cases that were Enrolled (n=63)

Variables	Mean / N (%)
Age	40.7
BMI	23.8
Gender	
Male	23 (36.5%)
Female	40 (63.5%)
Types of Tumor	
Hurthle Cell Carcinoma	30 (47.5%)
Follicular Cancer	23 (36.5%)
Papillary Cancer	10 (15.9%)

Among the total patients, 33 (52.4%) had cancer in the contralateral lobe (Figure 1).

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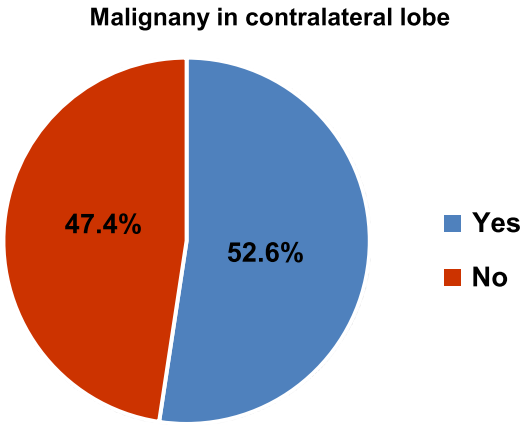

Figure 1: Prevalence of Cancer in the Lobe on the Opposite Side

Hypocalcemia was detected in 18 instances (28.6% of the total). Thirteen females and five males constituted up the eighteen patients with hypocalcemia (Table 2).

Table 2: Distribution of Hypocalcemia among study participants

Variables	N (%)
Hypocalcemia	
Yes	18 (28.6%)
No	45 (71.4%)
Gender of Hypocalcemia	
Female	13 (20.6%)
Male	5 (7.9%)

Fourteen instances (77.8%) had transitory hypocalcemia (Figure 2).

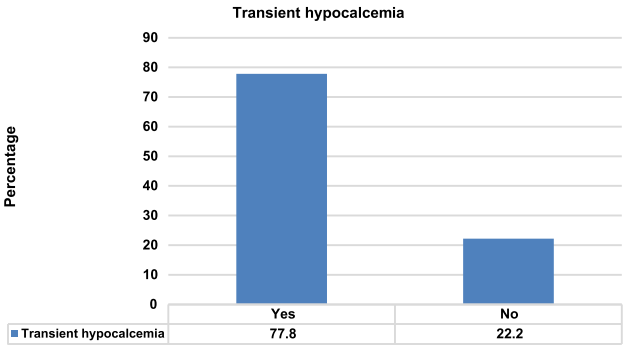

Figure 2: Frequency of Transient Hypocalcemia

In seven cases (38.9%), the retrosternal of the goiter was detected, while in eleven cases (61.1%), no such extension was detected (Table 3).

Table 3: Examinations Connected Hypocalcemia with Retrosternal Extension upon Discharge (n=18)

Retrosternal Extension	N (%)
Yes	7 (38.9%)
No	11 (61.1%)

Additional postoperative problems that were observed in all instances were seroma, temporary hoarseness of voice, and a hematoma in the neck (Figure 3).

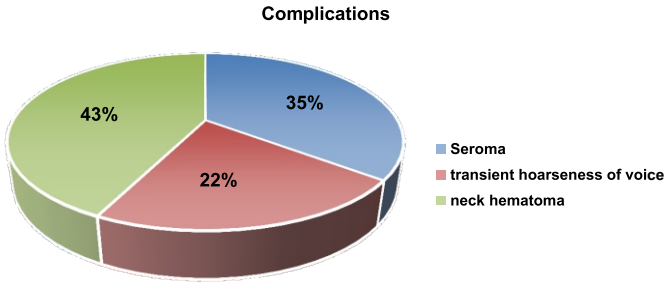

Figure 3: The Incidence of Additional Complications among Patients

DISCUSSION

It was found that 28.6% of patients experienced hypocalcemia following thyroid surgery are in line with the worldwide incidence recorded by Aghsaiefard Z et al [14]. Following a month of follow-up, not all patients had symptoms or signs of hypocalcemia. The percentage of patients with clinical hypocalcemia was a mere 6%. Since this is the population that would require more care, it is more reliable to utilize the percentage of patients experiencing symptoms. These results demonstrate that postoperative blood calcium levels are not enough to determine whether patients undergoing thyroid surgery are at risk of clinical hypocalcemia. A significant risk factor for surgical patients was hypocalcemia. After a total thyroidectomy, 78.6% of patients experienced transient hypocalcemia, and 21.4% developed persistent hypocalcemia [15]. In current study, included cases had age 40.7 ± 20.38years and BMI 23.8 ± 5.73 kg/m2. There were more females than males among the 63 patients. In terms of tumor kind, papillary cancer, follicular cancer, and Hurthle cell carcinoma were the most prevalent. These findings were comparable to a few of the earlier studies [15, 16]. Malignancy in the contralateral lobe was detected in 28 instances (52.6%) [17]. The results of this study were very comparable to those of a Greek study that analyzed data from 2043 thyroid surgeries performed at a university hospital [18]. Patients who underwent a full thyroidectomy were 40.4% more likely to experience hypocalcemia than those who underwent a near-total or partial thyroidectomy, with rates of 24.7% and 9.05 percent, respectively, for these procedures. In contrast to persistent hypocalcemia, which can range from 0.5 to 24%, transient hypocalcemia can vary between 5.4% and 26%, as reported by Zobel MJ et al [19]. Hypocalcemia was most common in patients who had full thyroidectomy, according to Tolone S et al [20]. Baldassarre RL et al., reported that between 0.33 and 66 percent of patients had hypocalcemia after a total thyroidectomy [21]. The incidence can be anywhere from 1.6% to 50%, as reported by Patricio Gac E et al [22]. While Van den Eynde F *et al.*, found a smaller range of hypocalcemia following total thyroidectomy, he confirmed that literature has shown a substantial frequency of 0.1% to 32% [23]. The results corroborated those of previous

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studies which found that twenty-five percent of hypocalcemia patients were transient and that five percent were persistent. There were more women than men among the 18 individuals with hypocalcaemia. Eleven instances (61.1%) did not have any evidence of a retrosternal goiter, whereas seven cases (38.9%) did. They were quite consistent with what had been found in other studies [24, 25]. Every single patient also had seroma, a temporary hoarseness of voice, and a hematoma of the neck as postoperative sequelae. Regarding references [26, 27]. Hypocalcaemia is a common complication that can develop soon after surgery. Hypocalcaemia following thyroid surgery has recently gained attention, and scientists are trying to figure out why. There is a great deal of debate on the best and timeliest ways to accurately anticipate whether a patient will experience transitory or chronic hypoparathyroidism following surgery [28]. A method or operation that is guaranteed to not fail Regular calcium monitoring after outpatient thyroidectomy is still recommended by Aldhafar A et al., even if postoperative PTH levels are detected. Even if the PTH level is incorrectly determined to be normal, this remains true [29]. The practice of thyroidectomy as an outpatient procedure has been authorized by two major international health organizations. Two such groups are the Australian Endocrine Surgeons Society and the American Thyroid Association [30]. The results of a Canadian study on outpatient thyroid surgery show that the procedure may be safely and effectively done as an outpatient therapy with minimal risk of complications. Assuming thorough patient evaluation and screening precedes surgery, this should be possible. Blood calcium concentrations are no longer used to diagnose post-operative hypocalcaemia; instead, PTH levels are used since they are more sensitive and specific for the early detection of both transient and permanent hypocalcaemia. The diagnosis of postoperative hypocalcaemia was previously based on blood calcium values. The postoperative PTH, sometimes called the fast PTH test, was able to predict persistent hypocalcaemia with an overall accuracy of 98% in this investigation. This research suggested that a thorough thyroidectomy is the best way to reduce the risk of problems and try again with the operation. [31]. Furthermore, it was shown that confirmed hypoparathyroidism was considerably more common in tumor pathology patients. Several studies have looked into the traits that have been associated with complications after thyroid surgery [32]. Age, gender, enlarging gland size, inflammation, fibrosis, thyroidectomy depth, and lymph node dissection are all variables to consider. Major surgery, recurrent treatments, and the surgeon's degree of experience can also induce hypocalcaemia following a thyroidectomy [33]. In individuals with Graves' disease or who have undergone redo surgery, this symptom might be caused by adhesions within the thyroid glands capsule and its parathyroid gland [34, 35].

