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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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ACKNOWLEDGEMENT

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Innovations in Cancer Diagnosis and Challenges

OPEN ACCESS

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Cancer is a disease that is characterized by the abnormal and uncontrolled growth of cells which can develop in any part of the body. For the diagnosis of cancer, the tissue sample, fluid or blood is submitted to the laboratory, where a team work of expert laboratory persons concludes a diagnose. In the past the role of pathologist and their team was limited up to diagnosing type and grade of cancer which was primarily based on light microscopic findings of hematoxylin and eosin stained slide. The challenges of diagnosing cancer increased with evolving complex classifications of cancer. The role of pathologist then expanded to incorporate a number of prognostic and predictive findings in the pathology report. To acquire these prognostic and predictive findings pathologist had to take more tissue sections and needed more special tests which expanded the work load of laboratory staff, yet it helped the oncologist to treat the patients. For pathologist, free accessible resource checklists are easily available for these prognostic and predictive factors at different websites.

Innovation of immunohistochemistry (IHC) was another milestone which has been a useful tool to solve difficult cases, in addition it also has prognostic and predictive role. Incorporation of molecular and cytogenetic techniques to cancer have evolved the personalized medicine which significantly improved the management of cancer patients. To achieve this goal collaborative efforts are required with oncologist who can inform the pathologists about the required molecular or cytogenetic tests. Artificial intelligence and machine learning for cancer diagnosis is challenging but thriving and still in phase of seeking accreditations.

The cardinal step in cancer diagnosis and optimal treatment is to integrate resource checklist, IHC, molecular and cytogenetic studies in the report, some of these studies are expensive but rewarding for the patient.

The biggest challenge to achieve these goals is resource availability, its high cost and instrument maintenance. To attain standardization of above mentioned tests and quality reports, the laboratories can develop standard operating procedures and follow them strictly. For other challenges and inter-observer variability of pathologist, enrolling into a Proficiency testing programs or Alternative assessment are reliable tools which also increase reliability and accuracy of results and testing processes. Medial audits followed by corrective actions, continuous medical education of laboratory staff and pathologist is also crucial. Last but not least the high-volume of work with inadequate number of experienced laboratory staff can significantly affect the results.

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Review Article

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Role of Gut Microbiota in Immune System Regulation

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ABSTRACT

The human gut is a densely populated organ system that bears hundreds of microbial species, including bacteria, viruses, and various protozoans. The gut microbiome expresses enormous functional diversity based on microbial community collection. However, this has remained unexplored for a long time, but in the recent past various researches have revealed its immense significance in host metabolism and immunity. Gut microbiota metabolize undigested substances and release various metabolites in response to microbial metabolism that have a significant effect on the immune system. The balance and stability of the immune system within the body are achieved and maintained through the complex interaction between the gut microbiota and the host mucosal immune system. Upon loss of control by the immune system, dysbiosis occurs, the modulation of the microbial community, which leads to different disorders, including inflammatory bowel disease and colorectal cancer. Moreover, dysbiosis is also associated with various autoimmune diseases such as rheumatoid arthritis, diabetes mellitus, and multiple sclerosis. Despite its intricate mechanism in autoimmune diseases, various therapeutic strategies are utilized to treat chronic diseases, including prebiotics treatment, personalized probiotics therapy, fecal microbiome transplantation, and narrow-spectrum antibiotic treatment. This review discusses the interaction of gut microbiome with the immune system, how this association becomes dysregulated, its various outcomes in the form of autoimmune diseases, and therapeutic interventions to cope with it.

INTRODUCTION

The microbial community in the mammalian gut consists of a diverse range of microorganisms such as bacteria, viruses, fungi, and other microbes. The information obtained from analyzing 16S rRNA sequencing indicates that Firmicutes and Bacteroidetes account for around 92% of the human microbiome, while the total number of bacterial species in the gut microbiota is estimated to be between 1,000 and 1,500 [1]. However, an individual typically harbors around 160 bacterial species [2]. Environmental factors and genetic inheritance also influence the composition and functioning of the gut microbiome. Mice with identical genotypes exhibit distinct microbiota configurations, influenced by diet, age, and inflammation [3]. The intestinal microbiome is influenced by both the host's genetic makeup and developmental processes, with synchronized interactions affecting intestinal balance and immune system function [4]. The gut's immune system has multiple components that foster symbiotic relationships. The host provides nourishment for the microbiome, while gut microbiota strengthens the intestinal immune system. It produces immunoglobulin A (IgA), develops gut structures, and promotes tolerance to

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dietary antigens [5]. Additionally, it maintains beneficial bacteria and protects against harmful pathogens through secretory IgA (SIgA) on mucosal surfaces. IgA functions as a primary barrier, preventing microorganisms from entering the epithelium [6]. It supports the complex interplay between commensal organisms, the epithelium, and the immune system. The gut microbiome and the immune system are responsible for regulating the mucosal ecosystem, but the disruption may have adverse effects on the gastrointestinal tract. Microbial colonization is crucial in the maturation of the immune system, as shown by studies on germ-free (GF) mice. These studies have demonstrated that the absence of gut microbiota leads to a notable impairment of the immune system [7, 8]. Moreover, the imbalance of gut microbiota has been strongly associated with various disorders, including obesity, type 2 diabetes, hypertension, necrotizing enterocolitis (NEC), and inflammatory bowel diseases (IBD), among others [9]. Moreover, various studies depict the involvement of gut microbiome in different autoimmune diseases. For example a reduction in the ratio of gut *Firmicutes* to *Bacteroidetes* in patients with systemic lupus erythematosus (SLE) [10]. Similarly, Porphyromonas gingivalis seems to be a potential initiator of anticitrullinated protein antibodies (ACPAs) from rheumatoid factor (RA) and a notable increase in the concentration of Lactobacillus in stool, while a decrease in *Bacteroidetes* [11].

In this article, we have focused on the interaction between the gut microbiome and the immune system of humans. Additionally, we explore the association of gut dysbiosis with the different autoimmune diseases and significant fluctuations in the gut microbiome.

Mechanisms of Microbiota-Immune System Interaction

The relationship between gut microbiota and the immune system is a mutual and multifaceted process that implies the use of various pathways and mechanisms.

Intestinal Epithelial Cells (IECs) and Short-Chain Fatty Acids (SCFAs)

Intestinal epithelial cells (IECs) control the immune response by passive and active methods and modify the nearby surroundings by recognizing and absorbing short-chain fatty acids (SCFAs) [12]. The balance of the gut ecosystem is maintained by the predominance of *Firmicutes* and *Bifidobacteriaceae*, which are obligate anaerobic bacteria. On the other hand, an increase in *Enterobacteriaceae*, which are facultative anaerobic bacteria, is a common indicator of gut dysbiosis, and unhealthy gut microbial composition. [13]. SCFAs facilitate the intracellular acidity of pathogens, hence protecting against pathogen infection. An essential role of propionate (It is a SCFA derived from the fermentation of dietary fiber by the gut microbiota mainly identified as butyrate-producing bacteria) is to restrict the growth of pathogens by promoting the acidification of the cytoplasm in Shigella and Salmonella, which modulates the intracellular pH equilibrium of the pathogens. [14]. The increase in concentration of SCFAs results in a decrease in pH that impedes the process of oxygen (O2) and nitrate (NO3) respiration, which in turn reduces the growth of facultative anaerobic bacteria such as *Enterobacteriaceae* [15].

Role of Peroxisome Proliferator-Activated Receptor Gamma (PPAR-γ)

During normal conditions of gut homeostasis, the IEC produces peroxisome proliferator-activated receptor gamma (PPAR-γ), which is activated by butyrate [16]. The butyrate produced by commensal bacteria is metabolized by IECs that promote the production of transforming growth factor β (TGF-β) and ultimately the accumulation of regulatory T cells (Treg cells) in the gut [17]. PPAR-γ facilitated the maintenance of a localized oxygen-deprived state by promoting the process of oxidative phosphorylation in colon cells [18] and the breakdown of SCFAs by the mitochondria through β-oxidation. SCFAs are produced by obligate anaerobic bacteria to make a suitable microenvironment for their growth, while the facultative anaerobic enteric pathogens experience inhibited growth [19]. Simultaneously, the activation of PPAR-γ reduces the levels of NOS2 in IEC, disrupting the production of both nitrate and inducible NO synthase, which are crucial energy sources for facultative anaerobic pathogens [20]. Furthermore, propionate confers resistance to the proliferation of harmful bacteria in a PPAR-γ independent manner, suggesting a parallel action of SCFAs [21].

Consequences of PPAR-γ Pathway Disruption

In contrast, blocking the PPAR-γ signaling pathway triggers changes in metabolism, disruption of the microbial balance in the gut, and depletion of SCFAs. This reprogramming stimulated the metabolic activity of colonocytes to shift towards anaerobic glycolysis, a phenomenon known as the Warburg effect [22]. As a result, the utilization of oxidative metabolism was restricted, leading to higher levels of lactate, nitrate, and oxygen in the lumen of the gut [23]. In addition, common virulence factors of *Salmonella* and *Shigella,* induce the recruitment of neutrophils across the epithelium, thus, decreasing SCFA levels [24]. It creates a detrimental feedback loop, promoting the proliferation of pathogens, and illustrating a cause-and-effect relationship between the metabolic activities of microbiota and the well-being of the gut epithelium [25].

The relationship between the gut microbiota and both the immune system and the development of autoimmunity. Many commensal bacterial-derived metabolites including SCFAs modulate the functionality of immune cells. Derangements in the composition of the gut microbiota

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(e.g., higher levels of competitive gut pathogens) increase the permeability of the gut wall and thereafter, microbial antigens and microbial metabolites are translocated to system circulation. Such factors in combination with genetic and environmental factors, can underlie an abnormal immune reaction where there is activation of Th17 cells, B cell differentiation into plasma cells, and the production of autoantibodies. Some of the signaling species and pathways that are involved with this process encompass; IL-6, TGF-β, IL-10, PPAR-γ, AhR ligands, NOD, TLR ligands, and molecular mimicry (Figure 1)

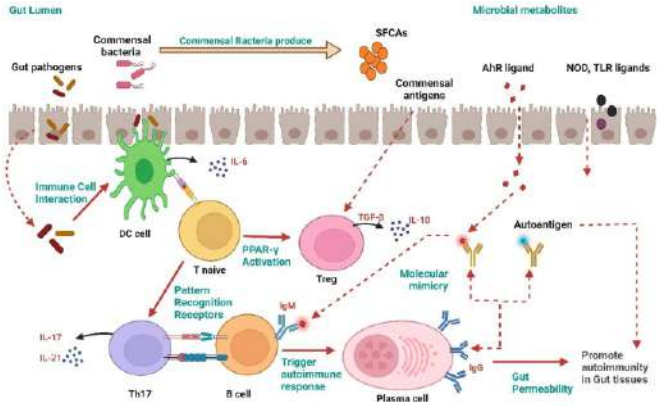

Figure 1: Relationship Between the Gut Microbiota and the Development of Autoimmunity

Pattern Recognition Receptors (PRRs) and Immune Response

Host immune systems employ various strategies to prevent the colonization of pathogens. Generally, the bacteria are recognized in the host by two pattern recognition receptor (PRR) systems: the toll-like receptors and nucleotide-binding oligomerization domain receptors (NODs) [26]. Various cells in the guts, like, IECs, macrophages, and dendritic cells express higher levels of PRR expression that can detect molecular patterns of pathogens and symbiotic microbes [27]. Once a microorganism has invaded the epithelium, the immune system initiates a specific immune response directed against the microorganism. When PAMPs are detected, pattern recognition receptors (PRRs) initiate multiple intracellular signaling pathways involving transcription factors, ligands, and kinases to evaluate the presence of infection in the host [28]. This signaling leads to modifications in gene expression, resulting in changes in the levels of various anti-microbial and pro-inflammatory cytokines, chemokines, and immunoreceptors [29]. The protective benefits seen were attributed to a reduction in the levels of pro-inflammatory cytokines, specifically IL-8, IL-12, and IL-23 [30]. This reduction was accompanied by an increase in the levels of anti-inflammatory cytokines, particularly IL-1s produced by Treg cells. Dendritic cells present the antigen to naive T-cells which provoke the generation of anti-inflammatory cytokines, leading to the establishment of both systemic and local tolerance [31].

Gut Permeability and Immune System Interaction

The composition of gut microbial communities varies throughout the gastrointestinal tract and different mucus layers. The immunological activity in the duodenum is significantly lower than in the ileum and colon [32]. However, the presence of enteric microorganisms in the gut evokes an increase in permeability, allowing large molecules and antigens to be absorbed from the gut into the bloodstream [33]. The permeability of the gut is strongly associated with both the commensal microbiota and components of the mucosal immune system [34]. It is affected by various causes, such as modifications to mucus layers, injury to the epithelial cells, and abnormalities in the composition of gut bacteria [35]. The products of fermentation by gut microbes and the components of cells are crucial in the immunological responses of the host that help preserve the integrity of the epithelium [36]. Flagellin is the primary constituent of bacterial flagellum which is recognized by TLR-5. In response to the recognition, bacteria enhance the expression of TLR-5 agonist which is further recognized by the B cells and CD4+ T-cells [37]. The activation of naïve B cells stimulates the differentiation into mature B lymphocytes that produce higher titers of IgA. Fully differentiated IgA specifically attached to microbial antigens and efficiently neutralizes the pathogens [38].

Pathogen Recognition and Response

Pathogenic bacteria inhibit the movement of phagocytes, which leads to the transmission of bacterial antigens to surrounding lymphoid tissues that trigger B-cell and T-cell activation [39]. Furthermore, pathogens stimulate dendritic cells and macrophages to generate pro-inflammatory cytokines. Consequently, the activation of pro-inflammatory immune responses occurs via the differentiation of naive T cells [40]. The activation of various Toll-like receptor (TLR) members is associated with the recognition of lipopolysaccharide (LPS) in gram-negative bacteria. Mammalian cells recognize LPS as a sign of bacterial invasion and use it to trigger innate immune responses [41]. The polysaccharide component of LPS serves as a protective strategy for bacteria, aiding in the prevention of complement assaults and allowing them to camouflage themselves among the carbohydrate residues of the host [42]. The TLR4/MD-2 complex after recognizing LPS, triggers various signal transduction pathways to activate the innate immune response in the host [43]. Nevertheless, the proliferation of probiotics that produce SFCAs had a considerable effect on the population of gram-negative bacteria, resulting in a subsequent reduction in LPS [44].

Dysbiosis and Immune Dysregulation

The gut microbiota of any individual is constantly changing

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due to factors such as age, nutrition, medication, and geographical location. The majority of bacteria are introduced into the body by exposure to the environment [45]. However, certain bacteria are temporary and cannot permanently establish themselves in the intestinal environment. These bacteria are either unable to compete with other beneficial microbes or are unable to adapt to the conditions of the intestines [46].

Assessment of Gut Microbiota Health

The assessment of the health of the microbiota in an individual can be determined based on its diversity, stability, resilience, and resistance [47]. So, it assesses the biodiversity of the ecosystem, its susceptibility to changes in composition and function, and its ability to restore itself to its initial condition [48]. Consequently, the equilibrium of the microbial ecology might be disrupted due to a decrease in variety, proliferation of harmful microorganisms, or decline of beneficial microorganisms [49].

Characteristics and Causes of Dysbiosis

Gut dysbiosis is characterized by alterations in the composition and functional capacity of the gut bacteria, resulting in detrimental consequences on the overall health of the host [50]. Commensal bacteria suppress the growth of opportunistic infections by producing SCFAs, which modify the pH of the intestines [51]. For instance, *Bifidobacterium* decreased the pH in the intestines while fermenting lactose, therefore inhibiting the growth of harmful *Escherichia coli* [52]. Various causes can contribute to dysbiosis, such as the presence of invasive intestinal pathogens, the use of antibiotics, physical harm to the mucosa, dietary choices, and genetic factors in the host [53].

Effects of Dysbiosis

Dysbiosis has increased vulnerability to enteric infection, and disruption of the commensal microbiota composition caused inflammation when antibiotics were used [54]. Commensal bacteria not only limit the virulence of diseases by altering the environment, but they also directly inhibit the expression of virulence genes in pathogens by releasing various metabolites [55]. *Shigella flexneri* relies on oxygen to effectively release virulence factors, but the other bacteria that live in the gut, take up the remaining oxygen [56]. As a result, the levels of *Shigella* virulence factors in the gut are reduced. In cases of gut dysbiosis in humans and mice, there is typically a drop in the prevalence of obligatory anaerobes, while the presence of potentially harmful facultative anaerobes such as *Shigella, Salmonella, E. coli, Proteus*, and *Klebsiella* [57] tends to increase Dysbiosis does not necessarily entail an escalation in the prevalence of pathogens, as the absence of crucial commensal bacteria alone might have detrimental effects [58].

Dysbiosis Without Pathogen Increase

Dysbiosis commonly arises when bacterial proliferation is reduced, in contrast to the growth of potentially harmful bacteria. Depleted commensals play significant roles, and restoring the absent microorganisms or their metabolites can potentially modify the characteristics linked to the disturbed gut [59]. The interaction between the immune system and gut microbiota is highly significant, as commensal bacteria strengthen the protective lining of the gut and stimulate the natural defense mechanisms of the body against harmful pathogens [60].

Interaction Between the Immune System and Gut Microbiota

The significance of diversity and abundance of gut microbiota in maintaining the health of the host has been confirmed, and alterations in diversity have been associated with several human disorders [61]. The extent to which the microbiota directly contributes to the development of all related disorders is yet uncertain.

Dysbiosis and Disease Correlation

Numerous studies have demonstrated that gut bacteria play a direct role in the development and progression of some diseases using an intricate network that connects metabolism and the immune systems of the host [62]. The correlation between mucosal inflammation and gut dysbiosis may be confined to dysbiosis only, or its associated disease, or simultaneous effect on both. The gut microbiota exhibited a significant correlation with the initiation and progression of inflammation in the mucosal layers of mice that were devoid of microorganisms [63].

Infections and Dysbiosis

Infections are a frequently reported factor that can lead to gut dysbiosis, as seen in both human and animal studies. Infectious diseases and their treatments have an impact on the human gut microbiota, leading to feedback loops that modify the nearby surroundings [64] and eventually, determine the influence of the infection on the host bacteria. Multiple investigations have confirmed the strong associations between infection and gut dysbiosis, establishing links with both gut bacteria and resident viruses [65]. For instance, patients with Clostridium difficile infection had substantial changes in their gut microbiota, which actively facilitated the advancement of the hepatitis B virus (HBV), the human immunodeficiency virus (HIV), and various other infectious disorders [66].

Gut-microbiota and Autoimmune Diseases

Autoimmune disorders are distinguished by the abnormal generation of autoantibodies. The immune system is influenced by both genetic and environmental variables, which result in the abnormal development of B cells that produce autoantibodies, T cells that react against the body's cells, and the excessive production of proinflammatory cytokines [67]. Various studies depict

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that the increase in the prevalence of autoimmune diseases can be attributed to significant alterations in the gut microbiota [68], which are caused by several factors such as extensive use of antibiotics and an imbalanced diet [69].