CONCLUSIONS

Hypocalcemia was more common in 28.6% of patients following thyroid surgery, according to this research. Without retrosternal extension, the majority of the cases were female. All patients also experienced seroma, temporary hoarseness of voice, and neck hematoma in addition to hypocalcemia.

Authors Contribution

Conceptualization: TJ
Methodology: TJ
Formal analysis: SB, MMZ, AA[1], AA[2]
Writing, review and editing: TJ, JMT, SB, AA[1]

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

Conflicts of Interest

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Systematic Review

Comparing The Efficacy of Incision and Drainage (I & D) Vs. Ultrasound-Guided Needle Aspiration (UGNA) Methods to Manage Puerperal Breast Abscess

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ABSTRACT

Puerperal breast abscess poses a significant challenge in clinical care as they refer to painful, inflamed lesions that occur in lactating women stemming from untreated mastitis complications and often require expedited intervention to alleviate pain and avert adverse effects. The management of puerperal breast abscess is a medical dilemma that ranges from non-invasive therapy to surgical intervention. **Objective:** To compare the efficacy of ultrasound-guided needle aspiration (UGNA) and incision and drainage (I & D) in the management of puerperal breast abscess. **Method:** A systematic review was performed based on Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. Epidemiological studies published from 2013 to 2023 were included from five databases based on the presence of qualitative and quantitative data. **Results:** UGNA demonstrated efficacy compared to I & D. The observed cure rate of UGNA was 83% to 92% and an acceptable failure rate of 17.5% was associated with more than one aspiration. Conversely, the I & D method was associated with a prolonged healing period, pain, interrupted breastfeeding, more visits to the hospital, regular wound dressing, scarring, and fistula development however, more suitable for larger abscesses. **Conclusions:** The UGNA method appears to be an effective first-line treatment for managing unilocular puerperal breast abscesses, particularly those smaller than 5 cm, due to its shorter healing time, fewer hospital visits, and better cosmetic outcomes compared to traditional surgical methods. However, future research on large-scale RCTs with extended monitoring is needed.

INTRODUCTION

Breast Abscess (BA) denotes the inflammation of the breast commonly affecting lactating women. It is accompanied by painful and tender abscesses with systemic manifestations and challenges encountered during breastfeeding [1]. The breast abscess is further divided into puerperal and non-puerperal breast abscesses. Puerperal breast abscess (PBA) refers to the localized accumulation of purulent within breast tissue. It causes acute inflammation due to aggravations of mastitis, typically during the postpartum period. The prevalence of BA among breastfeeding women is 0.1–3% [2]. Puerperal mastitis is mostly reported during the initial postpartum weeks [3], with progression to PBA in 0.4% to 3% of all cases [4]. Traditionally, nipple fissures and milk stasis were considered the common contributors to acute mastitis during breastfeeding [5]. However, recent research has unveiled a more intricate picture, showing mastitis as a multifaceted condition influenced by a combination of factors; including individual variations in immune response, hormonal balance, and nipple anatomy along with dysbiosis, an imbalance in the microbiome of the breast, contribute to inflammation and mastitis

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development [6]. Due to a decline in their resistance ability, bacteria that enter through the terminal duct of the nipple are provided with lactoserum culture derived from milk stagnation, which penetrates mammary glands and causes deep tissue infection within the breast. Patients frequently exhibit symptoms of breast redness, swelling, tenderness, and insufficient milk secretion in the early stage. As the disease advances, it exhibits the formation of breast lumps and is associated with fevers, chills, fatigue, headache, and other clinical signs. If the inflammation is not managed promptly, the symptoms ultimately lead to puerperal breast abscess [7]. The most common microorganisms associated with the risk of infection are Staphylococcus aureus and methicillin-resistant Staphylococcus aureus [8]. Identifying other risk factors with particular emphasis in the context of Pakistan, a prospective study included advancing age, diabetes, and smoking with statistically significant association to PBA [9]. The other risk factors are poor breastfeeding techniques, sore nipples, and a gestational age of more than 41 weeks (Figure 1). If the abscess is left untreated it becomes severe and may lead to pus discharge from the skin, fistula formation, breastfeeding cessation due to loss of milk, and pain among lactating women indicating a significant infection and need for medical treatment. The diagnosis of puerperal breast abscess is clinical and established by ultrasound scan when available [10]. Despite improvements in maternal hygiene, nutrition, and early use of antibiotics, the true management of breast abscess remains a significant problem in developing countries [11]. Traditionally, lactational breast abscesses have been managed with surgical incision and drainage which involves the drainage of the purulent material with antibiotic administration [12]. However, this treatment is associated with massive trauma, prolonged healing time, multiple visits to the hospital for regular dressing, increased risk of breastfeeding cessation, milk fistula, intolerable pain during wound dressing, and suboptimal cosmetic outcomes with ugly scarring, which negatively impacts the patient's quality of life [13]. Now, in the era of image-guided therapy and minimally invasive surgery, UGNA is providing a better alternative to the I & D method. The minimally invasive aspiration involves the insertion of a thick needle into the abscess cavity under the guidance of ultrasound for precise targeting of the abscess and aspiration of pus buildup [14]. This approach has the advantage of minimal trauma, early healing, less pain and visits to the hospital, uninterrupted breastfeeding, no scar formation, and satisfactory cosmetic outcomes [15]. Therefore, UGNA is recommended as first-line treatment with surgical drainage being retained for larger-size abscesses that are not resolved with aspirations and in cases of tissue necrosis [16]. The question of whether to opt for conventional I & D treatment or UGNA is a point of contention and lacks a unified stance from the surgical community. To date, limited comprehensive studies are comparing the effectiveness of I & D and UGNA on puerperal breast abscess. Therefore, this systematic review aims to augment the existing literature by providing a comprehensive comparison of the efficacy of two approaches for the management of puerperal breast abscess. This will involve the evaluation of factors of healing period, scar formation, pain levels, patient satisfaction, and cosmetic outcomes.

This systematic review aimed to assess the efficacy of the UGNA and I & D approach will provide valuable information to healthcare professionals in determining which approach yields better outcomes in the management of lactational breast abscess and in optimizing treatment protocol.