A Complex Relationship between Gut Microbiota and Autoimmune Disorders

The gut microbiota has a significant role in starting and intensifying the progression of disease in individuals with autoimmune disorders. Possible processes encompass molecular mimicry, effects on the mucosal permeability of the gut, the microbiota-stimulated immunological response, and antigenic mimicry [70]. Therefore, changes and fluctuations in microbial communities are always associated with host health and their significant involvement in autoimmune disorders [71]. The gut microbiome can impact immunological sense in distinguishing between self and non-self, perhaps playing a role in the development of autoimmune disorders [72]. Individuals suffering from autoimmune disorders frequently exhibit indications of compromised intestinal barriers, leading to potential immune system exposure to beneficial gut flora [73]. Furthermore, a disruption in the body's ability to tolerate the presence of the gut microbiota results in abnormal and harmful immunological reactions, ultimately worsening the severity of the disease [74].

Table 1: Gut Microbiota associated with various Autoimmune Diseases

Autoimmune Disease	Gut Microbiota Involved	References
Rheumatoid Arthritis	*Prevotella copri, Lactobacillus spp.*	[75]
Multiple Sclerosis	*Akkermansia muciniphila, Acinetobacter calcoaceticus*	[76]
Inflammatory Bowel Disease (IBD)	*Bacteroides fragilis, Faecalibacterium prausnitzii*	[77]
Type 1 Diabetes	*Bifidobacterium spp., Firmicutes*	[78]
Systemic Lupus Erythematosus	*Lactobacillus reuteri, Ruminococcus gnavus*	[79]

Molecular Mechanisms

Genetic and Environmental Influences

Autoimmune diseases are influenced by both genetic and environmental variables, such as complicated geographical location, genetic elements, immunologic derangement, patient exposure, and viral infections [80].

Aryl Hydrocarbon Receptor (AhR)

Aryl hydrocarbon receptor (AhR) may have a role in autoimmune diseases by attaching various cellular, dietary, and microbe-derived substances and converting external and internal signals into cellular responses [81]. Likewise, lower levels of innate IL-22 in AhR-deficient animal models led to an increase in commensal segmented filamentous bacteria (SFB) (an immune activator) and the growth of Th17 cells [82]. The inherent manifestation of AhR has a defensive function in T-cell-driven experimental colitis by inhibiting the development of harmful Th17 cells [83]. Various AhR ligands, such as 2,3,7,8-tetrachloro dibenzo-p-dioxin (TCDD) cause changes [84] in the microbial communities of *Bacteroides fragilis* (an immune suppressor) and SFB in mice when compared to levels observed in a typical gut microbiota [85]. Furthermore, the host response triggered by TCDD was greatly influenced by the presence of SFB in the gut microbiome, indicating a potential therapeutic relationship between AhR ligands and important commensal microorganisms [86].

Dysbiosis and Immune Dysregulation

The presence of an imbalanced gut microbiota has been recognized as a potential cause of autoimmune disorders [87]. These diseases are believed to be influenced by various variables in humans, although the specific role of the gut microbiota is still not fully understood. The association between an imbalance in gut microbiota and autoimmune diseases can be ascribed to various mechanisms that can impact the operation and reaction of the human immune system [88]. With the stimulation of antigen-presenting cells and host immune responses, it is possible to induce antigen presentation and the generation of cytokines, which can then impact the differentiation and function of T cells [89]. In addition, this influence disturbs the balance between T regulatory cells (Tregs) and T helper 17 (Th17) cells in homeostasis [90]. The gut microbiota contributes to autoimmunity by modifying autoantigens at the molecular level through posttranslational modification and exhibiting cross-reactivity with autoantigens [91]. The movement of living gut bacteria through a malfunctioning gut barrier at the cellular level leads to direct contact with immunological and tissue cells, which in turn triggers systemic autoimmunity [92].

Molecular Mimicry and Antigen Presentation

Antigenic mimicry can cause foreign antigens to resemble self-antigens, leading to the activation of autoreactive T and B lymphocytes generated by infections [93]. This activation has the potential to facilitate the progression of autoimmunity [94]. However, the permeability of the intestinal mucosa is altered as a result of the modification of tight junction protein expression [95].

Therapeutic Approaches and Implications

Based on several researches, the administration of prebiotics, probiotics, antimicrobial compounds, and fecal microbiota transplantation (FMT) can effectively control the composition of the gut microbiota [96]. Nevertheless, there is a correlation between improper antibiotic usage and the alteration of gut microbiota composition. This correlation also extends to non-antibiotic medications that are intended for human use [97]. Accumulating empirical and medical evidence has indicated that the persistent inflammatory reaction caused by an imbalance in gut microbiota might significantly contribute to the onset of

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autoimmune disorders [98]. In general, germ-free animal models are better suited for investigating the impact of the host microbiome on the progression and formation of various illnesses [99]. Overall, the microbiota can either initiate autoimmune in individuals with genetic susceptibility or protect against autoimmunity in others [100].

Future Recommendations

Extensive research has been performed on gut microbiome but still, it contains multiple research gaps that demand further research on gut microbiota. Currently, detailed molecular mechanisms by which gut microbiota influence the immune system remain incompletely understood. Moreover, Identification of specific microbial species that play a crucial role in modulating immune responses. Similarly, the role of microbiota-derived metabolites (such as short-chain fatty acids) in immune modulation and autoimmunity. Importantly, the mechanism and identification of short-chain fatty acids in immune system modulation is more important. The understanding of variations in microbial composition and its contribution to the development or prevention of autoimmune diseases. The microbial influence on the differentiation and function of various immune cell types should be investigated. The impact of early life microbiota colonization on the development of the immune system and its long-term effects on autoimmunity. The mechanism of host genetics interacts with gut microbiota to influence immune responses and autoimmune disease susceptibility. The role of environmental factors (such as diet, antibiotics, and infections) in shaping gut microbiota and their subsequent effects on immune function and autoimmunity. These are the various research gaps that should be studied in later research.

CONCLUSIONS

The gut microbiome also plays a critical role in shaping and regulating immune system development and function. Healthy gut bacteria release SCFAs that help in immune regulation of the colon, and altered bacterial ecology of the gastrointestinal tract termed dysbiosis can potentially result in autoimmune disorders. Thus, therapeutic modification of the composition of gut microbiota has been considered as a perspective direction for the treatment of autoimmune diseases, so further study of the relationships between the gut microbiome, immune system, genetic factors, and the environment is needed.

Authors Contribution

Conceptualization: TA
Methodology: TA, AFA, SK, FN, IH, RA, HKK
Formal analysis: MS
Writing-review and editing: SS, FF
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

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Comparison of Deferasirox and Desferrioxamine in Term of Mean Serum Ferritin Levels in Patients of β-Thalassemia Major with Iron Overload

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ABSTRACT

Iron chelation treatments as adjuvant therapy can reduce iron stores to minimize the related morbidity and mortality in patients with thalassemia major. **Objective:** To compare Deferasirox (DFX) and Desferrioxamine (DFO) in terms of mean serum ferritin levels in patients of β-thalassemia major having Iron overload. **Methods:** This randomized controlled trial was conducted at the Thalassemia Center of Hematology Department, "The Children's Hospital and The Institute of Child Health", Multan, Pakistan from January 2023 to September 2023. After randomization, children in DFO group were given DFO in a dose of 50mg/kg, through subcutaneous route by infusion pump five days a week. Children in DFX group were given DFX in a dose of 30mg/kg, orally in tablet form once daily. Baseline serum ferritin levels were measured and the change in mean serum ferritin level for each group was calculated and compared for both groups after 6-months of treatment. **Results:** In a total of 142 children, 87 (61.3%) children were male. The mean age was 7.08 ± 2.41 years. The mean number of blood transfusions at the time of enrollment were 13.4 ± 4.2. After 6 months of treatment in DFO versus DFX groups, the net change in mean serum ferritin levels from baseline to post-treatment was 947.2 ± 454.0 µg/L for DFO and 1053.5 ± 389.8 µg/L for DFX, with no statistically significant difference between the groups (p=0.1367). **Conclusions:** Once-daily oral deferasirox has good compliance, acceptable tolerability and appears to have similar efficacy to desferrioxamine in reducing iron burden of transfused patients with beta thalassemia major.

INTRODUCTION

Thalassemia is a frequently occurring genetic blood condition brought on by a mutation in the globin gene that causes a high level of red blood cell lysis [1]. The global scenario surrounding inherited substantial hemoglobinopathies reveal staggering numbers, with approximately 400,000 children born annually with these conditions, while around 80 million individuals carry β-thalassemia [2, 3]. These conditions manifest across three clinical states of increasing disease intensity; the asymptomatic β-thalassemia carrier state, thalassemia intermedia, and the severe thalassemia major (TM) [4]. The β-thalassemia carrier state, stemming from heterozygosity for β-thalassemia, exhibits no clinical symptoms but presents distinct hematological characteristics [5]. Chronic transfusion therapy leads to iron overload, which creates a need for iron chelation treatments as adjuvant therapy so that iron stores in the body can be reduced to minimize the related morbidity and mortality in TM [6, 7]. Right now, Deferasirox (DFX), Deferiprone (DFP), and Desferrioxamine (DFO) are the most commonly adopted iron chelators accessible for therapeutic usage. DFO has nevertheless been regarded as a standard treatment approach managing iron overload in the last several decades, despite its short half-life, poor compliance, and requirement for regular subcutaneous or intravenous injections five to seven days a week [8]. The first iron chelator, DFP, had good compliance but was associated with several major adverse effects, including arthropathy, neutropenia, agranulocytosis, and gastrointestinal disorders [9]. On the other hand, DFO and

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DFP together have a synergistic effect on patient compliance and iron elimination [10]. While there are a few moderate side effects associated with DFX, certain researchers have suggested that it lowers liver iron levels and increases patient compliance. A study from Iraq reported that DFO exhibited notably higher serum ferritin levels (8160 ± 234 ng/dL) compared to DFX (3001 ± 188 ng/dL; p<0.001), highlighting a distinct impact of these iron-chelating medications on iron status [11]. DFX is considered the latest oral chelator to be utilized in the treatment of chronic iron overload. In contrast DFP, DFX underwent more thorough scientific investigation during development. Numerous investigations have addressed the efficacy and safety of DFX, even though there is still scarcity of long-term outcome data. This study was planned to compare deferasirox and desferrioxamine in terms of mean serum ferritin levels in patients of β-TM having Iron overload. Choosing an effective iron chelator is crucial to increasing iron chelation therapy compliance. Not much local data exists in Pakistan comparing the effectiveness of DFX and DFO.

This study would be helpful in providing baseline data and formulating new protocols for iron chelation therapy, in which DFX may be a useful oral alternative to parenteral DFO.

METHODS

This randomized controlled trial was conducted at the Thalassemia Center Hematology Department, "The Children's Hospital, and the Institute of Child Health," Multan, Pakistan, from 1st January 2023 to 30th September 2023. The inclusion criteria were transfusion-dependent patients of either gender, aged 2-15 years, diagnosed with β-TM by hemoglobin electrophoresis, and iron overloaded. The exclusion criteria were patients with other transfusion-dependent anemias, TM with cardiomyopathy or arrhythmia, chronic renal failure, chronic liver disease (ALT >200 IU), hypersensitivity to either DFX or DFO, or those who were already on combined chelation therapy. Iron overload in "transfusion-dependent β-TM" was defined as "serum ferritin level above 1000 µg/L" [12]. After explaining details in terms of the benefits and risks of the study, informed and written consents were acquired from parents/guardians. Approval from the "Institutional Ethical Committee" was obtained (reference number: 1870). Sample size of 122 (61 in each group) was calculated using G*Power software considering effect size (d) as 6%, alpha error probability as 5% with 95% confidence level and allocation ratio of 1:1. For this trial 142 (71 in each group) children were considered. This clinical trial was registered at clinicaltrials.gov, with trial numbered as NCT06468423. All of the necessary information, like age, gender, weight, height, date of chelation, and number of blood transfusions, were noted at the time of presentation. Baseline serum ferritin levels were measured for all patients in both groups through the institutional laboratory using Vitros Immunodiagnostics employing chemiluminescence methodology, and ferritin reagent kit was used. Then, using the lottery method, 142 children were allocated randomly to both study groups. DFO group (n=71) included children who were given DFO at a dose of 50 mg/kg through the subcutaneous route by infusion pump five days a week. DFX group (n=71) included children who used oral (tablet) DFX at a dose of 30 mg/kg once daily. Monthly follow-up was done for the children in both groups, ensuring compliance as assessed viewing the empty medicine containers. Blood samples for serum ferritin were analyzed at the end of 6 months. The change in mean serum ferritin levels from the baseline to after 6 months of treatment was calculated. A special pre-designed proforma was used to record all of the relevant study information. Data analysis was performed using "IBM-SPSS Statistics" version 26.0. Age, weight, baseline serum ferritin levels, and the mean serum ferritin level at the end of 6 months were shown as mean and standard deviation (SD). Frequency and percentage were calculated for gender. The comparison of serum ferritin levels in two groups was done by applying independent sample t-test. P-value below 0.05 was taken as significant.

RESULTS

In a total of 142 children, 87 (61.3%) children were male and 55 (38.7%) female. The mean age was 7.08 ± 2.41 years. The mean number of blood transfusions at the time of enrollment was 13.4 ± 4.2. Table 1 shows comparison of baseline characteristics between children of study groups.

Table 1: Baseline Characteristics (n=142)

Variables		DFO Group N (%) / (Mean ± SD)	DFX Group N (%) / (Mean ± SD)	p-Value
Gender	Male	47 (66.2%)	40 (56.3%)	0.2279
	Female	24 (33.8%)	31 (43.7%)	
Age (Years)		7.3 ± 2.9	6.7 ± 2.1	0.1602
Weight (Kg)		24.42 ± 8.9	22.8 ± 6.7	0.2282
Height in (cm)		109.88 ± 12.2	107.9 ± 10.7	0.3008
Number of Blood Transfusions		13.6 ± 5.9	12.9 ± 2.4	0.3560

After 6 months of treatment, both DFO, and DFX groups experienced a reduction in mean serum ferritin levels. However, the observed difference in mean serum ferritin levels between the two groups was not statistically significant (p=0.2298). When examining the net change in mean serum ferritin levels from baseline to post-treatment, it was found to be 947.2 ± 454.0 µg/L for the DFO group and 1053.5 ± 389.8 µg/L for the DFX group (0.1367), as shown in table 2.

Table 2: Comparison of Desferrioxamine and Deferasirox in Mean Serum Ferritin Levels (n=142)

Mean Serum Ferritin Level	DFO Group (Mean ± SD)	DFX Group (Mean ± SD)	p-Value
Baseline (µg/L)	4128.6 ± 2171.6	3914.2 ± 1828.2	0.5255

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Post-Treatment(µg/L)*	3181.4 ± 1717.6	2860.7 ± 1438.4	0.2298
Net Change (µg/L)	947.2 ± 454.0	1053.5 ± 389.8	0.1367

*after 6 months of treatment

DISCUSSION

The present findings suggested that both DFO and DFX contributed to a decrease in serum ferritin following six months of treatment, although there wasn't a significant difference observed between the two treatments. Some Randomized Controlled Trials (RCTs) have shown that none of the contemporary treatment options are superior in reducing iron overload or preventing end organ damage. Data show that strong evidence is missing advocating the use of combination of DFP and DFO in comparison to monotherapy in terms of reduction in iron stores [13-15]. This lack of clear superiority or consistent benefits highlights the requirement for future research than can aid in better understanding about the comparative efficacy of contemporary treatment options aiming prevention of iron-related organ damage. Taher A *et al.*, evaluated the effectiveness of DFX in heavily iron-overloaded thalassemia patients and found it efficacious when given at 30 mg/kg/day to most of the patients. DFX showed effectiveness in lowering liver iron concentrations and serum ferritin levels to a greater extent [16]. Rasalkar DD *et al.*, revealed that DFX was as effective as DFO for iron chelation among TM patients and these findings stand consistent with what we noted [17]. Arya A *et al.*, from Iran reported that among the iron-chelating agents DFX, DFP, and DFO, there was no discernible difference in their efficacy for reducing ferritin levels in patients with thalassemia [18]. Consequently, the choice of chelating agent can be made considering factors such as cost, availability, the patient's condition, and their preference. This suggests that treatment decisions can be tailored based on individual circumstances and considerations beyond just the comparative efficacy of these agents in reducing ferritin levels. Our findings are also very consistent to a recently published local study where Syed A *et al.*, from Lahore revealed no statistically significant difference in the effectiveness of DFX of DFO as chelation therapy among patients with β-TM [19]. The shift to a once-daily, oral regimen, as seen with DFX, typically enhances patient compliance compared to parenteral treatments. This improved adherence to therapy is anticipated to result in decreased morbidity and mortality associated with iron overload. With adequate laboratory oversight, the availability of DFX as a safe and effective oral option holds promise in averting complications stemming from iron overload, offering a more convenient and potentially impactful approach to chelation therapy [20]. In comparison to the present study, some researchers have documented different observations. A study from Iraq revealed that DFX exhibited greater efficacy in managing iron overload compared to DFO in patients reliant on blood transfusions due to β-TM [11]. However, notably, this superiority was not observed concerning the immunological profile. Despite the effectiveness of DFX in addressing iron overload, DFX did not show a significant advantage over DFP in terms of impacting the patient's immune system parameters. Although, this study has revealed very useful results, a large, long-term, and multicenter local trial is required for the validity of our findings. Single center study design and a relatively small study treatment duration were some of the limitations of this study.

CONCLUSIONS

Once a day oral deferasirox had good tolerability and provided relatively similar effectiveness to desferrioxamine in decreasing the iron overload in transfused patients with beta thalassemia major.

Authors Contribution

Conceptualization: KI, ZA

Methodology: FA, AS

Formal analysis: ZA, FA, AS, MH

Writing, review and editing: FA, AS, 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

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Barriers Against Seeking Professional Care for Perceived Mental Stress among Medical Undergraduate Students: A Cross-sectional Survey at a Private Medical University of Islamabad

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ABSTRACT

Medical students persistently face a burden of stress which may be a risk factor for depression, suicide, or substance abuse. **Objective:** To assess barriers in seeking professional care for perceived mental stress in medical undergraduate students and to assess their stress. **Methods:** A cross-sectional survey was designed and conducted for six months. Using stratified random sampling, 41 medical students were selected from all five years. A structured questionnaire was used which included a modified BACE 3 scale to find frequencies of perceived barriers and PSS scale to assess perceived stress. Chi square test was applied to look for associations. Ethical approval and informed consent were taken. **Results:** Out of 205 respondents, 78(24.4%) were male and 127(75.6%) were female. Mean age was 21 years ± 1.69 SD. 76.96% of respondents reported experiencing moderate stress. Among all years, third year students (26.8%) reported the highest level of severe stress. The barrier reported by majority students was that students wished to solve the issue on their own (72.7%), second was that the issue would resolve by itself (45.4%). The barriers that were considered least frequently, were being unsure where to get help (19%) followed by being too sick to ask for help (18.5%). Chi square test showed significant association between categories of stress and year of education with a significant p value. **Conclusions:** Majority of the students faced moderate stress. However, when dealing with it, the majority wanted to solve the problem on their own.

INTRODUCTION

University students come across a high degree of different issues concerning their mental health and sometimes suffer worsening of some of them like, insomnia or stress [1]. For medical practitioners, postgraduate medical residency is sometimes the most difficult time. Research evidence has found that stress among the residents was associated with poor academic performance, truancy, and poor health of the residents. It was concluded from survey that long work hours (66.2%), a lack of vacation days (52.3%), an unfavorable work environment (35.4%), and academic pressure (41.3%) were the main causes of the stress among medical professionals [2]. According to the results of a cross-sectional study that collected data over the course of a month, 56% (n = 356) of medical students

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had overall psychiatric morbidity. Participants most frequently expressed fear of stigmatization (63%; n = 401), desire for handling the issue alone (60%; n = 379); fear of the unknown (59%; n = 365); and inability to recognize symptoms (58%; n = 366) [3]. Medical students encounter numerous obstacles to mental healthcare, many of which stem from their concern of confidentiality violations and of facing consequences in their education and careers. It seems that many medical students find it difficult to get the help they need, even in the face of recent initiatives to lessen the stigma associated with mental illness [4]. The most common mental health issues faced by university students are anxiety and depression [5]. The current research focused on the perceived stress of medical students. It is known that chronic stress increases the risk of developing mental health issues in an individual's future life. Mental illnesses are a common issue of concern in medical students and health workers. Although mental health issues are on the rise in university students in general, they are particularly prevalent in medical students as seen in a meta-analysis conducted on various cross-sectional studies in China [6]. Along with this, medical students consistently reported a high level of stress. A few reasons identified in this study included a high workload and frequency of exams [7]. 86 percent of the students demonstrated health care needs inclusive of mental health issues to minor ailments; however, due to confidentiality and the peculiarity of health education/training institutions, many students either sought help outside the institution [8]. When comparing stress levels between medical and non-medical students: a study from Egypt suggests that medical students feel higher levels of perceived stress compared to non-medical students [9]. A study conducted in Karachi, Sindh, Pakistan showed that levels of stress were much raised in medical undergraduate students in comparison to students of other disciplines [10]. However; another study from Saudi Arabia showed that non-medical students have a higher level of stress [11]. A common theme, though, is that medical students face high levels of stress. It was crucial to start addressing this issue, since (as previously mentioned) stress could have led to mental illness which in turn could lead to complications like substance abuse, self-harm, or impairing the ability of the person to perform their duties. To gather sociodemographic information, a semi-structured pro forma was employed, and the Barriers to Access to Care Evaluation Scale was utilized to determine the reasons behind the lack of mental health treatment. According to the study's findings, 26% of the individuals needed mental health treatment but did not seek it [12, 13]. So, one can conclude, it is important to seek treatment for these issues; however, an analysis of data from Asia and Europe showed a huge proportion of young adults with mental illness do not seek help [14]. A meta-analysis reveals common problems in not seeking help were limited mental health knowledge and stigmatizing beliefs among others [15]. Pakistan, being a developing country, suffers from the fact that there is vast unawareness on many topics including this one. Mental health literacy is very low in this region. People may prefer going to faith healers and may not even recognize these ailments as actually being illnesses that required treatment [16]. Generalized anxiety and stress disorder is a leading psychiatric illness in Pakistan, also among young students. It can lead to several complications that may be preventable by early intervention.

This study, aimed to assess the perceived stress of medical students and the barriers in seeking professional help. Assessing this high-risk group was particularly important in gaining firsthand data to use it to recognize the areas which needed attention. The survey aimed to assess the perceived stress levels among medical undergraduate students of Foundation University Islamabad (FUI) and to determine barriers in seeking care for mental issues among medical undergraduate students of FUI.

METHODS

A cross-sectional survey was carried out on medical undergraduate students enrolled in all 5 years at Foundation University College of Medicine for six months from September 2022 to February 2023. Foundation Medical College, Islamabad's Ethical committee's approval was taken. Ethical Committee no FF/FUMC/215-221-1 PHY/22. Stratified Random Sampling was performed after an informed consent was taken. Inclusion criteria was medical students of all five years in FUMC. Exclusion criteria was those medical students who were already under psychiatric treatment and students who refused to participate. Sample size was calculated using equation-n=z2 p(1-p)/e2, Population size of FUMC= 750, Margin of error= 5%, Confidence interval= 95%, Sample size=184. After adjusting for 10% non-response rate, sample size became 205. According to the inclusion criteria, a sampling frame was developed for all the students enrolled in MBBS from 1st year to 5th year. These lists were obtained from the admission office of FUMC. The students were further divided into 5 strata taking 41 students from each stratum for the final study by applying simple random sampling technique. A structured questionnaire was developed in English language to collect data for this study. The 1st section of questionnaire consisted of the demographic characteristics of the respondents (age, study year, gender) followed by section 2 including the Barrier to Access to Care Evaluation (BACE-3) scale to evaluate and assess barriers in seeking help for mental illnesses. The BACE is a scale with 30 items, the response categories range from 0 (not at all) to 3 (a lot) with higher scores denoting a greater barrier. Out of these we selected the 21

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questions that were relevant to our study population. The tool comprises of a 12- item stigma scale, as well as instrumental and attitudinal barrier items. To calculate the overall score, the mean of rating for all the items is calculated. The percentage of respondents who experienced a barrier to any degree and those experiencing a barrier as a major barrier (i.e., % circling 3) are also be accessed. Section 3 of the questionnaire consist of perceived stress scale (PSS), to assess levels of stress in the participants. In this scale we asked 10 questions like "In past month, how frequently have you experience that you were not able to control the vital and important things in life?" The respondents selected an option from the 5 given options (0=never, 1= almost never, 2=sometimes, 3=fairly often, 4=very often). The Scores of each question were compiled and summed up to get a total score for each participant which ranged from 0-40, with higher scores highlighting a raised in the level of stress.

- 0-13 was denoted as low stress
- 14-26 was marked as moderate stress
- 27-40 was high perceived stress

All the participants, selected by stratified random sampling, were given the questionnaire to complete within a specified time slot considering their availability. The privacy and discretion were assured to the best of our abilities. The analysis was performed using software named Statistical packages of social sciences (SPSS) version 21.0. For continuous variables, mean and standard deviation were calculated whereas categorical variables were represented in percentages. Any associations between variables were calculated through chi-square test and was interpreted as significant if P-value is < 0.05.

RESULTS

A total of 204 participants from FUMC completed the questionnaire. Demographics characteristics of participants are described (Table 1).

Table 1: Demographic Profile of Respondents (N=205)

Category		Mean ± SD / (%)
Age		21.1 ± 1.696
Gender	Male	38.0
	Female	62.0

The percentage of respondents who reported each barrier item as a major barrier from acquiring professional care. Every barrier was also ranked in accordance with the items being rated a 'major barrier'. The table shows that out of the stigma related barriers the most reported was 'Assuming the problem would resolve by itself' with 45.4% reporting it as a main barrier. Non-stigma items of the scale are further categorized into attitudinal and instrumental barriers. Among the instrumental items the most reported barriers are 'Not in a position to pay the finances involved' and 'Do not have anyone who could help me seek expert care' 22% considered it as a major hurdle. For the attitudinal items the most reported is 'Wish to solve the issue on my own' which is also the overall highest reported barrier in the entire BACE scale with 72.7% saying that it would be a main barrier in seeking expert help for a mental illness in the future (Table 2).

Table 2: Percentage Table for BACE 3 Scale (N=205)

Item No.	Barrier	Type of Barrier	Mean ± SD	% Reporting as Major Barrier (a lot)	Rank (1=Item has Highest Ranking as Main/Major Barrier)
1	Not sure where to seek expert/professional care	N-S	1.19 ± 0.393	19	18
2	Wish to solve issue on my own	N-S	1.73 ± 0.447	72.7	1
3	Perception that I might be considered as timid/weak for suffering a mental health issue	S	1.27 ± 0.444	26.8	11
4	Fear of being hospitalized forcefully	N-S	1.20 ± 0.405	20.5	17
5	Thinking the problem would go on its own	S	1.45 ± 0.499	45.4	2
6	Worried about how my family might feel, think, say or do	N-S	1.39 ± 0.488	38.5	5
7	Feeling embarrassed or ashamed	N-S	1.24 ± 0.428	23.9	13
8	Preferring to seek other forms of care	S	1.24 ± 0.430	24.4	12
9	Unable to pay financial expenditure involved	S	1.22 ± 0.415	22	15
10	Worry that I might be considered 'crazy'	N-S	1.23 ± 0.421	22.9	14
11	Assuming that expert care might not work	N-S	1.28 ± 0.449	27.8	9
12	Being too sick to ask for help	S	1.19 ± 0.390	18.5	19
13	Concern that acquaintance might find out	N-S	1.28 ± 0.449	27.8	9
14	Uncomfortable in opening about my thoughts, feelings and emotions	S	1.54 ± 1.519	43.4	3
15	Worry how others will treat me if they got to know about me seeking professional care	N-S	1.27 ± 0.447	27.3	10
16	Concerns about the treatments available	N-S	1.38 ± 0.485	37.6	6
17	Not wanting a mental health issue to be on my medical history	S	1.36 ± 0.481	36.1	7
18	Previous bad experiences with mental health treatment	N-S	1.21 ± 0.408	21	16
19	Preferring to seek care from peers, relatives, family, friends	S	1.40 ± 0.492	40.5	4
20	Feeling I do not have a mental health issue	N-S	1.33 ± 0.470	32.7	8
21	Do not have anyone who could assist me in getting expert care	S	1.22 ± 0.415	22	15

Majority of students (76.96%) were found to be in moderate stress range. 15.69% were showing high stress while only

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7.35% lie in the low perceived stress category (Figure 1).

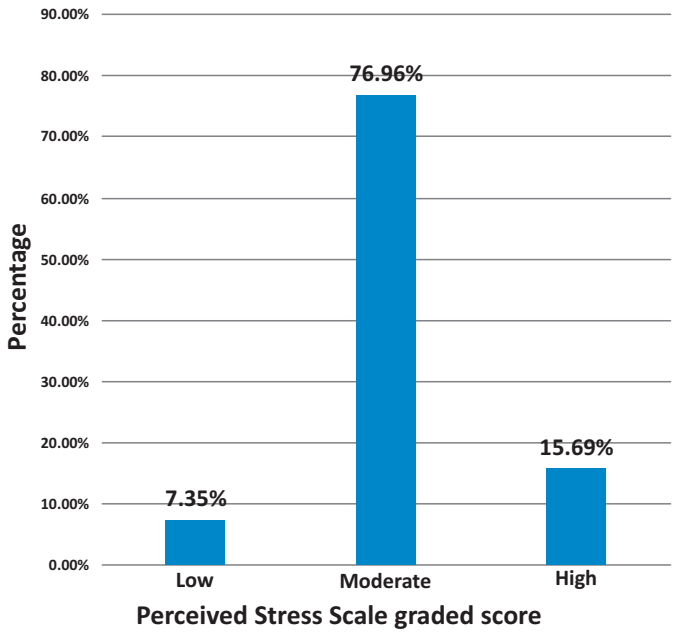

Figure 1: Perceived Stress Scale Graded Score

Majority of the participants in all five years were having a moderate level of perceived stress. 3rd year students had the highest perceived stress levels with 26.8% reporting high stress, followed by 4th year (17.1%) then 1st year (12.5%). 5th year (12.2%) and 2nd (9.8%) year students had the least participants in the high stress category. P Value less than 0.05 (Table 4).

Table 4: Percentages of Respondent's in PSS Categories (N=205)

PSS CATEGORIES					
Respondent's MBBS Year	Low Stress %	Moderate Stress %	High Stress %	Total	p-value
1st year	0.0	87.5	12.5	100.0	<0.05
2nd year	7.3	82.9	9.8	100.0	<0.05
3rd year	4.9	68.3	26.8	100.0	<0.05
4th year	17.1	65.9	17.1	100.0	<0.05
5th year	7.3	80.5	12.1	100.0	<0.05

DISCUSSION

The present survey has tried to identify the barriers that are obstacles in seeking expert care for perceived mental stress among medical undergraduate students. The final sample consisted of 204 participants from FUMC. Respondent's mean age was 21.17 years with a standard deviation of 1.696. The survey reported majority respondents as female (75.6%) and only (24.4%) male; these findings bore similarity to a study conducted in Karachi in which (83.5%) of the respondents were female and (16.5%) were male [17]. The results from attitudinal items illuminated "Wish to solve the issue on my own" as the most common barrier in the entire BACE scale with 27.3% considering it to any degree while 72.7% saying that it would be a major hurdle in seeking expert care for a mental illness in the future. Similar results were reported by a study done in Mansoura University, Egypt where 55.99% of the medical students revealed "I want to solve the issue on my own" as main barrier that hindered them from seeking professional healthcare [18]. Majority respondents (76.96%) reported that they experienced moderate stress. This result is analogous with a study carried out in Lahore [19]. Yet another study performed in Syria highlighted 87.6% of Syrian undergraduate medical student's experienced moderate stress [20]. A small sample size, data from students of only one medical college and cross-sectional nature of the study limits generalization of the findings. Future research studies in this area should be designed taking these limitations into account so that higher quality evidence is generated which is both reproducible as well as generalizable.

CONCLUSIONS

Majority of medical undergraduate students faced moderate stress levels. Most students are aware of the resources regarding seeking care for mental health but are hesitant to use them.

Authors Contribution

Conceptualization: SZ, UIS, JK

Methodology: MFH

Formal analysis: SZ, FAB, AW

Writing, review and editing: AW, SAR

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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Impact of Sociodemographic and Dental Clinic Related Factors Causing Dental Anxiety in Patients

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ABSTRACT

Dental anxiety has been reported to be impacted by an individual's sociodemographic characteristics like age, gender, marital status and level of education. This anxiety can be attributed to the pain experienced during dental treatment. **Objective:** To evaluate the impact of sociodemographic and dental clinic related factors causing dental anxiety in patients. **Methods:** A descriptive cross sectional study was conducted on 196 patients in Sharif Medical and Dental College, Lahore. Those with any psychological, systemic disorders and on medications were excluded. Participants who underwent dental extraction irrespective of their age, marital status, gender and education were included. Modified Norman Corah Dental Anxiety scale was used as data collection tool. Chi square was used to find the association between sociodemographic factors and dental anxiety level. **Results:** The study was done on 196 participants with 49% females and 51% males. Most of the patients (64.3%) were below 35 years of age while 35.7% were above it. Majority of the patients suffered severe dental anxiety (38%) followed by high (22%), moderate (20.9%) and mild (18.4%). Significant associations between gender and anxiety while taking dentist`s appointment (p=0.048), being next in turn at the clinic (p=0.029), being on the way to clinic (p=0.023) were seen. Significant impact of marital status on anxiety caused in patients going to the clinic was seen (p=0.039). Age also significantly affected dental anxiety in patients undergoing dental extraction (p=0.017). **Conclusions:** Severe dental anxiety was higher in the older age group. The impact of sociodemographic factors on dental anxiety due to dental clinic related factors (getting an appointment, waiting for their turn in clinic and on their way to the dentist) showed males and those who were married generally had a relaxed state of mind.

INTRODUCTION

Dental anxiety is a widespread condition that affects people of all ages [1]. While there are many reasons why some people are afraid of dental procedures, sociodemographic factors are important in determining how anxious a person is about dental treatment [2]. Comprehending these elements is essential to formulate tactics that are effective to reduce dental anxiety and enhance oral healthcare consequences [3]. Age is an important sociodemographic factor that determines dental anxiety [4]. Fear of the dentist is most common in childhood and adolescence and decreases as people get older [5]. Gender also impacts dental anxiety [6]. According to studies, women often report higher levels of dental anxiety than men, suggesting that gender may play a role in this phenomenon [7]. There are a number of possible reasons for this disparity, such as communication preferences, cultural or societal expectations, and painful dental experiences in the past [8]. People belonging to a strata of population with low education levels are unaware of oral health importance and are therefore, more likely to suffer from dental anxiety [9]. Delays in receiving dental treatment can be caused by these factors, which can

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increase anxiety [10]. Acquiring oral health education not only improves one's comprehension of it but also gives them the ability to cope with stress and anxiety associated with their dental issues [11]. Dental professionals can help reduce discomfort and anxiety by using distraction techniques, topical numbing agents, and gentle insertion methods during the procedure [12]. Following a procedure, dentists can give patients precise instructions on how to manage numbness, reassure them that it will only last temporarily, and provide instructions for oral hygiene and pain management after procedures [13]. Throughout the dental care process, dental anxiety can appear at different points such as when a patient is waiting for an appointment or is experiencing a particular procedure [14]. In order to reduce anxiety and guarantee a positive dental experience, it is crucial to recognize the triggers and put coping mechanisms into place.

The aimed of our study was to evaluate the impact of sociodemographic and dental clinic related factors causing dental anxiety in patients.

METHODS

The study was presented to the ethical committee of Sharif Medical and Dental College, Lahore and data collection commenced after that (No. SMDC/SMRC/178-21). The study was conducted in College of Dentistry, Sharif Medical and Dental College, Lahore over a period of 4 months starting from June 2021 and ending in September 2021. The study design was descriptive cross sectional. Participants who had a history of undergoing dental extraction irrespective of their age, marital status, gender and educational level were included in the study. Those with any psychological disorder e.g. Schizophrenia, Bipolar disorder etc. and systemic disorders e.g. hypertension, diabetes etc. and those on medications were excluded from the study. Using an online sample size calculator Scalex Sp 1.0.01 the sample size was calculated to be 196 by keeping a precision of 5%, confidence level 95% and prevalence of dental anxiety to be 85% [15]. The data collection proforma included information on sociodemographic factor of age, gender, marital status and level of education. The patients were scheduled for dental extraction. After the extraction data were collected from them using the modified Norman Corah Dental Anxiety scale was used for data collection. Modified Norman Corah Dental Anxiety scale [16]. The Dental clinic related factors causing dental anxiety were extracted from Modified Norman Corah Dental Anxiety scale and included getting dental appointment, on way to the dentist, waiting for your turn in cline Prior to data collection informed consent was obtained. The questionnaire had a total of eleven questions. The questions in the scale were modified to record the dental anxiety experience of patients undergoing extraction, therefore, it was subjected to reliability testing after modification. The modified questionnaire had a Cronbach alpha value of 0.89. A score of 1 was given to relaxed, score 2 was given to a little uneasy, score 3 was uneasy, score 4 was assigned to tense and 5 was given to extremely tense. Based on these scores the classification of levels of anxiety was done. Mild anxiety (score 11 to 17), moderate anxiety (18 to 22), high anxiety (23 to 29) and severe anxiety (30 to 55). SPSS version 24.0 was used for data analyses. P≤0.05 was regarded a significant. The statistical test used for analyses was Chi square. Chi square was used to find the association between sociodemographic factors and dental anxiety level. It was also used to find the association of gender and marital status with dental anxiety associated with factors related to dental clinic.

RESULTS

The study was done on 196 participants in which 49% were female and 51% were males. The percentage of individuals above 35 years was 35.7% while 64.3% were below 35 years of age. Among the sample 54% individuals were married and 82% were educated. It was seen majority of the patients suffered severe dental anxiety (38%) followed by high (22%), moderate (20.9%) and mild (18.4%). Table 1 shows that severe anxiety was the most prevalent in all groups. Age and level of dental anxiety were significantly associated with each other. The association of gender, marital status and educational status were insignificant with dental anxiety.