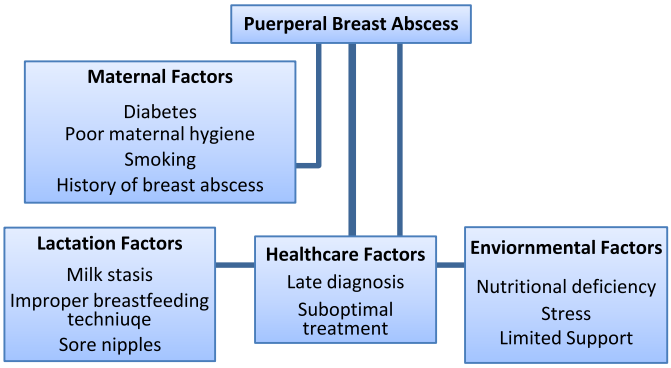

Figure 1: Risk Factors Associated with Puerperal Breast Abscess

METHODS

Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed to write this systematic review. The data from 2013-2023 was collected using several databases (PubMed, Google Scholar, Sci-hub, and Science Direct) using Boolean logic "AND" and "OR", Medical Subject Headings (MeSH Terms). Different keywords were used to explore the literature including "Efficacy'', "Ultrasound-guided needle aspiration", and "Incision and drainage" combined with "Puerperal or lactational breast abscess" A total of 101 articles were retrieved from the included databases. Out of these, 60 studies were excluded as non-relevant after reading the titles and not written in English, 10 were based only on the presence of qualitative data, 3 after being duplicates, and then 16 more were excluded because they do not directly compare the efficacy of UGNA and I & D in management of puerperal breast abscess. After applying all these inclusion/exclusion criteria, only 11 articles were considered eligible after applying inclusion/exclusion criteria and deleting the duplicates and irrelevant articles (Figure 2).

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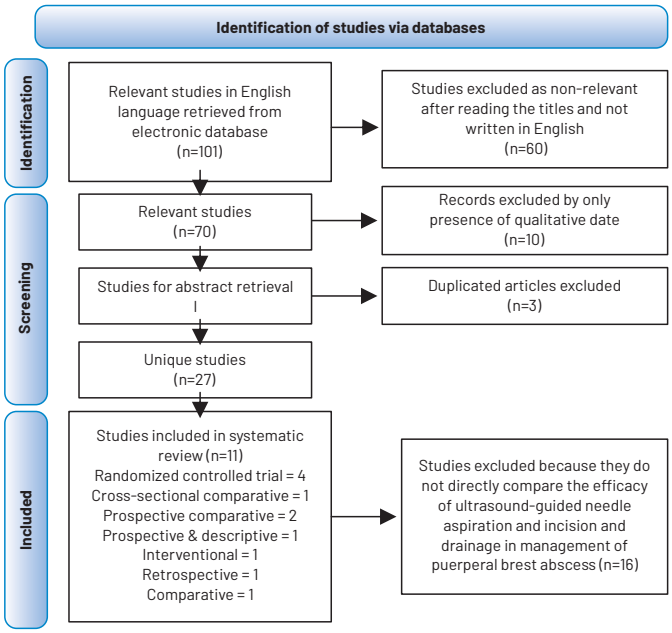

Figure 2: PRISMA Flowchart Depicting the Study Selection Process

RESULTS

All of the identified studies [1, 16, 19-27] compare the effectiveness of ultrasound-guided needle aspiration and incision and drainage methods in the management of puerperal breast abscesses by comparing the outcomes of patients who underwent UGNA against patients treated with surgical drainage. The endpoints of the study included success rate, pain level, reoccurrence rate, hospital visits, fistula development, healing time, and scar formation. The UGNA method has a success rate of 83%, 92%, and 91%, and an acceptable success rate of 70% [1, 19, 20, 27]. However, UGNA associated with an acceptable failure rate and reoccurrences, required repeated aspirations sometimes for complete recovery and even a switch to surgical drainage [20, 24]. Overall studies reveal that the UGNA offers less pain, faster recovery in terms of shorter healing time, fewer hospital visits, better cosmetic outcomes [1, 16-27], and lower incidence of fistula development [21] as compared to I & D. UGNA could be an effective alternative and first-line treatment especially for smaller abscess <5cm [19, 20] and incision and drainage should reserve for larger and delayed abscesses [26]. The available data compares the UGA and incision and drainage methods in the management of puerperal breast abscess (Table 1).

Table 1: Summary of Comparison Between UGNA and I & D Methods in the Management of Puerperal Breast Abscess

Sr. No.	Age	Patients	Healing Period	Scar	Pain	Mammary Fistula	Patients Treated	Key Outcomes	Remarks	Study	Reference
1	**UGNA Group**							Mean healing time& pain are lesser in the UGNA group as compared to the I & D group/Patient satisfaction /Cost-effective/Needle aspiration is effective for small abscess	UG-Needle Aspiration is Effective Method/ Success Rate 83%	Prospective comparative	Ranjeesh and Kotha [17]
	30y	30	19.20/ Shorter	no	Pain Relieved / Persistent to Next Follow-Up	NR	25				
	I & D group							For larger abscess should consider I & D/Prolonged healing time /Scar formation	UG-Needle Aspiration is Effective Method /Success Rate 92%		
	30	30	30.1677 /Longer	yes/ 5had	Pain Relieved / Intolerable Pain During Dressing	NR	30				
2	**UGNA group**							Mean healing time & pain lesser in the UGNA group as compared to the I & D group/Fewer hospital visits/No scar/ Reparative aspiration required/ Effective for small abscess <5cm	UG-Needle Aspiration is Effective Method /Success Rate 92%	Comparative perspective	Voruganti *et al* [18]
	25y	25	Shorter	no	Pain Relieved/ No Dressing Required	NR	25				
	I & D group							Prolonged healing time/ Scar formation/More visits to hospital	UG-Needle Aspiration is Effective Method/ Success Rate 92%	Comparative perspective	Voruganti *et al* [18]
	25y	25	Longer	yes	Painful/ Wound Dressing Required	NR	25				
3	**UGNA group**							Mean healing time & pain were lesser in the UGNA group as compared to the I & D group	Needle Aspiration is Effective for Small Abscess	Cross-sectional comparative	Manzoor *et al* [1]
	25y	52	Shorter	5.67 %	Pain Relieved	NR	52				

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	I & D group										
	25y	56	Longer	YES / 100 %	Intolerable During Dressing	NR	56	100% scar formation/ Longer healing time			
4	**UGNA group**								UG-Needle-Aspiration is Effective	Randomized controlled trial	Dar *et al* [14]
	25-30y	35	Shorter	NR	NR	NR	NR	Healing time is shorter as compared to the I & D group			
	I & D group										
	25-30y	35	Longer	NR	NR	NR	NR	Prolonged healing time			
5	**UGNA group**								UG-Needle-Aspiration is Effective	Prospective comparative	Bhatti *et al* [19]
	25y	28	Shorter	No	NR	No	47% Complete Resolution	UGNA yields better outcomes/less incidence of fistula development			
	I & D group										
	25y	28	Longer	yes	NR	Yes/ 5%	47% Complete Resolution	Development of fistula is higher			
6	NR	59 UGNA group	91.10%	NO	2 Patients had Pain	NR	5.3% had Complication	Minimally invasive/ 91.1% cure rate/good cosmetic results	UGNA is Effective	Prospective & descriptive	Tran *et al* [20]
7	**UGNA group**								UFND is an Effective Alternative to I & D	Randomized controlled trial	Khan *et al* [21]
	28y	35	Shorter	NR	NR	NR	94.10%	UGNA yields better outcomes/ early success rate			
	I & D group										
	29y	35	Longer	NR	NR	NR	77.14%				
8	**UGNA group**								UFND is an Effective Alternative to I & D with an Acceptable Failure Rate	Interventional	Suthar *et al* [22]
	NR	35	Shorter	No	Pain Relieved	Yes	6 Patients Required I & D	Better outcome results/Higher failure rate for abscesses >5 cm			
	I & D group										
	NR	35	Longer	yes	Intolerable During Dressing	yes/3 patients	All	pain &Fistula /scar formation are drawbacks			
9	33y	UGNA group	NR	NR	NR	NR	ALL/Single Aspiration was Sufficient in 643% of Cases	Effective alternative to surgery/ UGNA group continued breastfeeding	Effective	Retrospective	Rigourd *et al* [23]

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10	**UGNA group**									
	24.8y	25	Shorter /11.4 Days	No	NR	NR	92% Cure Rate/ Failure 7 %	Early healing/less hospital visits/ resumption of breastfeeding	UGNA is an Effective and First-Line Treatment for Smaller Breast Abscesses	Randomized	Saharan *et al* [24]
	I & D group									
	24.8y	25	longer /11.4 Days	No	NR	NR	100%	Surgical scar formation/more hospital visits/should be considered for larger abscesses			
1	**UGNA group**									
	29.79	17	Shorter /11.6	No	Less Pain	No	70% of Patients Treated	Healing time & pain are lesser in UGNA	UGNA is an Effective Alternative/Acceptable Success Rate	Randomized	Fathy *et al* [25]
	I & D group									
	29.79	24	Longer /22.21	Yes	Intolerable Pain	NR	100% of Patients T reated	Prolonged healing time/Scar formation			

Abbreviations: UGNA ultrasound-guided needle aspiration, I & D: incision and drainage, NR: Not reported, BA: Breast Abscess, SD: Standard deviation.

In consideration of the homogeneity of the data, the standard deviation (SD) of the healing time outcome was taken for the comparison of the efficacy of both methods. The reported SD was recorded from five studies [1, 16, 20,23, 27]. The standard deviation of healing time was statistically converted to the SD ratio and mean days of healing time were compared. Based on the less variability and lower mean healing time of the UGNA group compared to the I & D group, the UGNA method appeared to be more consistent and effective in prompting faster recovery in terms of the healing period. However, for a comprehensive assessment of the overall efficacy of both methods, other relevant clinical and statistical factors are important and should be considered. Here in the context of homogeneity of data, only the healing outcome was included. The SD ratio of 0.462 which is less than 1 shows that the UGNA group has approximately 0.462 times the variability of the I &D in terms of healing time and less spread in data around the mean compared to the I &D group. The UGNA group has a lower mean healing time of 8.59 days compared to the I &D group of 18.6 days which suggests that the UGNA group to a shorter time to heal than the I &D group. The UGNA group indicates less variability compared to the I &D group which demonstrates higher consistency in outcome healing time. The mean healing time was lower in the UGNA group implying that the UGNA method is more effective in promoting faster healing compared to the I &D group. Based on variability and mean healing time the UGNA method appears to be more consistent and effective or has higher efficacy compared to the Incision and drainage method (Table 2).

Table 2: Comparison of Mean Healing Days and Standard Deviation Ratio for Determining the Efficacy of UGNA and I & D

Sr. No	UGNA S.D.	I & D S.D.	S.D Ratio	UGNA / Mean Days	I & D / Mean Days	Standard Deviation Ratio	Reference
1	14.44 ± 4.28	24.68 ± 5.07	0.5847	14.44	24.68	**UGNA Group:** 8.59 ± 1.89 **I & D Group:** 18.6 ± 5.00 **SD Ratio =** SD of UGNA/SD of I & D **SD Ratio =** 8.59/18.6= 0.462	Voruganti *et al* [18]
2	8.59 ± 1.89	18.6 ± 5.00	0.4618	8.59	18.64		Manzoor *et al* [1]
3	21.0 ± 1.97	44.23 ± 3.15	0.473	21	4.23		Dar *et al* [14]
4	22.0 ± 1.86	43.2s1 ± 2.14	0.509	22	43.21		Khan *et al* [21]
5	11.16 ± 2.01	22.2 ± 13.12	0.502	11.6	22.2		Fathy *et al* [25]

DISCUSSION

To compare the efficacy of ultrasound-guided needle aspiration (UGNA) and incision and drainage (I & D) in the management of Puerperal breast abscess, Voruganti *et al.*, conducted a 3-year comparative prospective trial [18] at Pinnamaneni Siddhartha Medical College in India. The study included a total of 50 cases of young women of age 25 with small breast abscesses < 5cm and were divided into two groups of 25 each. Group A was managed by UGNA

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using a 16G needle and Group B was managed by I & D. According to the findings of the study, UGNA had better outcomes with a recovery of 92%. The mean duration of the healing period was lower 14.44 ± 4.28 in group as compared to group B 24.68 ± 5.07. The number of hospital visits was lower in group A, 3.96 ± 0.97 as compared to group B 8.72 ± 1.54, due to the need for regular wound dressing and intense pain. The results of the study are similar to a comparative study conducted by Kumar *et al.*, on 100 female patients aged 18-60, stating UGNA as statistically significant (p <0.05) compared to I & D [26, 27]. A randomized controlled trial (RCT) was conducted by Dar *et al.*, at Holy Family Hospital Pakistan to compare the healing period outcomes between UGNA and I & D (n = 35 each) in the management of PBA [14]. The study found a lower healing period in the UGNA group 21.0 ± 1.97 as compared to the I & D group 44.23 ± 3.15. It is in line with the findings of a 2-year RCT conducted by Muhammad Naeem *et al.*, in the hospital of Karachi, which reported a mean healing time of 19.13 ± 15.56 of patients who underwent UGNA as compared to 45.3 ± 24.04 in patients of I & D [10]. Both studies concluded that UGNA is a better treatment method supplemented with antibiotic coverage. An interventional study was undertaken by Suthar *et al.*, in India to compare the management of puerperal breast abscess by UGNA versus I & D with the outcome of resolution and complication [22]. The study reported that patients (n=35) in the I & D group experienced pain and needed daily hospital visits for wound dressing, mammary fistula in 3 patients, and scarring. No scar or mammary fistula was observed in the UGNA group. However, resolution time was less in the aspiration group and 6 patients were moved to surgical drainage after aspiration. The study concluded that UGNA has an acceptable failure rate of 17.14% for larger abscesses and is an effective alternative to I & D for small and early abscess sizes. Bhatti *et al.*, conducted a 1-year comparative investigation at Liaquat University Hospital of Karachi to compare the efficacy of UGNA and surgical drainage approach in the management of lactational breast abscess among 59 female patients [19]. The patients in the I & D group developed a mammary fistula (5.0%) and the resolution rate was 44.06%, whereas in the UGNA group resolution was 47.45% and no fistula formation was observed. The study findings suggested that UGNA is a better treatment intervention than the I & D in terms of low incidence of fistula development. At any site and time where an ultrasound facility is accessible, ultrasound-guided needle aspiration should be the first-line treatment as it is minimally invasive, cost-effective, precise, and reduces the risk of mammary fistula development [28, 29]. Allied Hospital Pakistan reported the higher efficacy of the UGNA group at 87.5% (n=30) as compared to the I & D group at 82% (n = 29). The limitations of the systematic review include limited availability of recent research, variations in study designs, outcomes, and patient population, small sample sizes, and limited follow-up, across studies included. Furthermore, heterogeneity in outcome measures can significantly impact the overall conclusions [30, 31]. A 1-year retrospective study was conducted by Rigourd *et al.*, at the Duroc Breast Imaging Center in France. The study aimed to analyze the effectiveness of UGNA among puerperal breast abscess patients (n=28) and breastfeeding continuation after the intervention [23]. From a total of 28 patients, 7 were referred to surgical drainage and avoided surgery in 75% of cases. The results showed that a single aspiration was sufficient in 64.3% of patients whereas others required two to three aspirations. The delay between the development of abscesses and the decision for abscess drainage was higher among patients who underwent I & D. A study showed that out of 43 patients with abscesses, 24 patients were able to avoid surgical intervension. The drainage procedure was effective in clearing the abscess cavity in 39 patients [32]. All patients continued breastfeeding after aspiration intervention and considered it an effective approach. The results are similar to a retrospective study [12] Some studies measure the frequency and risk factors of lactational mastitis [33]. Among 54 patients, 80.6% were successfully treated with UGNA. Saharan *et al.*, executed a randomized controlled trial to compare the effectiveness of UGNA and I & D in young women (n=25 each) of age 24 with puerperal breast abscesses [24]. The study found that patients in the UGNA group had early healing and resumption of breastfeeding, no surgical scar, fewer visits to the hospital, less pain, and resolution of breast abscesses with one or two aspirations as compared to the I & D group. The ultrasound-guided needle aspiration is an effective treatment method especially for unilocular breast abscesses whereas I & D is specifically reserved for multilocular abscesses. Breast abscesses pose a significant healthcare challenge, particularly in South Asia. Khan *et al.*, conducted a 6-month randomized trial at Allied Hospital Pakistan, evaluating the efficacy of both approaches as outcomes [21]. Of a total of 70 patients, 35 patients of age 28 underwent UGNA and 35 patients of age 29 underwent I & D intervention. The healing period was significantly lower in the UGNA group 22.0 ± 1.86 as compared to I & D, 43.21 ± 2.14, whereas the efficacy of ultrasound aspiration 94.29% was higher than I & D, 77.14%. A meta-analysis performed by Fu Bing *et al.* [29] in the ultrasonography department in China encompassed 8 randomized controlled trials. It showed that the mean