Table 1: Association of Dental Anxiety with Sociodemographic Factors

Sociodemographic Factors		Dental Anxiety Level of Patients				Total N (%)	p-Value
		Mild Anxiety N (%)	Moderate Anxiety N (%)	High Anxiety N (%)	Severe Anxiety N (%)		
Age	Above 35	12 (6.1%)	23 (11.7%)	11 (5.6%)	24 (12.2%)	70 (35.7%)	0.017*
	Below 35	24 (12.2%)	18 (9.2%)	33 (16.8%)	51 (26.0%)	126 (64.3%)	
Marital Status	Married	17 (8.7%)	29 (14.8%)	19 (9.7%)	41 (20.9%)	106 (54.1%)	0.061
	Single	19 (9.7%)	12 (6.1%)	25 (12.8%)	34 (17.3%)	90 (45.9%)	
Gender	Female	17 (8.7%)	19 (9.7%)	20 (10.2%)	43 (21.9%)	99 (50.5%)	0.515
	Male	19 (9.7%)	22 (11.2%)	24 (12.2%)	32 (16.3%)	97 (49.5%)	
Educational Status	Unedu-cated	6 (3.1%)	10 (5.1%)	4 (2.0%)	15 (7.7%)	35 (17.9%)	0.288
	Edu-cated	30 (15.3%)	31 (15.8%)	40 (20.4%)	60 (30.6%)	161 (82.1%)	

Table 2 showed that majority of the individuals were relaxed while getting a dental appointment for extraction and on their way to the dentist while most expressed a little uneasiness waiting for their turn in the clinic.

Table 2: Dental Clinic Related Factors Affecting Dental Anxiety

Dental Anxiety	Getting a Dental Appointment N (%)	Way to the Dentist N (%)	Waiting for your Turn in Clinic N (%)
Relaxed	108 (55.10%)	82 (41.80%)	53 (27%)
A little Uneasy	54 (27.60%)	66 (33.70%)	78 (39.80%)

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Uneasy	28 (14.30%)	38 (19.40%)	45 (23%)
Tense	5 (2.60%)	10 (5.10%)	18 (9.20%)
Extremely Tense	1 (0.50%)	0 (0%)	2 (1%)

The impact of sociodemographic factors on dental anxiety due to dental clinic related factors was assessed. Among all the sociodemographic factors only gender and marital status was found to have significant association with dental anxiety associated with dental clinic related factors. Table 3 showed that in all three scenarios males had a higher relaxed state of mind. Females on the other hand expressed distress and tension and the association between these factors associated with dental clinic and gender were significant.

Table 3: Effect of Gender On Dental Anxiety Associated with Dental Clinic Related Factors

Dental Clinic Related Factors	Dental Anxiety	Gender		Total N (%)	p-Value
		Male N (%)	Female N (%)		
Getting an Appointment	Relaxed	60 (30.6%)	48 (24.5%)	108 (55.1%)	0.048*
	A Little Uneasy	27 (13.8%)	27 (13.8%)	54 (27.6%)	
	Uneasy	10 (5.1%)	18 (9.2%)	28 (14.3%)	
	Tense	0 (0.0%)	5 (2.6%)	5 (2.6%)	
	Extremely Tense	0 (0%)	1 (0.5%)	1 (0.5%)	
Way to the Dentist	Relaxed	43 (21.9%)	39 (19.9%)	82 (41.8%)	0.023*
	A Little Uneasy	39 (19.9%)	27 (13.8%)	66 (33.7%)	
	Uneasy	11 (5.6%)	27 (13.8%)	38 (19.4%)	
	Tense	4 (2.0%)	6 (3.1%)	10 (5.1%)	
Waiting for your Turn	Relaxed	30 (15.3%)	23 (11.7%)	53 (27.0%)	0.029*
	A Little Uneasy	44 (22.4%)	34 (17.3%)	78 (39.8%)	
	Uneasy	19 (9.7%)	26 (13.3%)	45 (23.0%)	
	Tense	4 (2.0%)	14 (7.1%)	18 (9.2%)	
	Extremely Tense	0 (0%)	2 (1%)	2 (1%)	

Table 4 showed that another sociodemographic factor that was found to significantly affect the dental anxiety in patients when they were on their way to dental clinic was married status. The patients who were married stated having a relaxed mind throughout the process while the unmarried individuals displayed signs of uneasiness and stress.

Table 4: Effect of Marital Status On Dental Anxiety Associated with Dental Clinic Related Factors

Dental Clinic Related Factors	Dental Anxiety	Marital Status		Total N (%)	p-Value
		Single N (%)	Married N (%)		
Way to the Dentist	Relaxed	33 (16.8%)	49 (25.0%)	82 (41.8%)	0.039*
	A Little Uneasy	35 (17.9%)	31 (15.8%)	66 (33.7%)	
	Uneasy	14 (7.1%)	24 (12.2%)	38 (19.4%)	
	Tense	8 (4.1%)	2 (1.0%)	10 (5.1%)	

DISCUSSION

Globally anxiety that has its connection with dental treatment was estimated to be between 9 to 20% [17]. Literature was more inclined towards the notion of dental anxiety being a more gender specific problem and was usually linked to the females more in comparison to the males [4]. These results were comparable to our study where 21.9% females were found to be severely anxious due to dental treatment or the anticipation of it in comparison to males (16.3%) but the association was insignificant (p=0.515). This behavior or inclination towards development of anxiety can have its roots in the fact that women were more vocal about their feelings as compared to males [18]. It can also be connected to a relative delicate nature and less ability to withstand pain in females. Another study reported results similar to our study where females were found to be less anxious than their male counterparts [4]. The reason of a finding so deviant form the predominant literature can be attributed to the particular group in question and their understanding of anxiety associated with dental treatment. Our study also assessed association of anxiety levels with marital status and educational level and age. Age was found to significantly impact dental anxiety (p=0.017). Individuals from both age groups predominantly experienced severe dental anxiety but it was higher in the older age group (26%) as compared to 12% in the younger one. The association of marital status (p=0.061) and educational status (p=0.288) were insignificant with dental anxiety but severe anxiety was most prevalent in all groups. Al Ansari et.al reported results comparable to our study. They reported that although the association between the sociodemographic factor of marital status and dental anxiety was insignificant, the participants reported suffering from moderate level of dental anxiety [15]. Ayata M and Eraslan R reported highly educated individuals to suffer from anxiety more in comparison to the lesser educated [9]. These findings were very similar to our study where educated people were more anxious than the un-educated ones. In our study we explored factors pertaining to the dental clinic in addition to the sociodemographic factors as reasons for causing dental anxiety. Our study reported that majority of the individuals were relaxed while getting a dental appointment for extraction (55%). Another study reported comparable results where 50% patients were comfortable with the thought of visiting a dentist. Our study found that most participants expressed a little uneasiness waiting for their turn (38.9%)in the clinic which was different from another study in which 49% expressed no feelings of distress while doing so [19]. In our study we assessed the association between sociodemographic factors and dental clinic and treatment related factors as causes of dental anxiety in patients. Our study reported that among all the sociodemographic factors only gender and marital status was found to have significant association with dental anxiety associated with dental clinic related factors. It was seen that in all three scenarios (getting an appointment, way to the dentist and waiting for your turn in the clinic) males had a higher relaxed state of mind i.e. 30.6%, 21.9% and 15.3% respectively. Females on the other hand expressed distress and tension and the association

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between these factors associated with dental clinic and gender were significant. Another sociodemographic factor that was found to significantly affect the dental anxiety in patients when they were on their way to dental clinic was married status. The patients who were married stated having a relaxed mind (25%) throughout the process while the unmarried individuals displayed signs of uneasiness and stress. There were no studies that evaluate this aspect of dental anxiety and therefore, no data were found in literature that had findings comparable to our study. Anxiety levels can be lowered and relaxation encouraged by furnishing the waiting area with relaxing or comfortable furnishings, calming music, and interesting reading material [20]. Establishing an understanding and building trust between patients and dental professionals can be achieved by having open lines of communication with staff regarding wait times, procedure specifics, and any concerns or preferences [21].

CONCLUSIONS

Individuals from both age groups predominantly experienced severe dental anxiety but it was higher in the older age group. The impact of sociodemographic factors on dental anxiety due to dental clinic related factors (getting an appointment, waiting for their turn in clinic and on their way to the dentist) showed the males and those who were married generally had a relaxed state of mind. On assessment of factors affecting dental anxiety in individuals irrespective of sociodemographic factors it was deduced that most of the individuals were relaxed while getting a dental appointment for extraction and on their way to the dentist but most of them expressed distressed while waiting for their turn in the clinic.

Authors Contribution

Conceptualization: AU, ANK, NRK, WM

Methodology: AU, ANK, NRK

Formal analysis: AU, ANK, NRK

Writing, review and editing: AU, ANK, NRK, WM, LM, AM

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

Conflicts of Interest

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Original Article

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Awareness and Knowledge Regarding the Concept of Shortened Dental Arches Among Dental Surgeons in Karachi, Pakistan

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ABSTRACT

Tooth loss remains a major oral health problem with a high public and individual health effect. impacting the majority of persons in their middle and older years. **Objective:** To evaluate knowledge and comprehension of the idea of shortened dental arches among dental surgeons of Karachi, Pakistan. **Methods:** A convenience sample of 300 dentists who work in private hospitals in Karachi was used to perform a descriptive cross-sectional survey. A self-administered questionnaire was given to the participants to ask opinions regarding awareness, function, aesthetics, and comfort of the shortened dental arch concept. SPSS version 25.0 was used to statistically analyze the data from June 2023 to December 2023. **Results:** The results of the study revealed that approximately 31.7% believed that shortened dental arches offer a generally good periodontal prognosis, 33.8% of dental surgeons revealed that few restorative treatments were available, 31.2% believed that shortened dental arches do not lower the risk of overtreatment, 32.66% prolong the retention of natural teeth, 30% decrease the occlusal vertical dimension and 32.4% had TMJ issues. **Conclusions:** Dental surgeons' attitudes and comprehension of the shortened dental arches concept were inadequate. Hence shortened dental arches provide a practical approach to dental care by preserving posterior tooth function without requiring complete arch restoration. By improving clinical decision-making, it was possible to improve patient outcomes by having a better understanding of the existing level of awareness and expertise among dental surgeons.

INTRODUCTION

A particular kind of dentition known as the Shortened Dental Arch (SDA) is characterized by an undamaged anterior region and a decrease in the number of posterior teeth that occlude each other, beginning posteriorly [1]. Although it is normally preferred, many people may not be able to achieve complete dental arch occlusion because people lose teeth as they age [2]. Molar teeth are the most susceptible to dental deterioration of all teeth and are often extracted. As a result, over time, there tend to be fewer posterior teeth and occluding tooth contacts [3-6]. When it comes to the dental arch and craniofacial structures, the natural dentition exhibits a balanced location between the tongue and the surrounding muscles. To provide a natural profile and effective restoration for patients who are edentulous or dentate, prosthodontic therapy may consider standard parameters such as the position of the anterior tooth and rearmost molar, as well as ridge breadth, length, and height. It is crucial to comprehend the natural form of the dental arch since prosthetic restorations can benefit from knowing the usual values of the arch's size and anatomical shape [7]. According to the research, dental arches that include the

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premolar and anterior areas satisfy the need for a functional dentition. However, each person has different functional needs, and different numbers of teeth are needed to meet those needs. As a result, dental care must be customized to each patient's unique needs and level of adaptability [8]. The development of functional disorders pertaining not only to the maxillofacial area but also as a whole is aggravated by anomalies of the occlusion, whose distinctive features include incorrect tooth position, absence of multiple dentition contacts, altered alveolar process shape, disturbed size of the jaw bones and their spatial arrangement in the skull, and altered alveolar process shape [9]. The idea of a shortened dental arch has drawn severe criticism from a large number of conventional practitioners. It has been believed that the untimely loss of molar teeth is associated with a relative risk factor for TMJ disorders [10] along with reduced masticatory function. Additionally, it has been proposed that shortened dental arches are linked to occlusal instability, which is brought on by tooth migration [11]. The loss of molar support can result in temporomandibular joint dysfunction, occlusal instability, and impaired mastication, dental professionals may maintain that all lost teeth should be replaced to maintain a satisfactory level of oral function and a healthy masticatory system [12]. The World Health Organization's oral health aim, which emphasizes the bare minimum of 20 teeth needed to maintain a healthy, naturally functioning dentition without the need for a prosthesis, is likewise consistent with the SDA philosophy. The public's contemporary perspective of dentistry is supported by the SDA concept, which emphasizes achieving the psychosocial aspects of oral health rather than just treating the need to replace missing teeth [13]. Nonetheless, there has been much debate over the theory that tooth loss will lead to less-than-ideal oral function and comfort [14]. The appearance of the grin may depend on a few posterior teeth, and tooth loss may also be influenced by other psychological variables. Although patients are more likely to desire the prosthetic replacement of front teeth than posterior teeth, they may also want the repair of a missing premolar for cosmetic reasons [12]. Patients with shortened dental arches can benefit from a well-established treatment option called cantilever resin-bonded fixed dental prosthesis [15].

Even while people now generally accept the idea of a shortened dental arch, it is still not used by most of the dental surgeons of Pakistan. Therefore, it's important to assess the disparity between the dentist's stance on shortened dental arches and the patient's desire for non-traditional methods of replacing lost posterior teeth. The purpose of the study was to evaluate the awareness and knowledge regarding the concept of shortened dental arches among dental surgeons in Pakistan.

METHODS

A descriptive cross-sectional survey was conducted among the dental surgeons of Karachi working in the private hospital from June 2023 till December 2023. The study used a convenience sampling strategy to select the participants. The study did not take dental assistants or students into account. Based on the tolerable margin of error (5%), the confidence level (95%), and the total number of licensed dental practitioners (n=27428), a minimum required sample size of 276 was determined through open epi. However, 300 participants in total were included to increase study power. This study used a self-administered, structured, consisting of close-ended questions. questionnaire was given to assess awareness and their knowledge. The questionnaire included twenty items on participants' awareness and attitudes concerning shortened dental arches in addition to demographic data on gender, age, work experience, etc. The questionnaire was created by reviewing related research that has been carried out globally by in 2020. The three-point Likert scale (very aware, somewhat aware, and not at all aware) was used to record responses. A five-point Likert scale was used for other item responses (strongly agree, agree, disagree, and strongly disagree). The research was approved ethical review committee of Sir Syed Medical and Dental College for Girls with Ref. No: sscms/college/principal(dental)/2023/085. Consent was taken from all the participants they were informed regarding the aim and objective of the study. Further, it was informed that the information in this research will kept private and utilized exclusively for study. SPSS version 25.0 was used to statistically analyze the data. Hence, descriptive statistics of frequency distribution and percentages were calculated for each of the category variables. The Chi-square test was used to compare the questionnaire item responses by specialization. A p-value of less than 0.01 was regarded as statistically significant.

RESULTS

The current study investigated dental surgeons' attitudes and levels of awareness of shortened dental arches. The survey was completed by 300 dental surgeons, the majority of whom 57.3% were male belonging to the age group of 26–30 years. Approximately 75% had less than 10 years of experience. The study participants' practice and demographic factors were displayed in table 1.

Table 1: Demographic Details of study Participants

Variables	N (%)
Gender	
Male	172 (57.3%)
Female	128 (42.6%)

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Age	
20-25	82 (27%)
26-30	106 (35.3%)
30-40	42 (14%)
41-50	48 (16%)
50 above	22 (7%)
Work Experience	
Less than 10 Years	225 (75%)
More than 10 Years	75 (25%)
Designation	
General Dentists	266 (88%)
Specialist	34 (11%)

Almost 31% were unsure about using shortened dental arches in occlusion with a single standing tooth, patients with periodontal disease and dental decay, which primarily affects molars 33%, were preferred candidates for shortened dental arches. Furthermore, 32% of research participants were unsure if the shortened dental arches caused speech issues and 29% were unaware of the fact that the unsupported molars may cause TMJ issues. On the contrary 31.6% of participants agreed that shortened dental arches offer a good prognosis for periodontal disease and it can be recommended to 33.3% of patients who have few options for restorative care as shown in table 2.

Table 2: Awareness and Knowledge of Dental Surgeons Regarding Shortened Dental Arches

S. No.	Statements	Strongly Agree N (%)	Agree N (%)	Not Sure N (%)	Disagree N (%)	Strongly Disagree N (%)
1	Can Individuals with One Standing Tooth and Appropriate Dental Occlusion Apply the Shortened Dental Arches Concept?	45 (15.0%)	75 (24.6%)	94 (31%)	40 (13%)	46 (15%)
2	Do the Ten Pairs of Occluding Teeth from The First Incisors to The Second Premolars Consist of a Shortened Dental Arches Concept?	42 (14%)	92 (30.6%)	95 (31.6%)	40 (13.3%)	31 (10.3%)
3	The Shortened Dental Arches Concept can be Recommended to Patients Who Have Periodontal Disease or Caries, Which Mostly Impact the Molar Dentition	41 (13.6%)	92 (30.6%)	100 (33%)	41 (13.6%)	26 (8.6%)
4	For Patients with an Overall Favorable Periodontal Prognosis, The Shortened Dental Arches Concept may be Considered	37 (12.3%)	95 (31.6%)	94 (31.3%)	34 (11.3%)	40 (13%)
5	The Shortened Dental Arches Concept Can Be Suggested to Patients Who Have Few Options for Restorative Care	44 (14.6%)	100 (33.3%)	85 (28.3%)	40 (13.3%)	31 (10.3%)
6	There are no Strict Criteria for using the Shortened Dental Arches Idea with Patients	35 (11.6%)	57 (19%)	90 (30%)	47 (15.6%)	71 (23.6%)
7	For a Patient, An Intact Dental Arch Spanning from The First Incisors to The Second Premolars Is Aesthetically Acceptable	38 (12.6%)	113 (37.6%)	82 (27.3%)	37 (12.3%)	30 (10%)
8	Adequate Oral Function Requires 10 or More Occluding Pairs of Teeth	47 (15.6%)	104 (34.6%)	85 (28.3%)	35 (11.6%)	29 (9.6%)
9	For elderly patients, the main goal of treatment planning should be to preserve the anterior and premolar sections of the dental arches	40 (13.3%)	102 (34%)	86 (28.6%)	37 (12.3%)	35 (11.6%)
10	Shortened dental arches do not worsen periodontitis in people with poor margins of margin bone.	37 (12.3%)	82 (27.3%)	95 (31.6%)	51 (17%)	35 (11.6%)
11	Shortened dental arches prevent the loss of occlusion in the vertical dimensions.	41 (13.6%)	92 (30.6%)	88 (29.3%)	42 (14)	37 (12.3%)
12	Shortened dental arches do not cause complications with the TMJ	48 (16%)	98 (32.6%)	87 (29%)	35 (11.6%)	32 (10.6%)
13	Shortened dental arches do not result in issues with speaking.	48 (16%)	93 (31%)	96 (32%)	29 (9.6%)	34 (11.1%)
14	Shortened dental arches enable people to keep their original teeth over extended periods.	51 (17%)	98 (32.6%)	81 (27%)	35 (11.6%)	35 (11.6%)
15	Shortened dental arches lower the possibility of overtreatment.	56 (18.6%)	95 (31.6%)	86 (28.6%)	31 (10.3%)	32 (10.6%)
16	Those Individuals who have a shortened dental arch	37 (12.3%)	93 (31%)	100 (33.3%)	38 (12.6%)	32 (10.6%)
17	Individuals who do not have molar support develop TMJ problems.	44 (14.6%)	68 (22.6%)	86 (28.6%)	62 (20.6%)	40 (13.3%)
18	Patients who have a self-esteem deficit are content with how their teeth seem.	49 (16.3%)	90 (30%)	92 (30.6%)	38 (12.6%)	31 (10.3%)
19	Patients with shortened dental arches report feeling comfortable in their mouths.	53 (17.6%)	83 (27.6%)	104 (34.6%)	28 (9.6%)	32 (10.6%)

Specialists generally agreed more with the concept of shortened dental arches than general dentists when it came to ten pairs of occlusive teeth, this idea was being suggested to patients with periodontal disease and caries, hence the overall favorable prognosis for periodontal disease in cases where patient options were limited and aesthetic acceptability was one of the factors. Examining the responses from specialists and general dentists, a comparable difference was found ($p<0.05$). Hence, shortened dental arches does not aggravate periodontitis specifically in those cases where the levels of marginal bone were low, lack of TMJ issues, and the applicability of these findings was more frequently reached by specialists than by general dentists ($p<0.05$) as shown in table 3.