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healing time in the UGNA group was less than in the I & D group. A six-month Randomized controlled trial undertaken by Randhawa *et al.*, at From August 2019 to March 2020 a comparative investigation was led by Fathy *et al.*, in Kasir Al-Ainy Hospital of Egypt to compare UGNA and I & D methods in the management of acute-puerperal breast abscesses among 48 female patients [25]. Most of the abscesses develop asa a complication of lactational mastitis but over recent years the availability of clinic-based ultrasound has made diagnosis easier [34, 35]. The mean age of patients included was 29. The results showed the mean time of intervention was less in the UGNA group than I & D group and healing time was 11.6 in the UGNA and 22.21 in the I & D group. The patients from the UGNA group had less pain and all were satisfied with cosmetic outcomes as compared to patients of the I & D group which had a 54% satisfaction rate. However, the success rate of UGNA was 70%, and surgical drainage was 100%. The study concluded the ultrasound aspiration method could be an effective approach with an acceptable success rate and better outcomes than I & D.

CONCLUSIONS

In comparison, ultrasound-guided needle aspiration emerges as an effective approach with an acceptable success rate in the management of puerperal breast abscesses. It offers advantages, especially for small breast abscesses in terms of less healing time, fewer hospital visits, lower incidence of fistula development, no scarring early, breastfeeding resumption, and better cosmetic outcomes compared to the I & D method. However, due to limitations in small sample sizes and limited follow-up, future research on large-scale RCTs with extended monitoring and assessment of patient outcomes such as pain, satisfaction, and impact on quality of life should be performed.

Authors Contribution

Conceptualization: HA

Methodology: SM, SQ

Formal analysis: MA, MI

Writing review and editing: HA

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

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

Investigating the Potential of Non-Invasive Breath Test Analysis for Early Detection of Oral Cancer: A Systematic Review

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ABSTRACT

Oral cancer is the 6th most common type of human cancer with a survival rate of around 50% originates in the squamous cells of the mouth and throat. Early diagnosis of oral cancer remains the cornerstone to enhance treatment outcomes as many cases are still diagnosed at advanced stages. The exhaled-breath-analysis tests identifying novel Volatile Organic Compounds (VOC) as biomarkers for oral cancer provide an emerging alternative as a non-invasive diagnostic tool. **Objective:** To investigate the potential of non-invasive exhaled breath test analysis using VOCs as biomarkers for the early detection of oral cancer. **Methods:** Epidemiological studies published from twenty years (2004-2024) were included from PubMed, Google Scholar, Sci-hub and Science Direct databases using preferred reporting items for systematic reviews and meta-analyses guidelines. **Results:** According to this systematic review breath analysis tests coupled with other methods could serve as a feasible supplemental tool with high sensitivity, specificity, and accuracy for identifying oral cancer. The cancer-associated 40 novel VOC biomarkers identified in this review mostly belong to groups including, Alkanes, aldehydes, Ketones, and alcohols. **Conclusions:** Exhaled breath analysis techniques including Gas-Chromatography (GC), Mass-Spectrometry (MS), Selected-Ion-Flow-Tube (SIFT) and Polymer-based e-nose identified 40 novel VOC biomarkers belonging to Alkane, Aldehyde, Ketone, and Alcohol Groups. The results indicate that the exhaled breath analysis tests could serve as a feasible, non-invasive diagnostic tool to supplement the traditional diagnostic procedures like biopsy and assist in generating results with high sensitivity, specificity, and accuracy for identifying oral cancer at an early stage.

INTRODUCTION

Oral cancer is a malignant neoplasm that develops on the lip or oral cavity and poses a significant challenge to global public health. It is typically defined as Oral Squamous Cell Carcinoma (OSCC) because in dental settings higher proportion of cancers stem from oral squamous cells [1]. It exhibits varying levels of differentiation and inclination for lymph node metastasis [2]. Oral cancer comprises 48% of Head and Neck Cancer Cases (HNSCC) [3]. Whereas Oral Squamous Cell Carcinoma (OSCC) accounts for 90% of oral cases based on histological diagnosis [4]. OSCC is a major type of HNSCC that specifically affects squamous cells originating in the oral cavity whereas Head and neck cancer is a broader term encompassing various anatomical sites and originates from the epithelial lining of the oral cavity, hypopharynx, oropharynx and larynx [5]. According to the incidence of cancers, oral cancer resides within the top 10

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rankings and despite the advancement in research and therapeutic interventions, significant improvements in survival outcomes have not been obtained in the recent years indicating a global health challenge for all. [1]. Oral cancers pose a challenge to the treatment regimen [4]. The progression of oral cancers involves multiple steps accompanied by changes in normal mucosa and persists until the development of invasive cancer and metastasis [6]. Oral cancer is a multifactorial lesion that involves various risk factors including tobacco and alcohol, ultraviolet radiation (lip cancer), genetic predisposition, immunosuppression, smoking and Human Papillomavirus Virus (HPV). Among them, alcohol consumption and smoking are deemed as primary factors in the development of malignancy in the oral cavity [7]. According to worldwide reports cancers across all the regions of the oral cavity and pharynx are collectively grouped, representing the sixth most common cancer globally [1]. Approximately 389,485 new cases and 188,230 death cases related to oral cancer were reported in 2022 and it is estimated that these cases will continue to increase globally. Asia accounts for around 50% of all reported cancers [8]. A global study of 195 countries spanning 28 years found the Age-Standardized Rate of Incidence (ASRI) of oral cancer to be highest in Pakistan (27.03/100,000, 95% CI = 22.13-32.75/100,000). In terms of national distribution figures, oral cancer is the second leading cancer (9.6%) in Pakistan [9]. Early cancer detection is crucial for increasing patient survival rate, improving effective therapy, and decreasing mortality rates. There is a need for reliable non-invasive diagnostic tools to attain this objective [10, 11]. Traditionally, procedures like Biopsy and cytology have served as gold standards for diagnosing oral cancer. However, they are invasive for patients, time-consuming, and require longer recovery. Moreover, by the time these procedures are performed, the cancers have spread and advanced to higher stages. Therefore, the main emphasis of recent research endeavours is centred on early detection and prevention of oral cancer, and new diagnostic procedures which are reliable, simpler, non-invasive, and cost-effective alternatives [12]. Recently, exhaled breath analysis has been employed to detect various cancers including gastrointestinal cancer, lung cancer, breast cancer and oral cancer at early stages [13-16]. It is relatively a reliable, simple, and non-invasive method based on principle for conducting a potential investigation of Volatile Organic Compounds (VOCs) as biomarkers in the human body [17]. Volatile organic compounds (carbon-based) produced through the metabolism of cells are released into the blood, reach the lung, get diffused and expelled through the exhaled breath and can provide useful information about the metabolic state of an organism [18]. VOCs generated and emitted through the cellular metabolism of cancer cells are considered innovative cancer-associated biomarkers for diagnostic application. Exhale breath analysis usually involves profiling VOCs present in the breath samples of cancer groups and healthy controls [19]. The specific oral cancer-associated VOCs can be detected within the breath which are emitted by normal cellular metabolism and distinguished from cancer cells [17]. The breath analysis technique and discovery of cancer biomarkers opened up a new domain for the possibilities of early detection of oral cancer [18].

Therefore, this comprehensive systematic review aimed to investigate the potential and performance of non-invasive breath tests in the early detection of oral cancer and to address the identified OSCC and HNSCC-associated VOC biomarkers. This involves compiling data from multiple studies concerning breath tests in oral cancer settings to establish a comprehensive overview of the potential of diagnostic tests. Volatile organic compound: Procedures and working.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to write this systematic review. The data of last twenty years 2004-2024 was collected using several databases (PubMed, Google Scholar, Sci-hub and Science Direct) using Boolean logic "AND" and "OR", Medical Subject Headings (MeSH Terms) and keywords. Different terminologies were used to explore the literature "Squamous cell carcinoma", "Head and Neck cancer", "Oral cancer", "breath analysis", and "Volatile organic compounds". A total of 90 articles were retrieved from the included databases. Out of all these articles. 15 articles were considered eligible after applying inclusion/exclusion criteria and deleting the duplicates and irrelevant articles. Five articles were case-control studies with four articles having cohort design 2, having feasibility, study design, and 2 having cross-sectional studies whereas the other two had prospective controlled and pilot studies (Figure 1).

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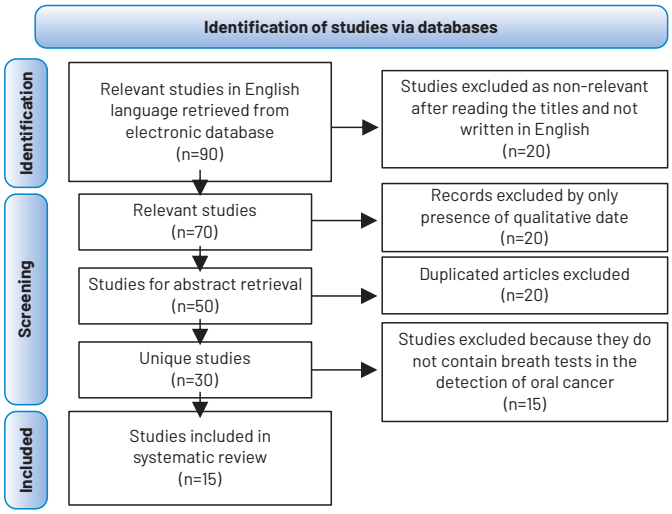

Figure 1: Prisma Flowchart Depicting the Study Selection Process

RESULTS

Figure 2 summarized the different factors this study found to be involved in the progression of oral cancer. It includes tobacco and alcohol, ultraviolet radiation, genetic predisposition, immunosuppression, smoking and Human Papillomavirus Virus(HPV).

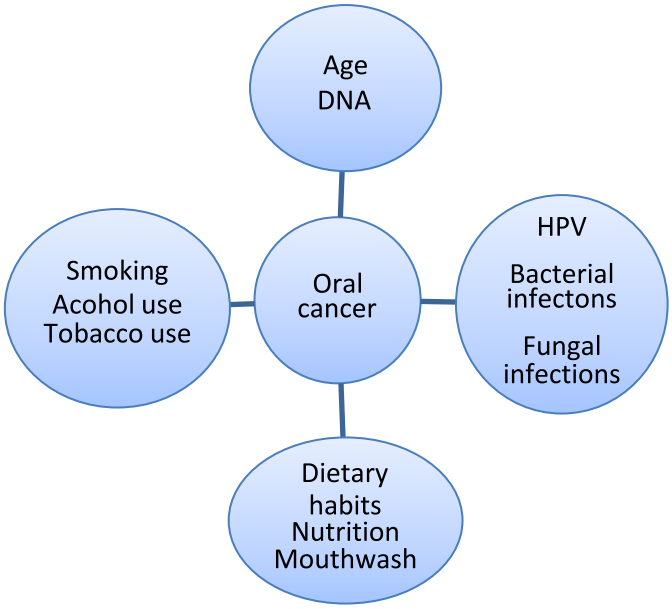

Figure 2: Factors Involves in the Progression of Oral Cancer

The studies included in this systematic review performed different exhaled breath analysis tests using VOCs as biomarkers for the early detection of oral cancer. The first step in the EBA procedures involved collecting breath samples from the cancer patients and healthy controls in an airbag like Tedler-Bag followed by different analysis techniques to analyze the VOC composition of samples. The most common techniques included Solid Phase Microextraction (SPME) used to collect and concentrate VOCs against a fiber coated with an absorbent material from exhaled breath for subsequent analysis using Gas-Chromatography (GC) which analysed the chemical properties to separate the VOCs, Mass-Spectrometry (MS) which used mass-to-charge ratio to distinguish the specific molecules and Selected-Ion-Flow-Tube (SIFT) in which pre-selected reactant ions were used to ionise the VOCs. Polymer-based e-nose is a relatively new technique, a specific type of e-nose that utilizes conducting polymers, organic materials with electrical conductivity that changes upon exposure to VOCs, as its sensor material. Following sample collection, chemical reactivity was used to separate VOCs, and based on the unique reaction patterns, the VOCs were recognized. To detect VOCs present in the breath samples studies used pure samples of hexadecane, nonanal, decanal, undecane, and 1-octene hydrocarbons as reference points. This assisted the researchers in comparing the retention times of unknown compounds in the samples to the retention times of the known standards, resulting in the recognition of VOCs present in the breath. SIMCA (Soft Independent Modelling of Class Analogy) technique was used to investigate samples in cancer and control groups and to classify them based on VOC profiles. Nonparametric tests like Kruskal–Wallis and Mann–Whitney were applied ($p \leq 0.05$) and zones with a higher average class prediction accuracy (threshold value above 0.65) were considered more likely to contain VOCs that could potentially be used as biomarkers for oral cancer. To determine the association of VOC biomarkers with oral cancer, only those studies with specificity and sensitivity mandated in their inclusion criteria were included in this systematic review. This included studies that compared the differential abundance VOC profiles between patients of oral cancer and healthy controls and utilized established diagnostic methods including biopsy and clinical examination for confirming oral cancer diagnosis. Studies also used cancer-free individuals having digestive issues as control by using the QuinTron Breath-Tracker (QBT), in conjunction with other techniques, which is commonly used to measure H2, CH4, and CO2, often linked to digestive issues as this ensured that the identified VOCs are specific to oral cancer. Studies also assessed the potential biological plausibility between specific VOCs and the metabolic processes in oral cancer development. As per previous studies, the increased levels of aldehydes are linked to enhanced lipid peroxidation, a process associated with inflammation and tissue damage in cancer. Moreover, elevated ketones indicate altered energy metabolism in cancer cells. Lastly, consistent findings across multiple studies further validated the VOCs for oral cancer. The data assessed through this systematic review indicates that non-invasive breath tests have the potential to diagnose and discriminate oral cancer patients from healthy controls based on VOC biomarkers (Table 1).