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Table 3: Awareness and Knowledge of General Dentists and Specialists Regarding Shortened Dental Arches

S. No.	General Dentists (%)					Specialists (%)					p-Value
	Strongly Agree	Agree	Not Agree	Disagree	Strongly Disagree	Strongly Agree	Agree	Not Agree	Disagree	Strongly Disagree	
1	12.70	25.80	32.20	13.10	16.20	22	19.30	27.50	15.60	15.60	0.136
2	10.80	31.50	33.40	13.10	11.10	24.80	25.70	24.80	12.80	11.90	0.008*
3	9.60	32.50	36.60	12.40	8.90	25.70	24.80	28.40	12.80	8.30	0.001*
4	9.90	32.50	33.10	10.80	12.70	21.10	26.60	26.60	11.90	13.80	0.034*
5	11.50	36.60	28.90	13.10	9.90	22.90	25.70	25.70	14.70	11	0.029*
6	10.80	19.40	30.60	15.60	23.60	11.90	18.30	29.40	15.60	24.80	0.994
7	9.60	38.50	30.30	11.50	10.20	22	33.90	20.20	15.60	8.30	0.005*
8	14	35.40	29.30	11.50	9.90	20.20	33	25.70	12.80	8.30	0.587
9	11.10	35.40	29.30	11.70	12.40	19.30	30.30	27.50	13.70	9.20	0.221
10	11.40	22.80	33.80	18	12.90	16.10	32.80	26.60	15.10	11.40	0.020
11	12.40	29.60	28.40	16.60	12.90	12	30.80	31.20	12.50	11.50	0.056
12	16.60	30.60	31	9.20	12.60	15.70	34.30	27.60	15.10	9.30	0.046*
13	13.30	32.60	31	10.50	12.60	18.30	31.70	31.20	9.40	9.40	0.067
14	17.70	29	31.90	8.90	13.10	18.70	37.90	23.40	13.50	10.40	0.207
15	19	27.30	32.90	9.10	11.70	18.80	35.90	23.90	11.50	9.90	0.176
16	11.40	27.10	34.80	14.60	12.10	16.60	33.40	32.30	8.80	8.90	0.034*
17	11.60	26.50	27.60	18.70	15.60	18.70	18.80	27.10	23.90	11.50	0.931
18	12.10	29.40	35.50	11.30	11.70	19.80	30.70	28.10	13	8.30	0.156
19	17.30	24.20	38.90	7.40	12.10	17.70	31.30	29.70	13	8.30	0.876

*p-value considered significant

DISCUSSION

The study presents unique data regarding awareness and knowledge of shortened dental arches among general dentists and specialists in Karachi, Pakistan. Studies indicate a significant lack of awareness and knowledge about shortened dental arches among dental surgeons in various regions [16]. One of the Indian studies conducted by Agrawal N. revealed that although few dentists practiced shortened dental arches, the majority of dentists had a positive opinion of the concept despite not being familiar with it. Raising awareness of shortened dental arches should be emphasized among dental surgeons [17]. Specialists had a positive attitude but concerns about management outcomes were always an issue [18]. The results of the study revealed that most of the dental surgeons were unsure regarding the concept of shortened dental arches. Further, the results of the study revealed that the specialists were more aware of the idea of shortened dental arches which was similar to a study conducted in Jordan by Abu-Awwad M *et al.*, in 2019 [1]. Results from a study conducted by Walter MH *et al.*, showed that dentists with master's degrees applied the concept of shortened dental arches more frequently than dentists with bachelor's degrees [18]. However, compared to general dentists, specialists had much more knowledge regarding shortened dental arches. The results of the study were consistent with the previously cited studies according to which shortened dental arches were preferred for the provision of conservative treatment [19, 20]. These findings were consistent with those of these studies for older individuals who have sufficient adaptive capacity, the standard shortened dental arches consisting of four occlusal units, often premolars satisfy their needs [21]. Research shows that individuals with shortened dental arches have a better prognosis for the remaining teeth, less expensive treatment, preservation of oral tissues, good occlusal stability, and easier maintenance of oral hygiene [22]. The main limitation of this study design was the small sample size which limits the study's findings' generalizability. It was noted that the study's results were generally consistent with those of other research which were conducted in different parts of the world belonging to similar nature but the intensity of the responses differed because of different mindsets regarding the concept of shortened dental arches. All of these findings emphasize the fact that all dental surgeons should have further education and training regarding the idea of shortened dental arches.

CONCLUSIONS

There was a lack of understanding and attitude among dental surgeons regarding the concept of shortened dental arches. Shortened dental arches provide a practical approach to dental care that was especially helpful for low-income and older patients since they preserve posterior tooth function without requiring complete arch restoration. By identifying educational gaps, guiding targeted training programs, and improving clinical decision-making, it was possible to improve patient

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outcomes and make more effective use of available resources by having a better understanding of the existing level of awareness and expertise among dental surgeons.

Authors Contribution

Conceptualization: KK
Methodology: KK, UAI, SM
Formal analysis: T, S, UAI
Writing, review and editing: T, A, SM

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Conflicts of Interest

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Measurement of Fetomaternal Outcome in Pregnant Patients with Sepsis

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ABSTRACT

Sepsis during pregnancy is a severe condition associated with significant maternal and fetal morbidity and mortality. It necessitates early identification and intervention to mitigate adverse outcomes. **Objective:** The study was aimed to evaluate and compare feto-maternal outcomes in pregnant patients with sepsis versus those without sepsis. **Methods:** This comparative cross-sectional study was conducted at Social Security Teaching Hospital, Lahore, from July 2023 to January 2024. A total of 240 pregnant women were included, with 120 diagnosed with sepsis and 120 without sepsis (control group). Obstetrically modified qSOFA and SOFA scores, were used for sepsis diagnosis. Data on vital signs, laboratory investigations, and fetal monitoring were collected and analyzed using SPSS version 24.0. Multivariate analysis was employed to adjust for potential confounders, and p-values of ≤ 0.05 were considered statistically significant. **Results:** The sepsis group exhibited significantly worse outcomes compared to the control group. The mean age was 27.8 ± 9.4 years, and mean Body mass index (BMI) was 25.3 ± 5.6. Maternal outcomes included 8.3 % oligohydramnios, 46.67% cesarean sections for non-reassuring fetal profiles, and 15 % preterm premature rupture of membranes. Maternal Intensive Care Unit ICU admission was necessary for 8.3% of patients, with a maternal mortality rate of 1.67%. Fetal outcomes included 5% intrauterine fetal growth restriction, 28.33% small for gestational age, 3.3% stillbirth, and 53.33% neonatal ICU admissions. **Conclusions:** Sepsis in pregnancy significantly increases the risk of adverse feto-maternal outcomes, including preterm birth, fetal distress, intrauterine growth restriction, and neonatal complications. Early detection and aggressive management are crucial to improving outcomes.

INTRODUCTION

Sepsis during pregnancy is a serious condition that can lead to significant maternal and fetal morbidity and mortality. It is the third leading cause of maternal death worldwide and treated as medical emergency [1]. The physical changes that occur during pregnancy could hide the symptoms of sepsis; thus, making it hard to diagnose. The main factors that cause sepsis at this stage include; dengue fever at 24.3%, while 14.4% have hepatitis E, another 12.2% suffer from Urinary Tract Infections (UTIs) [2]. Sepsis increases risks for multiple organ dysfunctions like Acute Respiratory Distress Syndrome (ARDS), Acute Renal Failure (ARF), and Disseminated Intravascular Coagulation (DIC) among pregnant women. This condition can also lead to preeclampsia and eclampsia thus worsening the overall health conditions of expectant mothers [3]. Diagnosis of sepsis in pregnant women is complicated by the physiological changes of pregnancy that can obscure typical sepsis indicators. The adaptation of the Sepsis-3 criteria to the obstetric population is still under debate. Key indicators include maternal tachycardia, fever, elevated white blood cell count, and hypotension, though these signs must be interpreted cautiously in the

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context of pregnancy [4]. Maternal sepsis is associated with an almost threefold risk of preterm delivery leading to complications for the newborn, including respiratory distress and developmental challenges. Studies have also shown a six- to eightfold increased risk of perinatal mortality in pregnancies complicated by maternal sepsis [5]. Maternal sepsis can affect placental function, leading to fetal growth restriction and babies born small for their gestational age [6]. Sepsis-related complications may necessitate cesarean delivery due to non-reassuring fetal status or intolerance of labor. Surgical delivery can have implications for both mother and baby. The combination of prematurity, low birth weight and potential neonatal sepsis contributes to this increased risk. Studies indicate neonatal mortality rates can be as high as 43.8% in cases of severe maternal sepsis [7]. Signs show that surviving infants may exhibit long-term neurodevelopmental problems following maternal sepsis. These could be among other things; -mental retardation, muscle weakness or even conduct issues. The causes are usually several hence assumed to be caused by, the baby's brain being infected directly and causing inflammation or even delivery before term [8]. The timing and mode of delivery in septic pregnancies are critical decisions influenced by gestational age, maternal condition, and fetal well-being. In cases of severe sepsis or septic shock, early delivery may be necessary to improve maternal outcomes, even if it results in preterm birth. The mode of delivery should be individualized, with cesarean delivery considered in cases of maternal instability or fetal distress [9]. Prompt administration of broad-spectrum antibiotics is critical in the management of sepsis in pregnancy. Empirical antibiotic therapy should be initiated within the first hour of recognition of sepsis, followed by adjustment based on culture results. Commonly used antibiotics include ceftriaxone, ampicillin, and metronidazole, tailored to cover common pathogens like Group B Streptococcus, Escherichia coli, and anaerobes. Intensive supportive care is essential for managing sepsis in pregnant women [10]. This includes fluid resuscitation, vasopressors for hemodynamic support, and oxygen therapy to maintain adequate oxygenation). Early involvement of a multidisciplinary team, including obstetricians, intensivists, and neonatologists, is crucial for optimal outcomes. Although there have been many studies on sepsis among overall populations, research focused on pregnancy is scanty when considering mother's and baby's fate as well as childbirth. There is insufficiently detailed data in literature about how the beginning of sepsis at different times during gestation can lead to different results, and how severe sepsis could be delivered [11]. Very little research has been conducted on preventive sepsis strategies in pregnancy. It is important to have studies that concentrate on the detection of threats as well as methods of prevention like immunization, preventive antibiotics and community based programs. Ethnic and economic factors' role in the rate and consequences of sepsis during pregnancy is still not clear [12].

The study was aimed to assess the impact of maternal sepsis on fetal health and development, as well as to determine the prevalence of adverse fetal outcomes associated with maternal sepsis. Additionally, the study seeks to identify potential risk factors that contribute to poor fetal outcomes in pregnancies complicated by sepsis. This research will provide valuable insights into the consequences of sepsis during pregnancy and help inform strategies for early detection, intervention, and management to improve both maternal and fetal outcomes.

METHODS

This was a comparative cross-sectional analysis conducted at Social Security Teaching Hospital, Lahore, from July 2023 to January 2024, following approval from the ethical review committee (Ref: 07/23). The primary objective was to evaluate and compare feto-maternal outcomes in pregnant patients diagnosed with sepsis from those without sepsis.

The sample size was determined using the following formula for comparing two proportions:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \times [p1(1-p1) + p2(1-p2)]}{(p1-p2)^2}$$

- Where:
- n = required sample size for each group
- $Z_{\alpha/2}$= Z value (the critical value) corresponding to a significance level of 0.05 (1.96 for a two-tailed test)
- Zβ= Z value corresponding to a power of 80 % (0.84)
- p1= expected proportion in the sepsis group (e.g., prevalence of sepsis-related outcomes)
- p2= expected proportion in the control group
- p1–p2= expected effect size or difference between the two groups

Assuming a prevalence of sepsis of 10% in the target population and an anticipated effect size (p1 – p2 p_ 1 – p _ 2p1– p2) of 0.2 for key maternal and fetal outcomes, the formula was applied to calculate the required sample size. The calculations were performed using standard statistical software, resulting in a need for 120 patients in each group to ensure adequate power. A multistage sampling technique was employed to select participants. Initially, all pregnant women (either singleton or multiple gestations) admitted to the Department of Obstetrics and Gynecology during the study period were screened for eligibility based on predefined inclusion and exclusion criteria. The sepsis group was composed of patients diagnosed with sepsis based on obstetrically modified quick Sequential Organ

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Failure Assessment (qSOFA) and Sequential Organ Failure Assessment (SOFA) scores, validated for use in the target population. The control group included pregnant women without any sepsis diagnosis, matched by age, parity, and gestational age. This approach ensured that the control group was comparable to the sepsis group in terms of key baseline characteristics, reducing potential confounding factors. The sample size was calculated 240 participants, with 120 patients in each group. A power analysis was conducted to detect significant differences in maternal and fetal outcomes between groups, with a 95% confidence interval and 80% power. A multistage sampling technique was employed. Participants included in the sepsis group were those diagnosed with sepsis during pregnancy, confirmed by obstetrically modified qSOFA and SOFA scores, and laboratory investigations. Exclusion criteria for both groups included pre-existing medical conditions known to affect fetal outcomes (e.g., hypertension, diabetes mellitus), gestational trophoblastic diseases, other rare pregnancy complications unrelated to sepsis, elective termination of pregnancy, or intrauterine fetal demise before the diagnosis of sepsis. Informed consent was obtained from all willing participants before enrollment. Baseline demographics, including age, gestational age, parity, medical history, and obstetric history, were recorded. Clinical parameters, including vital signs, complete blood count, blood culture results, and fetal monitoring data such as fetal heart rate, were documented for both groups. The obstetrically modified qSOFA and SOFA scores were used to diagnose sepsis, incorporating specific parameters adjusted for pregnancy. These scores have been validated in the target population through a prior pilot study to ensure accuracy and reliability in this cohort. Primary outcomes included fetal growth restriction, oligohydramnios, hypertensive disorders of pregnancy, cesarean delivery for non-reassuring fetal status or labor intolerance, infants born small for gestational age, and stillbirth. Secondary outcomes encompassed individual components of placental dysfunction, as well as other maternal and neonatal complications. To address potential confounders, multivariate analysis techniques were applied, adjusting for variables such as maternal age, parity, pre-existing medical conditions, and gestational age at diagnosis. Data were entered and analyzed using SPSS version 24.0. Descriptive statistics, including means, standard deviations, and percentages, were calculated. Inferential statistics, including chi-square tests, t-tests, and multivariate logistic regression, were used to assess associations between sepsis and maternal and fetal outcomes, comparing the sepsis group with the control group. p-values of ≤0.05 were considered statistically significant.

RESULTS

In this cross-sectional study, 240 pregnant patients were evaluated, with 120 diagnosed with sepsis (sepsis group) and 120 without sepsis (control group) to measure and compare maternal and fetal outcomes. The clinical parameters, including vital signs, laboratory investigations, and fetal monitoring data, were thoroughly documented and analyzed. The mean age of the participants in the sepsis group was 27.8 ± 9.4 years, while in the control group, it was 28.1 ± 8.9 years (p = 0.71). The mean Body Mass Index (BMI) was 25.3 ± 5.6 in the sepsis group and 24.8 ± 5.4 in the control group (p = 0.43). The mean gestational age at presentation was 33.2 ± 4.2 weeks in the sepsis group and 34.1 ± 3.8 weeks in the control group (p = 0.12) (Table 1).

Table 1: Characteristics of Study Population

Variables	Sepsis Group (n = 120)	Control Group (n = 120)	p - value
Age (Mean ± SD) (Years)	27.8 ± 9.42	28.1 ± 8.9	0.71
BMI	5.3 ± 5.6	24.8 ± 5.4	0.43
Gestational Age at Presentation (Mean ± SD) (Weeks)	33.2 ± 4.2	34.1 ± 3.8	0.12
Gestational Diabetes	18 (15%)	10 (8.3%)	0.09
Pregnancy-Induced Hypertension	24 (20%)	16 (13.3%)	0.13

The average heart rate in the sepsis group was 105 ± 15 beats per minute, the mean systolic blood pressure was 112 ± 10 mmHg, and the average temperature was 38.5°C ± 0.8°C. In the control group, the average heart rate was 80 ± 10 beats per minute, the mean systolic blood pressure was 120 ± 8 mmHg, and the average temperature was 36.8°C ± 0.5°C. Laboratory investigations revealed that the mean white blood cell count was significantly elevated in the sepsis group at 15,000 ± 5,000/mm^3 compared to 8,000 ± 3,000/mm^3 in the control group (p < 0.01). Hemoglobin levels were slightly lower in the sepsis group (10.5 ± 1.2 g/dL) compared to the control group (11.8 ± 1.0 g/dL) (p = 0.02). Positive blood cultures were found in 30 % (n = 36) of the sepsis group, while no positive cultures were observed in the control group. Elevated C-reactive Protein (CRP) levels were observed in 65 % (n = 78) of the sepsis group compared to 10 % (n = 12) in the control group (p < 0.01). Abnormal fetal heart rate patterns were observed in 45% (n = 54) of the sepsis group, compared to 12% (n = 14) in the control group (p < 0.01). Reduced fetal movements were reported in 25 % (n = 30) of the sepsis group, compared to 5% (n = 6) in the control group (p < 0.01) (Table 2).