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Table 1: Summary of Extracted Data on the Potential of Non-Invasive Breath Analysis Techniques Based On Voc Profile

S.No.	Cases	Control	Oral Cancer Type	Breath Analysis Technique	Key Outcomes	Study	References
1	22	19	HNSCC	GC/MS	Clearly Distinguish HNSCC from Controls and Benign Tumor	Feasibility	Gruber *et al.*, 2014 [20]
	21		Benign		Cost-Effective/Reliable Screening Tool		
2	50	50	HNSCC	SIFT-MS	Early Detection / Accurate / Practical	Cohort	Dharmawardana *et al.*, 2020 [21]
					Sensitivity 80% and Specificity 86%		
3	22	40	HNC	GC/MS and E-NOSE	Distinguish HNC from H	Cross-Sectional	Hakim *et al.*, 2011 [22]
					Cost Effective/Reliable Screening Tool		
4	26	26	OSCC	GC/MS	Clearly Distinguish OSCC from H Based on VOC	Cross-Sectional	Bouza *et al.*, 2017 [12]
5	50	50	OSCC	GC	Effective Accessory Non-Invasive	Case-Control	Kwon *et al.*, 2022 [16]
					Sensitivity 68.0% and Specificity 72.0%		
6	10	40	SCC	GC/MS	Feasible Test Approach	Prospective Cohort	Hartwig *et al.*, 2017 [23]
					Based on Absence of Cancer Associated VOC after Therapy		
7	49	35	OSCC	E-nose	Sensitivity 88% and Specificity 71%	Cohort	Mohamed *et al.*, 2021 [24]
8	35	50	OSCC	GC/IMS	Average Accuracy 80-90%/reliable	Prospective Controlled	Mentel *et al.*, 2021 [25]
9	91	72	HNSCC	E-nose	Sensitivity 72% and Specificity 79%	Feasibility	Van de Goor *et al.*, 2020 [26]
					Portable/non-invasive		
10	23	21	HNSCC	SIFT-MS	Sensitivity 91% and Specificity 76%	Pilot	Chandran *et al.*, 2019 [27]
11	15	15	HNC	Polymer base e-nose	Not Identified Specific VOC /Cost-Effective	Case-Control	Anzivino *et al.*, 2022 [28]
12	74	61	HNSCC	Quintron Breath-Tracker and SIFT-MS	Novel-Non-Invasive Can Assess Gut Fermentation Activity Linked to Cancer	Case-Control	Dharmawardana *et al.*, 2020 [21]
13	11	20	Laryngeal Carcinoma	SPME/GCMS	Discriminated Cancer Group from Healthy Control	Case-Control	García *et al.*, 2014 [29]
					Based on VOC Pattern		
14	42	13	OSCC/ Bronchial/ Laryngeal	E-Nose Cyranose 320	Sensitivity 100% and Specificity 80%	Case-Control	Fielding *et al.*, 2020 [30]
					Distinguish Cancer from Controls by VOC Analysis		
15	36	23	HNSCC	E-Nose	Sensitivity 90% and Specificity 80 %	Cohort	Leunis *et al.*, 2014 [31]

Abbreviations: GC-MS, gas chromatography-mass spectrometry; HNSCC, Head and Neck squamous cell; OSCC, Oral squamous cell carcinoma; e-nose, electronic nose; SPME; solid phase microextraction, VOC; Volatile organic compound; SIFT; selected ion flow-tube. Ten studies used different methodologies and breath analysis techniques to collect and analyze the VOC composition of exhaled breath air from the cancer patients' group and healthy controls [20,23,24,12,16,25-29]. The remaining five studies used e-nose technology based on portable e-nose devices [30-34]. The samples in these studies were analyzed using Gas Chromatography-Mass spectrometry [GC-MS; 20, 12, 25, 23, 24, 26], Solid phase microextraction preconcentration followed by (SPME/GC-MS; 29), Selected Ion Flow-Tube-Mass spectrometry (SIFT-MS; 27, 23, 28]. Whereas in the study conducted by Kwon IJ *et al.*, a new simple GC system was employed for the diagnoses of OSCC [16]. An overview of clinical characteristics of the study group (cancer group and healthy controls) including age, gender, smoking/alcohol status and cancer stage is given in the supplementary information in table 2 titled Clinical characteristics of the study groups attached as a supplementary file. Due to heterogeneity in extracted data, clinical features were not correlated with oral cancer. However, smoking and alcohol are regarded as primary factors found in 90% of cases of oral cancer [35, 36].

Novel VOC Biomarkers for HNSCC and OSCC

Nine studies identified 40 novel VOCs potential biomarkers within the group encompassing alkanes, ketones, aldehydes, alcohols and thiols for the detection of oral cancers. Sixteen VOC biomarkers were identified by Bouza M *et al.*, for HNSCC [12]. Of these compounds benzaldehyde and 3, 7-dimethyl undecane exhibited a significant correlation ($p < 0.05$) with tumor size and recurrence. There was a significant correlation observed between Butyl acetate and the histological degree of differentiation.

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Markar SR *et al.*, identified three VOC biomarkers for HNSCC [33]. Removed Garcia RA *et al.*, also found ethanol and 2-butanone as significant biomarkers for the identification of laryngeal OSCC [29]. In the study by Chandran D et al., the level of HCN biomarker was observed to be significantly different between the HNSCC group and healthy controls [27] (Table 3).

Table 3: VOCs Identified as Potential Biomarkers for HNSCC and OSCC

S. No.	Cancer Biomarkers / VOC Profiling	Group	Ora Cancer Type	References
1	Undecane	Alkane	HNSCC	Gruber *et al.*, 2014 [20]
	2-Propenenitrile	Nitrile		
	Ethanol	Alcohol		
2	Formaldehyde	Aldehyde	HNSCC	Dharmawardana *et al.*, 2020 [21]
	Methyl Mercaptan	Thiol		
3	4,6-Dimethyl-Dodecane	Alkane	HNC	Hakim *et al.*, 2011 [22] And Bouza *et al.*, 2017 [12]
	2 ,6 Dimethyl Propanoic Acid			
	5-Methyl-3-Hexanone	Ketone		
	2,2-Dimethyl-Decane	Alkane		
	Limonene	Terpene		
4	2,2,3-Erimethyl-, exobicyclo [2.2.1]heptane	Ketone	OSCC	
	Udecance	Alkane		
	Dodecane	Alkane		
	Decanal	Aldehyde		
	Benzaldehyde			
	3,7-Dimethyl Undecane	Alkane		
	4,5-Dimethyl Nonane	Alkane		
	1-Octene	Alkene		
	Butyl Acetate	Ester		
	Hexadecane	Alkane		
	Styrene	Alkene		
	Benzyl Alcohol	Alcohol		
	2-ethyl-1-Hexanol	-		
	Toluene	Benzene		
	Dodecanal	Aldehyde		
	Nonanal	Aldehyde		
5	Ch3SH	Thiol	OSCC	Kwon *et al.*, 2022 [16]
	H2S	Thiol		
6	Dimethyl Disulfide (DDS)	Disulfides	OSCC	Hartwig *et al.*, 2017 [23]
	Decamethylcyclo-pentasiloxane	Cyclic Siloxanes		
	P-Xylene (PX	Xylene		
	N-Heptane	Alkane		
	Methyl Ethyl Ketone	Ketone		
	Toluene	Benzene		
	1-Heptene	Alkene		
	Dibutylhydroxytoluene	-		
7	HCN		HNSCC	Chandran *et al.*, 2019 [27]
8	CH4:H2	Alkane hydrogen	HNSCC	Dharmawardana *et al.*, 2020 [21]
9	Ethanol	Alcohol	Laryngeal Carcinoma	García *et al.*, 2014 [29]
	2-Butanone	Ketone		

Abbreviations: HNSCC, Head and Neck Squamous Cell; OSCC, Oral Squamous Cell Carcinoma; T3, Tumor Stage 3

DISCUSSION

In this systematic review, we present a comprehensive overview of different studies concerning the diagnostic performance of exhale breath tests based on volatile organic compounds in the detection of oral cancer [28]. As per the analysis of the results, the exhaled breath analysis tests could serve as feasible tools to supplement the traditional diagnostic procedures like biopsy and assist in generating results with high sensitivity, specificity, and accuracy for early identifying oral cancer. The cancer-associated 40 novel VOC biomarkers identified in this review mostly belong to groups including, Alkanes, aldehydes, Ketones, and alcohols. These VOCs hold promise as an efficient non-invasive diagnostic approach and also underscore the importance of further research in the identification of other novel oral cancer-associated VOC biomarkers. Based on evident studies, in an initial effort to analyze the exhaled breath for the diagnoses and distinction of HNSCC and benign tumor from the healthy controls Gruber M *et al.*, used a breath test with Gas Chromatography/Mass Spectrometry (GC/MS) and in their analysis, found undecane, 2-propenenitrile and ethanol as potential biomarkers of these cancers [20]. To ascertain whether the breath profile can be used for discrimination of patients with or without HNSCC, Markar SR *et al.*, used an ion flow-tube mass spectrometer to analyze the breath for VOCs and concluded that the diagnostic approach is feasible (higher Sensitivity of 80% and Specificity of 86%) for early detection and distinction of HNSCC from controls [31]. They identified Formaldehyde and Methyl mercaptan as potential VOC biomarkers related to cancer. Various methods have been applied and reported in different studies up to now. Using GC/MS Bouza M *et al.*, identified several VOCs such as Undecane, dodecane, decanal, benzaldehyde, 3,7-dimethyl, undecane 4,5-dimethyl nonane, 1-octene as biomarkers for the diagnoses of OSCC and concluded that existing of aldehydes within the oral cavity may constitutes potential biomarkers [12]. In another study carried out by Hakim M *et al.*, electronic nose containing nanoparticle-based sensors was used to analyze the exhaled breath to diagnose HNS patients from healthy controls and concluded the method was cost-effective and reliable [22]. To assess the viability of detecting VOC biomarkers in the breath of patients, GC/MS employed by Hartwig S *et al.*, involved comparing the presence of VOCs in the breath sample before and after therapy [23]. The study results confirmed the absence of three cancer-associated VOCs (Dimethyl disulfide, Decamethyl-cyclopentasiloxane, p-xylene) in the breath samples after the therapy for HNSCC ensuring the feasibility of the diagnostic method. In a study performed by Kwon IJ *et al.*, comparative analysis of exhaled breath was conducted between patients with Oral Squamous Cell

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Carcinoma OSCC and healthy controls via using simple Gas chromatography [16]. The study aimed to investigate whether the exhaled breath test can serve as a novel non-invasive and effective diagnostic test for oral squamous carcinoma. The study results demonstrated significantly elevated concentrations of hydrogen sulfide and methyl mercaptan in the OSCC group than in the healthy controls affirming the non-invasive method. However, in comparison to other studies, breath test conducted in this study exhibited low sensitivity 68.0% and specificity 72.0% indicating that breathe analysis through a simple GC system requires refinement in clinical practice. Dharmawardana N *et al.*, conducted a study using an ion flow-tube mass spectrometer and a Quintron BreathTracker to discriminate breath samples of the HNSCC group from healthy controls based on methane and hydrogen ratio increased with tumor stage [21]. In another study conducted by Mohamed N *et al.*, 12 VOC was extracted from the saliva of OSCC patients as potential OSCC biomarkers. Using e- nose base technology study was conducted by Shield KD *et al.*, in Sudan to distinguish the OSCC group from the healthy control [24, 36]. A portable e-nose device was used to collect and analyze the breath samples. Observed diagnostic accuracy of the test was 81% with good sensitivity at 88% and specificity of 71% concluded that this diagnostic strategy is cost-effective and efficient with limited resources to confront the burden posed by OSCC. Another study using e-nose technology was performed by van de Goor RM *et al.*, and found an average accuracy of 72% at a sensitivity of 79% and specificity of 63% indicating that the diagnostic method correctly discriminated the HNSCC group from healthy controls [26]. Leunis N *et al.*, employed an e-nose with metal oxide-based sensors and verified that the VOCs pattern was different between the HNSCC group and a control group with a sensitivity of 90% and a specificity of 80% [31]. In comparison, studies on the use of breath tests in diagnoses of other cancers including breast and lung, have revealed similar findings with higher levels of sensitivity and specificity [37, 38]. In comparison to the non-invasive diagnosis technique, the biopsy method is invasive and could spread the disease [32, 39]. If future research can provide stronger evidence for the utilization of breath test methods, we believe that these tests could be used in screening initiative that may improve the rates of diagnoses of oral cancer at earlier stages and improve disease prognosis [40]. Oral cancer is one of the leading causes of mortality and a global burden due to its late diagnosis at early stages. Exploring the potential of non-invasive breath test methods and VOC compounds facilitates the healthcare community by providing insights into the accuracy, feasibility and reliability of these methods for the early detection of oral cancer [41]. Furthermore, it provides information on the specific oral cancer-associated (HNSCC and OSCC) VOC biomarkers aiding in the advancement of diagnostic tools and contributing to the early detection and monitoring of condition of oral cancers. By assessing the evidence base for breath tests the systematic review assists the clinicians in making informed decisions regarding the integration of these diagnostic approaches in oral cancer settings ultimately, improving patients care and outcomes. While EBA shows promise for non-invasive oral cancer detection, overcoming the following limitations is crucial. The technology for EBA is still evolving, and widespread availability and standardization remain concerns. Limited research conducted so far has resulted in insufficient data for many potential VOC markers which might need further validation in larger clinical trials to confirm their effectiveness for routine clinical use. Moreover, early-stage oral cancers might not produce significant changes in VOC profiles, potentially leading to missed diagnoses. Lastly, natural variations in breath VOCs due to genetics can affect the test's sensitivity.

CONCLUSIONS

The systematic review provides a comprehensive summary of the exhaled breath analysis techniques like Gas-Chromatography (GC), Mass-Spectrometry (MS), Selected-Ion-Flow-Tube (SIFT) and Polymer-based e-nose which identified 40 novel VOC biomarkers belonging to Alkane, Aldehyde, Ketone, and Alcohol Groups. The results indicate that the exhaled breath analysis tests could serve as a feasible, non-invasive diagnostic tool to supplement traditional diagnostic procedures like biopsy and assist in generating results with high sensitivity, specificity and accuracy for identifying oral cancer at an early stage.

Authors Contribution

Conceptualization: MRT

Methodology: MM, NI, SAT, SPS

Formal analysis: ATA

Writing, review and editing: SPS, SA, MRT

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

Conflicts of Interest

The authors declare no conflict of interest.

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