Table 2: Baseline Characteristics and Clinical Parameters

Parameter	Sepsis Group Mean ± SD / n (%)	Control Group Mean ± SD / n (%)	p - value
Age (years)	27.8 ± 9.42	28.1 ± 8.9	0.71
BMI	5.3 ± 5.63	24.8 ± 5.4	0.43
Gestational Age at Presentation (weeks)	3.2 ± 4.2	34.1 ± 3.8	0.12
Heart Rate (bpm)	105 ± 15	80 ± 10	<0.01
Systolic Blood Pressure (mmHg)	112 ± 10	120 ± 8	<0.01

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Temperature (°C)	38.5 ± 0.8	36.8 ± 0.5	<0.01
WBC Count (x10^3/mm^3)	15,000 ± 5,000	8,000 ± 3,000	<0.01
Hemoglobin (g/dL)	10.5 ± 1.2	11.8 ± 1.0	0.02
Positive Blood Culture	36 (30%)	0 (0%)	N/A
Elevated CRP	78 (65%)	12 (10%)	<0.01
Abnormal Fetal Heart Rate	54 (45%)	14 (12%)	<0.01
Reduced Fetal Movements	30 (25%)	6 (5%)	<0.01

Among maternal outcomes, 8.3% (n = 10) in the sepsis group experienced oligohydramnios compared to 3.3% (n = 4) in the control group (p = 0.07). Cesarean sections due to non-reassuring fetal profiles were more common in the sepsis group (46.67%, n = 56) compared to the control group (28.33%, n = 34) (p = 0.01). Preterm premature rupture of membranes occurred in 15% (n = 18) of cases in the sepsis group compared to 8.3% (n = 10) in the control group (p = 0.11). Intra-amniotic infections were reported in 11.67% (n = 14) of patients in the sepsis group, while none were observed in the control group (p<0.01). Additionally, postpartum hemorrhage was more common in the sepsis group (35%, n = 42) compared to the control group (13.3%, n = 16) (p < 0.01), and postpartum infections occurred in 3.3% (n = 4) of patients in the sepsis group compared to none in the control group (p=0.04). Maternal ICU admission at delivery was necessary for 8.3% (n = 10) of patients in the sepsis group compared to 1.67% (n = 2) in the control group (p = 0.02), and maternal mortality was reported in 1.67% (n = 2) of cases in the sepsis group, with no cases in the control group (p=0.15). Significant differences in maternal and fetal outcomes were observed between the two groups (Table 3).

Table 3: Maternal and Fetal Outcomes in Sepsis During Pregnancy

Variables	Sepsis Group (n = 120)	Control Group (n = 120)	p - value
Maternal Outcomes			
Oligohydramnios	10 (8.3%)	4 (3.3%)	0.07
Cesarean Section Due to Non-Reassuring Fetal Profile	56 (46.67%)	34 (28.33%)	0.01
Preterm Premature Rupture of Membranes	18 (15%)	10 (8.3%)	0.11
Intra-Amniotic Infections	14 (11.67%)	0 (0%)	<0.01
Postpartum Hemorrhage	42 (35%)	16 (13.3%)	<0.01
Postpartum Infections	4 (3.3%)	0 (0%)	0.04
Maternal ICU Admission at Delivery	10 (8.3%)	2 (1.67%)	0.02
Maternal Mortality	2 (1.67%)	0 (0%)	0.15
Fetal Outcomes			
Intrauterine Fetal Growth Restriction	6 (5%)	2 (1.67%)	0.14
Small for Gestational Age	34 (28.33%)	20 (16.67%)	0.04
Stillbirth	4 (3.3%)	2 (1.67%)	0.41
Preterm Birth			
<34 Weeks	32 (26.67%)	20 (16.67%)	0.02
34-37 Weeks	22 (18.33%)	10 (8.3%)	0.05
Neonatal ICU Admissions	64 (53.33%)	32 (26.67%)	<0.01
5 Min Apgar Score <7	18 (15%)	10 (8.3%)	0.12
Fetal Mortality	4 (3.3%)	2 (1.67%)	0.41

Intrauterine fetal growth restriction was observed in 5% (n = 6) of cases in the sepsis group compared to 1.67% (n = 2) in the control group (p = 0.14). Infants small for gestational age were more common in the sepsis group (28.33%, n = 34) compared to the control group (16.67%, n = 20) (p = 0.04). The stillbirth rate was 3.3% (n = 4) in the sepsis group and 1.67% (n = 2) in the control group (p = 0.41). Preterm birth occurred more frequently in the sepsis group, with 26.67% (n = 32) before 34 weeks (p = 0.02) and 18.33% (n = 22) between 34 and 37 weeks (p = 0.05), compared to 16.67% (n = 20) and 8.3% (n = 10) in the control group, respectively. Neonatal ICU admissions were required for 53.33% (n = 64) of newborns in the sepsis group compared to 26.67% (n = 32) in the control group (p < 0.01) and 15% (n = 18) had a 5-minute Appearance, Pulse, Grimace, Activity, and Respiration (APGAR) score of less than 7 in the sepsis group compared to 8.3% (n = 10) in the control group (p = 0.12). Fetal mortality was 3.3% (n = 4) in the sepsis group and 1.67% (n = 2) in the control group (p = 0.41) (Table 4).

Table 4: Organ System Involvement and Severity of Infection

Variables	Sepsis Group (n = 120)
Organ System Involved	
Kidney	52 (43.33%)
Pulmonary	46 (38.33%)
Gastrointestinal	10 (8.3%)
Genital tract	14 (11.67%)
CNS	4 (3.3%)
Severity of Infection	
Antepartum ICU Admission	14 (11.67%)
qSOFA Score > 2	38 (31.67%)
Gestational Age at Sepsis	
0-24 Weeks	54 (45%)
>24 Weeks	66 (55%)

These findings highlight the significant maternal and fetal risks associated with sepsis during pregnancy and emphasize the importance of monitoring clinical parameters and comparing outcomes with those of non-septic pregnancies to better understand the impact of sepsis.

DISCUSSION

Severe immunological reaction to an infection that causes systemic inflammation throughout the body is a major health risk known as sepsis. This illness is frequently referred to as an infection-induced systemic inflammatory response syndrome (SIRS) [13]. Pneumonia is the most common infection in pregnant women that precedes sepsis, with diseases of the reproductive system coming in close second. Lung inflammation incidents seem to be more common during childbirth, but infections related to vaginal delivery or medical treatments frequently become more apparent in the postoperative period [14]. Septic shock usually develops from Streptococcus species infections more quickly than from infections caused by

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other bacteria [15]. Thus, in order to reduce sepsis-related maternal mortality, it is critical to quickly diagnose and treat group A streptococcal infection. Particularly after giving birth, postpartum individuals show a noticeably higher risk of contracting these diseases than do non-pregnant individuals [16, 17]. The study elucidates the significant impact of sepsis on both maternal and fetal outcomes in pregnancy, with multiple organ systems being affected, high severity of infection, and critical timing of onset. The study further demonstrates significant maternal outcomes associated with sepsis. Oligohydramnios was observed in 8.3% of cases, and cesarean sections due to non-reassuring fetal profiles were performed in 46.67% of patients. Preterm premature rupture of membranes occurred in 15% of cases, intra-amniotic infections in 11.67%, post-partum hemorrhage in 35%, and post-partum infections in 3.3%. Additionally, 8.3% of patients required maternal ICU admission at delivery, and maternal mortality was reported in 1.67% of cases. In 12% of obstetric patients, sepsis results in respiratory failure that necessitates intubation [18]. 17 Pregnancy-related complications associated with this infection include atrial fibrillation, pneumothorax, and pericardial tamponade (4%) [19]. These findings underscore the severe impact of sepsis on maternal health, leading to complications that necessitate advanced medical interventions and increase the risk of mortality [20]. Fetal outcomes are equally concerning, with intrauterine fetal growth restriction observed in 5% of cases, and 28.33% of newborns being small for gestational age. The stillbirth rate was 3.3%, and preterm birth occurred in 26.67% of cases before 34 weeks and in 18.33% between 34 and 37 weeks. Neonatal ICU admissions were required for 53.33% of newborns, and 15% had a 5-minute APGAR score of less than 7. Fetal mortality was 3.3%. These statistics indicate a high burden of adverse fetal outcomes in pregnancies complicated by sepsis, highlighting the need for vigilant prenatal care and early intervention to mitigate risks and consistent with the findings of previous work [21]. These perinatal correlates with the findings of another study that stated 11.9% small for gestational age births, 5.1% cases of preterm premature rupture of membranes, 33.9% cesarean deliveries and 23.7% cases of post-partum hemorrhages due to sepsis in pregnancy [22]. The dysregulated host response to maternal infection during sepsis significantly impacts placental development and function, resulting in poor perinatal outcomes. In case a pregnant woman gets sepsis, this results from a broken mechanism of the body that fights immunity against attacks and leads to SIRS. The volatility of inflammatory cytokines like TNF-alpha, IL-1, and IL-6 during sepsis might cause inflammation in the placenta. Sepsis also causes malfunctioning endothelial cells and abnormal blood clotting thus interfering with normal blood flow within the placental blood vessels [23]. When inflammation and reduced blood circulation are combined, placental hypoxia and oxidative stress can occur, which further damage its tissues and impair its functionality, thus leading to adverse fetal outcomes. The results of this paper could support the development of local-driven clinical guidelines on the management of sepsis in pregnancy which can help healthcare policymakers formulate policies aimed at minimizing the occurrence as well as enhancing management of sepsis in pregnancy [24]. Current knowledge and practice gaps were identified in the study, thus creating more scope for researching innovative diagnostic tools as well as management techniques on how to treat sepsis during pregnancies. Differences in the management of sepsis and pregnancy care can introduce variability that affects outcomes.

CONCLUSIONS

This study underscores the severity of sepsis as a significant risk factor for adverse fetal outcomes, including preterm birth, fetal distress, intrauterine growth restriction, and neonatal complications. These findings emphasize the importance of early recognition and prompt management of sepsis in pregnant women to mitigate the potential adverse effects on fetal well-being.

Authors Contribution

Conceptualization: ZEH, AJ, SJ, MA, UA, NS
Methodology: DC
Formal analysis: CR, DC
Writing-review and editing: ME

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

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Cardiovascular Events and Related Factors in Routine Hemodialysis Patients with Chronic Kidney Disease (CKD) at a Tertiary Care Hospital in Pakistan

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ABSTRACT

Cardiovascular-related events were a significant problem in patients receiving dialysis. These patients were at a higher risk due to the complex interplay of factors such as hypertension, anemia, and other comorbid conditions. **Objective:** To find the cardiovascular events and related factors in routine hemodialysis patients with Chronic Kidney Disease (CKD) at a tertiary care hospital in Pakistan. **Methods:** This Cross-sectional retrospective study conducted in routine dialysis patients in a tertiary care hospital, from October 2022 to December 2023. Patients that experienced cardiovascular events were included in the study, with those not experiencing any cardiovascular event were excluded from the research. Informed consent was taken from patients to collect the data. **Results:** The study included 255 dialysis patients (mean age 60.5 years ±10.2), with 128 males (50.1%) and 127 females (49.8%). Heart failure was the most common cardiovascular event, followed by pleural effusion, while sudden cardiac death was one of the least frequent but significant. Hypertension and anemia were the major risk factors for cardiovascular events in end-stage renal disease, with thyroid function issues being the least associated. **Conclusions:** Managing CKD and cardiovascular risks in Peritoneal Dialysis (PD) and Hemodialysis (HD) patients requires strict control of blood pressure, lipids, and glucose, and careful monitoring of volume status. Lifestyle changes and advancements in dialysis equipment show promise, but more research is needed to optimize treatment and improve outcomes. Clinicians can reduce cardiovascular risk and enhance life expectancy and quality of life by addressing these factors.

INTRODUCTION

Cardiovascular-related events are a significant problem in the group of patients receiving dialysis; they remain a major cause of morbidity and mortality higher than rates in other patients. Therefore, yet again, dialysis will put the cardiac patient at high risk of experiencing Major Adverse Cardiovascular Events (MACE) that encompasses Myocardial Infarction (MI), Stroke, Sudden Cardiac Death (SCD), pericarditis, as well as pleural effusion. Such factors exposed the patients to a lower immune system strength that has several relations to CKD and processes of dialysis [1]. In addition to traditional cardiovascular risks occurring in all inhabitants of developed countries, such as hypertension, elevated level of LDL-cholesterol and reduced level of HDL-cholesterol, diabetes mellitus, patients on dialysis have a set of complications that arise with end-stage CKD. Such include mineral bone disorder characterized by disorders in calcium, phosphorus, parathyroid hormone, which results to vascular calcification and increased arterial stiffness [2]. Anemia which is frequently reported among CKD patients due to decrease in erythropoietin causes increased loading on the cardiovascular system by providing less oxygen to the tissues and organs [3]. The global CVD prevalence remains a cause of significant morbidity and mortality; for CKD patients, risks are somehow magnified. Thus, CKD patients who are on routine HD are at a more vulnerable position for cardiovascular event occurrence due to modifications of traditional and non-traditional risk factors. There is a clear association between CKD and CVD; the progression of CKD is known to substantially raise the risk for cardiovascular

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events. This is especially true in Low-and Middle-Income Countries (LMICs) like Pakistan because the health sector is fraught with many problems, such as poor availability of home care resources and testing techniques and subsequent restrictive therapeutic options [4]. Hemodialysis, one of the common treatments for CKD patients unfortunately, does not reduce the chances of having cardiovascular complications. Instead, it can bring extra factors that can worsen the cardiovascular morbidity and mortality rates among patients with diabetes [5]. Emphasis has been attributed to factors like; fluid overload, electrolyte imbalance, inflammation, oxidative stress, and use of anticoagulants as part of the dialysis procedure. Moreover, chronic, regular, and often severe risk factors such as hypertension, diabetes, dyslipidemia, smoking, which prevail in the general population, are worsened and more difficult to be controlled in patients with CKD, which aggravates the risk [6]. Regarding the epidemiology of CKD and Cardiovascular Disease (CVD) in Pakistan, many factors make it a different arena altogether. A growing number of patients with CKD as a result of diabetes, hypertension, and late diagnosis, along with the high rate of CVD, indicate the need to direct research and interventions toward these issues more than ever before [7]. However, literature describing the cardiovascular disease risks for Pakistani CKD HD patients is scarce, which restricts the ability of healthcare personnel to proactively formulate optimal CKD risk mitigation strategies. Further, advancement in dialysis which comprises of Dialysis membranes, dialysate solution, and approach towards intradialytic hypotension modulation may decrease the cardiovascular load and improve the condition of the patients [8]. Close cooperation with team members from the departments of nephrology, cardiology, endocrinology, and other faculty as well as the allied health team is imperative to ensure that management strategies that address cardiovascular risks in dialysis patients are part of the patients' individualized care plans [9]. Altogether, the interdependent impacts of CKD elements, conventional cardiovascular dangers and shrewd complexities of dialysis considerably raise the rates of essential coronary episode in dialysis patients. Approaching these issues holistically and continuously working to advance the science and practice of clinical care, clinicians can begin to aspire to alleviate the immense toll that cardiovascular disease imposes and enhance the lives of the people managing the challenges of CKD and dialysis [10].

The main objective of the study was to find the cardiovascular events and related factors in routine hemodialysis patients with CKD at a tertiary care hospital in Pakistan.

METHODS

This retrospective study was conducted in routine dialysis patients in a tertiary care hospital, from October 2022 to December 2023. Permission for the project was granted by the ethical review committee of Islamabad Medical and Dental College, Islamabad, Pakistan (ref no. 40/IMDC/IRB-2023). Patients that experienced cardiovascular events were included in the study, with those not experiencing any cardiovascular event were excluded from the research. Informed consent was taken from patients to collect the data. Demographic information including age, sex, ethnicity, and any comorbid conditions that may impact cardiovascular risk were noted. A sample size of 255 with a 95% confidence level and a 5% margin of error were calculated using the WHO sample size methodology. Patients diagnosed with chronic kidney disease (CKD) and undergoing hemodialysis were included in the study. A retrospective study design was chosen, where data from patients' hospitalizations was analyzed to determine whether they had experienced any cardiovascular events and to identify any existing risk factors that might predispose them to such events. Patients who were not diagnosed with chronic kidney disease or were not on hemodialysis were excluded from the study. Data was analyzed using SPSS version 29.0.

RESULTS

The study included 255 patients undergoing dialysis treatment at a tertiary care hospital. The mean age of the patients was 60.5 ± 10.2 years. Cardiovascular events were prevalent among routine hemodialysis patients, with heart failure being the most common, affecting 37% of the patients (n = 94). Myocardial infarction occurred in 22% (n = 56), while arrhythmias were observed in 26% (n = 67) of the patients. Stroke was the least frequent cardiovascular event, affecting 15% (n = 38) of the study population (Table 1).

Table 1: Prevalence of Cardiovascular Events

Cardiovascular Events	Number of Patients N (%)
Myocardial Infarction (MI)	56 (22%)
Stroke	38 (15%)
Heart Failure	94 (37%)
Arrhythmias	67 (26%)

In terms of risk factors attributed to cardiovascular events, hypertension was the most common risk factor present in 78% of the cases (n=199), followed by anemia, being present in 62% of the cases (n=158). Dyslipidemia was the least common risk factor present in patients, as a mere total of 43% had the disease (Table 2).

Table 2: Risk Factors Associated with Cardiovascular Events

Risk Factors	Number of Patients N (%)	Significance	P-Value
Hypertension	199 (78%)	–	–
Diabetes Mellitus	138 (54%)	Significant with MI	<0.01
Dyslipidemia	110 (43%)	Significant with Stroke	<0.05
Anemia	158 (62%)	Significant with Heart Failure	<0.01

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DISCUSSION

Cardiovascular disorders constitute one of the acts intimidating amongst the patients on dialysis given that it was one of the leading causes of morbidity and mortality among these patients. Cardiovascular disease was much more common among dialysis patients than among the general population, and the multifactorial etiology of CVD and lack of effective preventive approaches further highlight the severity of the problem [11]. CKD per se was a potent risk factor contributing for cardiovascular diseases. With progressive loss of kidney function there were various changes that occur in the form of pathophysiological processes like; first of all, alterations in mineral metabolism including hyperphosphatemia and secondary hyperparathyroidism; secondly, retained volume; thirdly, chronic inflammation; fourthly, oxidative stress; and lastly endothelial dysfunction [12]. These processes as a whole enhance atherosclerosis, calcification of vessels, and hypertrophy of the left ventricle, which threaten dialysis patients in terms of myocardial infraction, stroke, heart failure and sudden cardiac death [13]. The findings of this study highlight the significant burden of cardiovascular events among patients undergoing dialysis treatment at a tertiary care hospital. With a mean age of 60.5 years, the population in this study was consistent with the demographic most at risk for cardiovascular complications [14]. The high prevalence of heart failure, affecting 37% of patients, underscores the vulnerability of this population to cardiac complications, likely exacerbated by the underlying kidney disease and the associated strain on cardiovascular health. The occurrence of myocardial infarction in 22% of the patients and arrhythmias in 26% further emphasizes the heightened cardiovascular risk in dialysis patients [15]. These findings align with existing literature that identifies cardiovascular disease as the leading cause of mortality in patients with End-Stage Renal Disease (ESRD). Stroke, although the least common cardiovascular event in this study at 15%, still represents a significant risk, reflecting the complex interplay between dialysis treatment and cerebrovascular health. The analysis of risk factors reveals important associations that could inform clinical management strategies. Hypertension, present in 78% of the patients, emerges as the most prevalent risk factor, although its direct significance in this study's cardiovascular outcomes was not established [16]. This high prevalence, however, underscores the necessity of stringent blood pressure control in dialysis patients to mitigate the risk of cardiovascular complications. Diabetes Mellitus, identified in 54% of the patients, showed a significant correlation with myocardial infarction ($p < 0.01$). This finding highlights the critical need for effective management of diabetes in dialysis patients, as hyperglycemia can exacerbate atherosclerosis and increase the risk of coronary artery disease [17]. Similarly, dyslipidemia, present in 43% of the patients, was significantly associated with stroke ($p < 0.05$), indicating that lipid management should be a priority in reducing cerebrovascular risks in this population. In addition, future innovations with regards to the methods in dialysis have the potential to offer better cardioprotective results [18]. For example, interventions which were targeted at prevention of falls in blood pressure during dialysis, the improvement of dialysis efficacy and the lessening of oxidative stress during dialysis were the tactics which were likely to improve cardiovascular status of dialysis patients [19]. New drug development for CKD-related cardiovascular disease based on new molecular targets deemed relevant for the progression of cardiovascular disease include FGF23 and calcimimetics for Mineral Bone Disorder [20]. While this study provides valuable insights into the prevalence and risk factors associated with cardiovascular events in patients undergoing dialysis, several limitations should be acknowledged. Firstly, the study was conducted in a single tertiary care hospital, which may limit the generalizability of the findings to other settings, particularly to smaller or rural healthcare facilities where the patient demographics and available resources may differ significantly. This hospital-based sample may not fully represent the broader population of dialysis patients, particularly those who receive care in different healthcare systems or regions.

CONCLUSIONS

Thus, the analyzed rates of MACEs in PD and HD patients denote the complexity of managing CKD risks, CV risk factors, and dialysis-related conditions. Thus, proper management requires a combination of strict blood pressure control, lipid levels and blood glucose levels, along with careful monitoring of volume status and Kt/V. Currently, lifestyle changes and new developments in dialysis equipage were potential ways allowing to improve the result of such patients' treatment; however, further investigation was needed to provide better treatments options and optimize cardiovascular management in this vulnerable population group. Thus, the considerations of all these factors in detail allow clinicians to potentially minimize cardiovascular risk and enhance the life expectancy and quality of life of patients with CKD and CVD treated by dialysis.

Authors Contribution

Conceptualization: JKK

Methodology: JKK, MA

Formal analysis: JKK, MA

Writing, review and editing: JKK, MA

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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Maternal Biochemical Markers and Risk of Preeclampsia

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ABSTRACT

Preeclampsia is a pregnancy disorder associated with a numerous feto-maternal complication. This condition prevails in developing countries, where it is an important reason for feto-maternal morbidity and mortality. **Objective:** To assess the role of maternal biochemical markers in the development of preeclampsia during pregnancy. **Methods:** A comparative cross-sectional study was carried out after ethical approval from the Institutional Review Board. The study included 200 participants: 100 patients with preeclampsia and 100 normotensive pregnant women as controls. Preeclampsia was diagnosed based on blood pressure readings above 140/90 mmHg and proteinuria levels exceeding 300 mg/24h. Independentsample t-test was applied to see the differences in both groups in SPSS version 25. **Results:** Significantly higher mean levels of cholesterol, triglycerides, LDL and Sodium were observed in women with preeclampsia ($p < 0.0001$). Conversely, the mean levels of high-density lipoprotein cholesterol ($p = 0.0169$), magnesium, calcium and potassium were lower in women with preeclampsia ($p < 0.0001$). **Conclusions:** Total cholesterol, triglycerides lipid profile and levels of calcium and magnesium were significantly disrupted and showed strong correlations with the severity of the disease. In clinical practice, these biomarkers could facilitate the timely detection of at-risk cases, potentially reducing the rate of feto-maternal complications.

INTRODUCTION

Preeclampsia (PE) is a pregnancy disorder associatedwith high blood pressure, and proteinuria after the 5 months gestation in women who previously had normal blood pressure, posing a significant risk to both maternal and perinatal health [1]. It affects 2-8% of all pregnancies worldwide, while in Pakistan, it is accountable for 5-15% of pregnancies [2]. PE is prevalent in developing countries, where it is animportantreason for complications and mortality of mother and fetus [3]. The exact causes of preeclampsia remain unclear, but genetic factors are believed to play a significant role. PE results from interplay of multiple pathological conditions that cause disruption of regulatory systems of inflammation and endothelial function beyond the normal changes of pregnancy [4]. It is a serious health issue resulting in devastating consequences [5]. A research study on maternal serum triglyceride levels and preeclampsia indicates that elevated triglyceride levels may be a risk factor and/or predictor for preeclampsia [6]. The linkage between serum lipid profile abnormalities and PE is well-established. Abnormal lipid levels are strongly linked to atherosclerotic Cardiovascular Disease (CVD) and contribute directly to endothelial dysfunction [7]. In contrast to normal pregnancy, PE is characterized by elevated levels of triglycerides, total lipids, and LDL cholesterol [8]. The link between altered lipid profiles and endothelial dysfunction has emerged as a crucial area of research related to pregnancy complications, particularly PE [9].

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Hypertension, a key feature of PE, results from vasospasm affecting the kidneys, placenta, brain, and uterus. A decrease in the PGI2 ratio due to lipid profile changes may play a significant role in hypertension during pregnancy [10]. Electrolytes are essential for regulating blood pressure, and imbalances can make blood vessels overly responsive to vasoconstrictors like vasopressin and Antidiuretic Hormone (ADH), contributing to hypertension [11]. Disruptions in Sodium (Na) and Potassium (K) levels play a role in the development of PE. Moreover, magnesium is thought to influence angiogenic and inflammatory responses, which can lead to reduced vascular contraction and lower hypertension in preeclampsia [12]. Approximately 24% of all maternal deaths in Pakistan are attributed to hypertensive pregnancy disorders [13]. While various theories have been proposed regarding the cause of preeclampsia, no definitive cause has been identified. This uncertainty hampers efforts to prevent and treat the condition. Based on previous observations, we hypothesized that changes in lipid profile parameters and electrolyte imbalances in early pregnancy might be directly linked to the development of complications.

Purpose of the present study was to assess the role of maternal biochemical markers in the development of preeclampsia during pregnancy.

METHODS

We selected lipid profile and electrolytes as biomarkers to evaluate causes of PE in pregnancy. Lipid profile was changed in PE, and has direct effects on the cardiovascular health. It results in endothelial damage and atherosclerotic changes that potentiate PE. Electrolytes imbalances affect PE by imparting their role in vascular tone and inflammatory responses. A comparative cross-sectional study was carried out at the Niazi Welfare Foundation Teaching Hospital in Sargodha, from 1st January, 2023 to 31st January 2024, following ethical approval from the Institutional Review Board (NM and DC-IRB-55). The sample size was determined based on a mean HDL level of 51.02 ± 16.01 in preeclampsia cases and 61.08 ± 25.03 in normotensive individuals, with a 90% confidence level and 80% power [14]. Using Open Epi, the calculated sample size was 98, rounded to 100. Therefore, the study included 200 participants: 100 patients with preeclampsia and 100 normotensive pregnant women as controls, all from the Obstetrics and Gynecology Department. Preeclampsia was diagnosed based on blood pressure readings above 140/90 mmHg and proteinuria levels exceeding 300 mg/24 hours or a + 1 on a dipstick test. Patients who were hospitalized were approached directly, and sociodemographic information was collected from both the patients and their attendants. Data collection was conducted using a consecutive sampling method, adhering to specific inclusion and exclusion criteria. Women aged 20 to 45 years with singleton pregnancies who developed hypertension with BP >140/90 mmHg on two separate occasions six hours apart and proteinuria >300 mg/24 hours or a +1 on a dipstick testduring pregnancy were included in the study. Exclusions were applied to women with chronic hypertension, gestational diabetes, cardiovascular disorders, renal disease, immunological disorders, PCOS, metabolic disorders, multiple pregnancies, or incomplete information. This study followed all ethical standardsto ensure safety and rights of participants. All the participants and their attendants were clearly explained regarding the purpose, procedure, potential risk and benefits related to this study. They were given free choice for participation and written informed consent was obtained from all participants and attendants. A 5 ml blood sample was drawn from the median cubital vein using aseptic techniques and placed into vacutainers without additives. The sample was then centrifuged at 3000 rpm for 10 minutes to separate the serum, which was stored in Eppendorf tubes at -20°C. The serum lipid profile and Ca++ and Mg++ levels were analyzed using a Beckman Coulter AU-680 chemistry analyzer via the spectrophotometric method. Serum electrolytes were assessed with an Easy Lyte analyzer using the ion-selective electrode (ISE) potentiometer method. All tests were conducted personally by the principal investigator in the Pathology/ Biochemistry Laboratory at NWFTH. The data were analyzed using SPSS version 25.0. For quantitative variables, Mean and Standard Deviation (SD) were computed. Qualitative variables were presented in frequencies and percentages, and presented in table. Independent t-test was used to see mean differences in two groups at 95% confidence interval, and p value <0.05. This methodology would help in finding and validating the biomarkersfor timely detection of PE, which could serve as a base for clinical practice in reducing feto-maternal consequences.

RESULTS

Demographics of control group showed man age of 30.0 ± 5.78 years, gestational age 30.21 ± .32 weeks, weight 74.04 ± 7.06 kg, BMI 26.83 ± 3.16, SPB 124.99 ± 3.12 mm/Hg while DBP 83.64 ± 1.80. Comparatively, study group presented with mean age 27.82 ± 6.36 years, gestational age 31.45 ± 2.81weeks, weight 81.63 ± 8.00 kg, BMI 29.51 ± 2.96, SPB 166.25 ± 11.21 mm/Hg while DBP 36.23 ± 20.85. p-values depicted significant differences in demographics of preeclampsia and normotensive group (Table 1).

Table 1: Demographic Variables of Cases and Control Groups (n=200)

Variables	Control (Mean ± SD)	Cases (Mean ± SD)	p-Value
Age (Years)	30.0 ± 5.78	27.82 ± 6.36	0.007
Gestational Age (Weeks)	30.21 ± .32	31.45 ± 2.81	0.003
Weight (Kg)	74.04 ± 7.06	81.63 ± 8.00	<0.001

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BMI	26.83 ± 3.16	29.51 ± 2.96	<0.001
SBP (mm/Hg)	124.99 ± 3.12	166.25 ± 11.21	<0.001
DBP (mm/Hg)	83.64 ± 1.80	36.23 ± 20.85	<0.001

In the normotensive pregnancy, TCwas found 174.88 ± 13.50 mg/dl, TGs184.65 ± 12.30 mg/dl, LDL 70.92 ± 2.62 mg/dl and HDL 40.08 ± 12.45 mg/dl. Whereas in preeclampsia group, TC were 210.14 ± 20.40 mg/dl, TGs 214.90 ± 15.59 mg/dl, LDL 101.78 ± 2.72mg/dl and HDL 34.23 ± 20.85 mg/dl. The mean levels of TC, TGs and LDL were significantly higher in women with preeclampsia compared to normal controls (p <0.0001), as shown in table 2. Conversely, the mean levels of HDL were significantly lower in women with preeclampsia than in normal controls (p = 0.0169). This study showed notable variations in lipid profileof cases and control group. The findings (mean ± SD) for these parameters are detailed in table 2.

Table 2: Lipid Profiles of Preeclampsia and Normotensive Pregnant Women(n=200)

Variables	Control (Mean ± SD)	95% CI		Cases (Mean ± SD)	95% CI		p-Value
		Upper	Lower		Upper	Lower	
Total Cholesterol (mg/dL)	174.88 ± 13.50	177.419	172.363	210.14 ± 20.40	213.97	206.319	<0.001
Triglyceride (mg/dL)	184.65 ± 12.30	186.993	182.329	214.90 ± 15.59	218.804	210.996	<0.001
LDL (mg/dL)	70.92 ± 2.62	73.226	68.62	101.78 ± 2.72	104.701	98.87	<0.001
HDL (mg/dL)	40.08 ± 12.45	40.59	39.5	34.23 ± 20.85	36.76	35.72	0.017

Estimation of minerals and electrolyte values in table 3 revealed Mg levels of 2.40 ± 0.25 mg/dl, Ca 8.69 ± 0.54 mg/dl, Na 137.35 ± 3.04mEq/L and K 3.78 ± 0.26mEq/L in control group. In preeclampsiagroup, Mg levels were 1.37 ± 0.35mg/dl, Ca 7.55 ± 0.42mg/dl, Na 147.55 ± 4.26mEq/L and K .15 ± 0.37mEq/L. Statistically, magnesium, calcium and potassium levels were lower in cases presenting with preeclampsia compared to controls (p <0.0001). Comparatively, sodium levels were high in preeclampsia women(p<0.0001)as detailed in table 3.

Table 3: Electrolyte Parameters of Pre-eclampsia and Normotensive Pregnancy(n=200)

Variables	Control (Mean ± SD)	95% CI		Cases (Mean±SD)	95% CI		p-Value
		Upper	Lower		Upper	Lower	
Mg (mg/dL)	2.40 ± 0.25	2.45	2.358	1.37 ± 0.35	1.431	1.303	<0.001
Ca (mg/dL)	8.69 ± 0.54	8.795	8.594	7.55 ± 0.42	7.633	7.475	<0.001
Na (mEq/L)	137.35 ± 3.04	137.929	136.80	147.55 ± 4.26	148.35	146.80	<0.001
K (mEq/L)	3.78 ± 0.26	3.835	3.740	3.15 ± 0.37	3.195	3.055	<0.001

DISCUSSION

The thorough evaluation of the lipid profile, including TC, TGs, LDL-C, and HDL-C levels, along with key minerals such as sodium, potassium, magnesium, and calcium, highlights the multifaceted nature of preeclampsia. Notably, in this study, preeclamptic pregnant women exhibited significantly lower HDL-C levels. In this study, we observed significantly elevated TC, TGs, LDL in preeclampsia, indicating abnormal lipid metabolism. Preeclampsia is typically associated with hypertriglyceridemia. This study also found decreased HDL-cholesterol levels, which are consistent with findings from other research studies on preeclampsia women [6]. Similarly, Tesfa E *et al.*, established a connection between preeclampsia and elevated TG and LDL-C levels in the African population [14]. Yadav S *et al.*, found that preeclamptic patients had significantly higher levels of blood TGs and free fatty acids [15]. Li J *et al.*, observed similar results in the Chinese population [16]. Additionally, a study by Ebogo-Belobo JT *et al.*, in Africa and Sakarde A *et al.*, demonstrated that TC and LDL-C levels are linked to blood pressure, highlighting the complex interaction of lipid parameters in the endothelial damage associated with the pathogenesis of the disease [17, 18]. In the present study, preeclampsia patients exhibited decreased levels of magnesium, calcium, and potassium, while sodium levels were increased compared to the controls. Ahmed NA *et al.*, reported similar findings [19]. Additionally, Aslam F *et al.*, noted reduced calcium and magnesium levels in preeclamptic patients in the South-Punjab region of Pakistan [20]. This study provided valuable insights in identification of biomarkers that are potential basis for PE. In clinical practice, these biomarkers could facilitate the timely detection of at-risk cases, potentially reducing the rate of feto-maternal complications. Timely diagnosis allows for the implementation of targeted interventions, effectively managing the devastating effects of Preeclampsia (PE) in routine clinical practice. Despite identifying significant findings, the study has certain limitations, including being conducted in a single hospital; there is a risk of selection bias, which may hinder the generalization of the findings to other populations or healthcare setting. Measurement bias could also impact the generalizability. Despite using standard laboratory procedures to measure biochemical parameters, variations in manual techniques and equipment calibration could introduce inconsistencies that affect the accuracy and reliability of the results across different settings. In future, there is a need to conduct multi-centered studies to effectively evaluate the effect of biomarkers on preeclampsia.

CONCLUSIONS

The study reveals significant changes in the lipid profile and mineral levels in preeclampsia patients. Notably, TC and TGs within the lipid profile, as well as calcium (Ca) and magnesium (Mg) among minerals, all demonstrated a strong association with blood pressure. These findings suggest that these parameters could potentially serve as biomarkers for preeclampsia. Integrating these parameters in clinical approach provides effective perinatal outcomes.

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Authors Contribution

Conceptualization: MFJ
Methodology: MFJ, SS
Formal analysis: SR, JHQ
Writing, review and editing: SA[1], SA[2]

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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Prevalence of Extensively Drug Resistant *Salmonella typhi* and its Susceptibility against Meropenem, Tigecycline, Fosfomycin and Azithromycin among Clinical Isolates from a Tertiary Care Hospital Laboratory

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ABSTRACT

The emergence of Extensively Drug-Resistant (XDR) *Salmonella typhi* in Pakistan has posed a significant public health challenge. Traditional antibiotics, including ampicillin, chloramphenicol, and fluoroquinolones, have become ineffective due to widespread resistance, necessitating the exploration of alternative treatment options. **Objective:** To assess the in vitro efficacy of four antibiotics fosfomycin, tigecycline, meropenem and azithromycin against XDR *Salmonella typhi* strains isolated from patients in Karachi, Pakistan. **Methods:** A cross-sectional study was conducted at the Department of Microbiology, Ziauddin University Hospital, Karachi, over six months. Blood samples from both inpatients and outpatients aged 1 to 60 years were collected for culture and sensitivity testing. Antibiotic susceptibility was determined using the standard disc diffusion method. Data were analyzed to evaluate the effectiveness of the selected antibiotics against XDR *Salmonella typhi*. **Results:** The susceptibility patterns of *Salmonella typhi* and XDR *Salmonella typhi* revealed that meropenem, azithromycin, tigecycline, and fosfomycin were effective in all tested samples. Conversely, antibiotics such as ampicillin, aztreonam, cefixime, ceftriaxone, chloramphenicol, co-trimoxazole, and ciprofloxacin demonstrated resistance, with varying patterns observed between *Salmonella typhi* and XDR *Salmonella typhi*. The distribution of XDR and Non-XDR *Salmonella typhi* cases by gender and age, with no significant association found between these variables and XDR status. **Conclusions:** Meropenem and azithromycin remain effective against XDR *Salmonella typhi*; however, fosfomycin and tigecycline present promising alternatives. These findings underscore the need for continuous surveillance and the development of new treatment strategies to combat the rising threat of XDR *Salmonella typhi* in Pakistan.

INTRODUCTION

Salmonella typhi is a gram negative enteric rod of the family *Enterobacterales.* When individuals become infected with Salmonellae they might present with a range of clinical symptoms, including Enteric fever, gastroenteritis and septicemia. In some cases, suppurative lesions may also develop [1]. According to the WHO, approximately 9 million people contract typhoid annually, and 110,000 die from it each year as of 2019 [2]. Based on international data, there are about 22 million new manifestations of typhoid fever annually, resulting in around 200,000 deaths? The regions of South Central and Southeast Asia have the highest rates of sickness and mortality [3]. Among countries in this region, Pakistan has the highest occurrence of typhoid fever, with a rough annual incidence of 412.9 cases per 100,000 individuals. According to a study, the rate of typhoid fever in Pakistan is 15.5/1,000 cases, seemed notably higher compared to other regions [4]. The primary antibiotics used for treating infections caused by

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Salmonella typhi, including chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole, have gradually become less effective due to the development of resistance. As a result, fluoroquinolones including ciprofloxacin have been adopted as a possible treatment option [5]. The omnipresent spread of *Salmonella typhi's* H58 Multi-Drug Resistant (MDR) haplotype has been an explicitly agitating development in current years. This MDR variation has developed wide spread in Asia and a few parts of Africa, and it is unsusceptible to a number of antibiotics, such as ampicillin, co-trimoxazole, chloramphenicol, and some fluoroquinolones. Cephalosporins have therefore been employed as an empirical therapy option for typhoid infections arising due to this multidrug resistant strain [6]. There was a significant outbreak of typhoid fever that was reported in Pakistan in February of 2018. This strain of *Salmonella enterica* serotype *typhi* causing the outbreak was unsusceptible to many different antibiotics, such as ampicillin, trimethoprim-sulfamethoxazole, and chloramphenicol both third-generation cephalosporins and *fluoroquinolones* [7]. It was therefore termed as an extensively drug-resistant strain of *Salmonella typhi.* The XDR *typhi* strain is resistant to a wide range of antibiotics, including carbapenems [8]. It has become a major concern in Pakistan [9]. The Sindh region of Pakistan had 8,188 cases of typhoid fever between 2016 and December 2018, 5274 of which were classified as XDR *typhi,* according to data from the World Health Organization (WHO). Provincial Disease Surveillance and Response Unit reported these cases in 14 districts (PDSRU) [10]. In Sindh province, the highest number of XDR *typhi* cases were reported in Karachi, the provincial capital, accounting for 69% of all cases, Hyderabad district followed with 27% of the reported cases, while the remaining 4% were distributed across other districts in the province [8]. *Salmonella typhi* has the capability to rapidly transform from MDR to XDR by obtaining a plasmid, which imparts resistance to all standard treatment options. The outbreak of XDR *Salmonella typhi* in Pakistan has been attributed to a specific H58 clade which harbors an IncY plasmid that carries the CTX-M-15 gene bla, resulting in resistance against fluoroquinolones and ceftriaxone. This plasmid plays a critical role in the progression of resistance, enabling the organism to survive and persist in the face of various antibiotics treatment [8]. At present, meropenem and azithromycin are the two primary treatment options available for combating drug-resistant *Salmonella typhi.* However, a case of azithromycin resistance has been reported from India, indicating the need for continuing monitoring of treatment efficacy and the advent of antibiotic resistance in this bacterial pathogen [11, 12]. Given the limited options for treating Extensively Drug-Resistant (XDR) *Salmonella typhi,* this study seeks to evaluate the efficacy of four antibiotics: fosfomycin, tigecycline, meropenem, and azithromycin. The findings could inform their potential use in combating these highly resistant bacteria. The study particularly emphasizes the need to conserve azithromycin, due to its broad-spectrum effectiveness, and meropenem, given its high cost and critical role in treating XDR Salmonella typhi. Since both drugs have shown significant efficacy against XDR *Salmonella typhi,* we are investigating the in vitro effectiveness of fosfomycin and tigecycline as alternative treatment options for this infection.

The primary objective of this study was to assessed the in vitro efficacy of four antibiotics fosfomycin, tigecycline, meropenem, and azithromycin against XDR Salmonella typhi strains isolated from patients in Karachi, Pakistan..

METHODS

It was a cross-sectional study conducted at the Department of Microbiology at Ziauddin University Hospital, Karachi. The duration of the study was six months, from 1st January to 31st July 2021. After obtaining informed consent, blood samples for culture and sensitivity tests were collected from both inpatients and outpatients using a convenience sampling method. This method involved selecting samples based on their availability and accessibility within the healthcare settings where the study was conducted in Karachi, Pakistan. The study included both males and females with an age range 1 to 60 years. Blood samples for culture and sensitivity showing growth other than bacteria like fungus or yeast and repeat and duplicative sample from the same patient were excluded. Written approval was taken from the institutional ethical committee (Reference Code: 0611118ZIMIC) and permission from the management of Ziauddin Hospital was obtained. The sample size was calculated through WHO Sample size calculator, taking statistics for meropenem sensitivity as 87% margin of error as 9% and 95% Confidence interval, the sample size came out as 54 [1]. Additionally, the whole study included 204 blood samples among which *Salmonella typhi* included 57 blood samples while XDR included 147 blood sample. Before beginning any antibiotic therapy, all blood cultures were taken from a peripheral vein while following the correct aseptic procedures. Blood cultures were taken in regular BACTEC bottles for the adult population and in pediatric BACTEC bottles for the pediatric population. The blood to broth ratio was 1:10, and the sample was incubated for five days at 35.5°C ± 1.5°C in a BACTEC 9240 blood culture equipment. The BACTEC device detects the development of germs using a fluorescence sensing technology. A gram-stained smear of the broth was used to assess the microbial growth that the flag and audible sound of the device could detect. The bacteria were then subculture on 5% sheep blood agar, chocolate and MacConkey agar plates and incubated at 37°C for 18 to 24 hours in order to isolate the bacteria. The MacConkey agar plates were kept

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at 37°C aerobically in incubator while chocolate agar and sheep blood agar were incubated in capnophilic atmosphere (5-10 % CO_2), Identification of *Salmonella typhi* clinical isolates was performed by standard microbiological methods and their characteristic appearance on gram staining, the oxidase test, the catalase test, motility, Triple- Sugar Iron (TSI) fermentation, colony morphology and for the ultimate confirmation, biochemical tests of the analytical profile index (API 20 E) were used [13]. Antibiotic susceptibility pattern of the isolates was done by Modified Kirby Bauer disc diffusion method on Muller-Hinton-agar in accordance with CLSI recommendations [14, 15]. The Muller-Hinton agar plates were placed aerobically at 35°C ± 2 for 18-24 hours. The control strains used were of Staphylococcus aureus ATCC-25923® and Escherichia coli ATCC-25922®. Data were entered and analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0. The results were presented as frequencies and percentages, with the post-stratification chi-square test applied to assess significance, setting the threshold at $p \leq 0.05$. Gender was stratified to control for its potential confounding effects on the relationship between antibiotic resistance and the presence of XDR Salmonella typhi. Quantitative variables, such as patient age, were summarized using summary statstics, including mean and SD. Qualitative variables, including gender, presence of XDR Salmonella typhi, and resistance profiles, were displayed using frequency distributions and percentages.

RESULTS

Table 1 presented the CLSI criteria for antibiotic resistance, detailing disc content and corresponding resistance thresholds for various antibiotics. For example, chloramphenicol is resistant if the zone is ≤12mm, while ciprofloxacin is resistant at ≤20mm. Similarly, resistance thresholds for other antibiotics like ampicillin, ceftriaxone, and meropenem are specified, aiding in the accurate assessment of antibiotic efficacy and guiding effective treatment choices [14, 15].

Table 1: Interpretative Criteria According to CLSI

Antibiotics	Disc Content (µg)	Resistance (mm)
Chloramphenicol	30	≤12
Ampicillin	10	≤13
Trimethoprim-Sulfamethoxazole	1.25/23.75	≤10
Ciprofloxacin	5	≤20
Ceftriaxone	30	≤19
Cefotaxime	30	≤22
Cefixime	5	≤15
Aztreonam [12, 13]	30	≤21
Meropenem	10	≤19
Azithromycin	15	≤12
Fosfomycin	15	≤14

Table 2 displayed the interpretative criteria for antibiotic resistance based on guidelines from the FDA or EUCAST. It specifies that tigecycline, with a disc content of 15 µg, is considered resistant if the zone diameter is 14 mm or less. This criterion helps in evaluating the effectiveness of tigecycline against bacterial strains and informs appropriate treatment decisions.

Table 2: Interpretative Criteria According to FDA or EUCAST

Variables	Disc Content (µg)	Resistance (mm)
Tigecycline	15	≤14

Table 3 presented a total of 204 blood samples were included. The patient population was made up of 59.3% male and 40.7% female. XDR *Salmonella typhi* was detected in 72.1% of patients, while *Salmonella typhi* was found in 27.9% of patients.

Table 3: Age and Gender Statistic of Patients

Variables	N (%) / (Mean)
Gender	
Male	121 (59.3)
Female	83 (40)
Age	
Age (all Patient)	11.42
Age (<10 Years)	4.72
Age (>10 Years)	22.93

Table 4 represented that meropenem, azithromycin, tigecycline, and fosfomycin were sensitive to all the isolates. 68.4% sensitive to ampicillin; 94.0% to aztreonam and ceftriaxone; 94.7% to cefixime; 54.4% to chloramphenicol; 47.4% to co-trimoxazole; and only 7.0% to ciprofloxacin.

Table 4: Frequency Distribution Susceptibility Pattern of *Salmonella typhi* (n=57)

Antibiotics	Sensitive (S) N (%)	Resistant (R) N (%)	Total
Meropenem	57 (100)	0 (0)	57
Azithromycin	57 (100)	0 (0)	57
Tigecycline	57 (100)	0 (0)	57
Fosfomycin	57 (100)	0 (0)	57
Ampicillin	39 (68.4)	18 (31.6)	57
Aztreonam	53 (94.0)	4 (7.0)	57
Cefixime	54 (94.7)	3 (5.3)	57
Ceftriaxone	53 (94.0)	4 (7.0)	57
Chloramphenicol	31(54.4)	26(45.6)	57
Co-Trimoxazole	27 (47.4)	30 (52.6)	57
Ciprofloxacin	4 (7.0)	53 (93.0)	57

Sensitive = S Resistant = R

Table 5 represented that meropenem, azithromycin, tigecycline, and fosfomycin were sensitive to all the isolates while ampicillin, aztreonam, cefixime, ceftriaxone, chloramphenicol, co-trimoxazole and ciprofloxacin were resistant to all the isolates against extensively Resistant *Salmonella typhi*.

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Table 5: Frequency Distribution Susceptibility Pattern of Extensively Drug-Resistant *Salmonella typhi*(n=147)

Antibiotics	Sensitive (S) N (%)	Resistant (R) N (%)	Total
Meropenem	147 (100)	0 (0)	147
Azithromycin	147 (100)	0 (0)	147
Tigecycline	147 (100)	0 (0)	147
Fosfomycin	147 (100)	0 (0)	147
Ampicillin	0 (0)	147 (100)	147
Aztreonam	0 (0)	147 (100)	147
Cefixime	0 (0)	147 (100)	147
Ceftriaxone	0 (0)	147 (100)	147
Chloramphenicol	0 (0)	147 (100)	147
Co-Trimoxazole	0 (0)	147 (100)	147
Ciprofloxacin	0 (0)	147 (100)	147

Sensitive = S Resistant = R

Table 6 represented distribution of XDR and Non-XDR *Salmonella typhi* cases by gender. Among males, 89 cases (73.6%) were XDR *Salmonella typhi* and 32 cases (26.4%) were Non-XDR *Salmonella typhi*. Among females, 58 cases (69.9%) were XDR *Salmonella typhi* and 25 cases (30.1%) were Non-XDR *Salmonella typhi*, total 83 cases. The p-Value for the comparison between genders was 0.566, indicating no significant difference in the distribution of XDR and Non-XDR *Salmonella typhi* between males and females. The analysis also included stratification by age, categorizing patients into two groups: those aged ≤ 120 months and those aged > 120 months. The distribution of XDR and Non-XDR *Salmonella typhi* cases across these age groups showed no significant association, as indicated by a p-value of 0.103.

Table 6: Distribution of XDR and Non-XDR *Salmonella typhi* Cases by Gender

Gender	XDR *Salmonella typhi* N (%)	Non-XDR *Salmonella typhi* N (%)	Total	p-Value[(a)]
Male	89 (73.6)	32 (26.4)	121	
Female	58 (69.9)	25 (30.1)	83	0.566**
Total	147 (72.1)	57 (27.9)	204	
≤120 months	98 (76.0)	31 (24.0)	129	
>120 months	49 (65.3)	26 (34.7)	75	0.103**
Total	147	57	204	

Note: (a)**Chi Square test

Figure 1 mentioned that the four antibiotics meropenem, tigecycline, fosfomycin, and azithromycin exhibited 100% effectiveness against XDR *Salmonella typhi*, as all tested isolates were found to be sensitive to them. It also showed varying degrees of resistance, which demonstrates the challenge in treating XDR infections and reinforces the critical role of these effective antibiotics in managing resistant cases. The percentage of XDR *Salmonella typhi* isolated that were sensitive or resistant to various antibiotics, including meropenem, tigecycline, fosfomycin, and azithromycin. The data highlighted the effectiveness of these antibiotics against XDR strains.

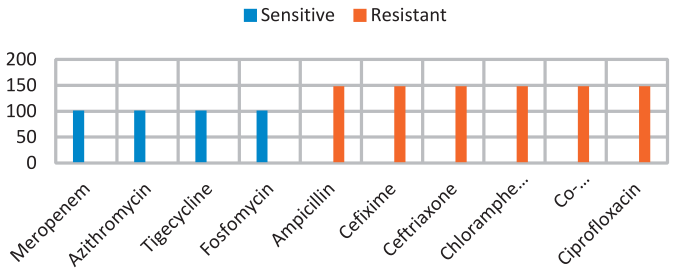

Figure 1: Susceptibility Pattern of Extensively Drug-Resistant *Salmonella typhi*

Figure 2 represented that antibiotic discs create zones of inhibition, which were clear were as around the discs where bacterial growth was prevented. The size of these zones indicates the effectiveness of the antibiotic against the bacteria. Antibiotic discs were placed on Muller-Hinton agar inoculated with XDR Salmonella typhi, and zones of inhibition were measured to determine bacterial resistance or sensitivity to the antibiotics tested.

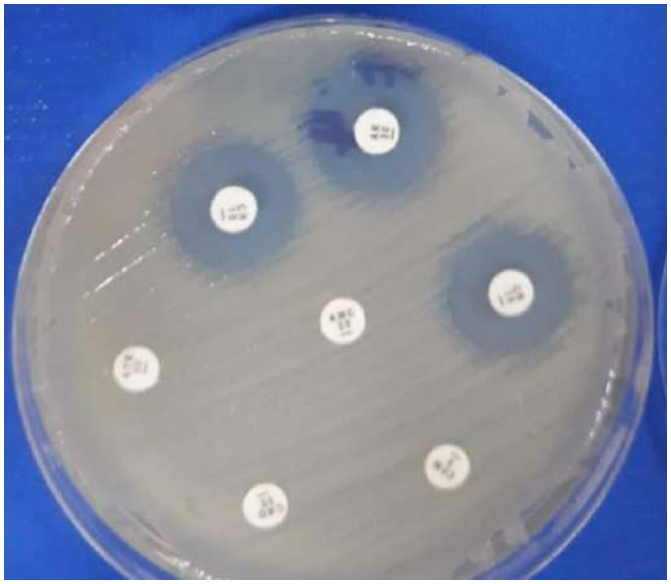

Figure 2: Modified Kirby Bauer Disc Diffusion Method on Muller-Hinton-Agar(Disc Showing Antibiotics).

DISCUSSION

The intent of this study was to address the issue of the emerging Extensively Drug Resistant (XDR) strain of *Salmonella typhi.* The previous treatment options for this strain, namely ampicillin, ciprofloxacin, ceftriaxone, chloramphenicol, and trimethoprim sulfamethaxazole, were once effective but their increasing resistance has made them less reliable. As a result, two new treatment options, meropenem and azithromycin, have been introduced. Azithromycin was an orally-administered antibiotic that was commonly used to treat typhoid fever, including in children. In our country, this antibiotic has been the preferred choice due to its effectiveness and low resistance rates. However, a recent case of extensively drug-resistant *Salmonella typhi* has been presented in a

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patient with suspected endocarditis and a prosthetic valve replacement [16, 17]. This strain was resistant to azithromycin, which was the first such case in our country. Fortunately, the patient responded well to intravenous meropenem treatment and had a smooth recovery. The resistance to azithromycin in *Salmonella typhi* was often linked to mutations in the AcrB efflux pump and the msrA gene [16-19]. Tigecycline was a broad-spectrum glycylcycline antibiotic that has been approved for the treatment of complicated skin and intra-abdominal infections, as well as community-acquired bacterial pneumonia. It has demonstrated in-vitro activity against both gram positive and gram-negative organisms. Due to its effectiveness against Multidrug-Resistant (MDR) Gram-negative bacteria, distinctly carbapenem-resistant Enterobacterales tigecycline was regarded as a last-resort antibiotic for the therapy of serious illnesse [20]. Fosfomycin was an antibiotic that kills bacteria by blocking the early stages of cell wall synthesis. It has a wide spectrum of activity for various types of Gram-positive pathogens, such as methicillin-resistant Staphylococcus aureus (MRSA), as well as drug-resistant Enterobacterales and Pseudomonas aeruginosa strains that produce Extended-Spectrum β-Lactamases (ESBLs) or were resistant to carbapenems. Fosfomycin was a likely choice due to its broad spectrum cover against the resistant organisms for the treatment of severe infections [20]. It was very beneficial in treating urinary tract infections as it can reach large amounts in urine. Despite the fact that fosfomycin was effective in treating resistant organisms, it's important to remember that there were few were restrictions on its usage. If it was continuously prescribed on routine infective cases it can lead to the development of resistance, also there was inadequate research regarding its safety and efficacy in specific populations, such as children and pregnant women Regardless of these disadvantages fosfomycin has proven to be a vital weapon against these resistant bugs. Based on its distinctive mode of action it provides to be an intriguing avenue for additional study and development [11]. Although often used to treat urinary tract infections, fosfomycin has shown benefit in the treatment of a variety of other infections, such as endocarditis, bacteremia and pulmonary infections [20]. In the dealing of Extensively Drug Resistant *Salmonella typhi* usage of meropenem and azithromycin along with tigecycline and fosfomycin can be used as an effective strategy.

CONCLUSIONS

As anticipated therapeutic drugs, azithromycin and meropenem have demonstrated good efficacy for the treatment of Extensively Drug Resistant *Salmonella typhi*. Additionally, fosfomycin and tigecycline have shown favorable in vitro results and can be adapted as an option in such cases.

Authors Contribution

Conceptualization: ZI
Methodology: FIA, HZ, YMP
Formal analysis: HZ
Writing, review and editing: AF, LF

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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Comparison of Serum Zinc and Iron Levels Among Pregnant Women of Rural and Urban Areas Visiting Tertiary Care Hospital Jamshoro

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ABSTRACT

Nearly two-thirds of pregnant women in underdeveloped nations suffer from anemia, which increases the risk of maternal illness and death as well as low birth weight for the baby. **Objective:** Hospitalized pregnant women from rural and urban locations were compared for iron and serum zinc levels in this study. **Methods:** Total 146 pregnant women were presented in this Comparative Cross sectional study. This study was conducted in Department of Pathology, Laboratory, Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad. A red tip simple tube and Ethylenediaminetetraacetic acid (EDTA) were used to disperse 10 milliliters of blood sample. Cobas 601 was used for the analysis of serum iron. Micro Lab 300 was used for the analysis of zinc and copper. **Results:** There were 66 (45.2%) females had age 21-25 years, followed by 32 (22%) cases had age 26-30 years, 28 (19.1%) cases had age 17-20 years and 20 (13.7%) cases had age >30 years. There were 96 (65.8%) cases had history of consuming iron folic acid. There were 67 (45.9%) cases had good meal intake per day. Anemia was found in 103 (75.5%) cases. It was found that deficiency of serum zinc in 86 (58.9%) cases. Frequency of serum ferritin level was severe low in 44 (42.7%) cases, 49 (47.5%) cases had low serum ferritin level and normal ferritin level was only observed in 10 (9.8%) cases. **Conclusions:** it was found that pregnant women have increased anemia rates. Rural pregnant women are more likely than metropolitan ones to have this condition.

INTRODUCTION

Among the many nutritional deficiency disorders that affect people around the world, anemia ranks high. While nutritional anemia can impact people of any age or gender, it disproportionately impacts women and is associated with low birthweight, maternal morbidity, and mortality [1]. Nutritional anemia is a serious health problem that impacts a large percentage of pregnant women in impoverished nations. The estimated frequency of anemia among non-pregnant women in underdeveloped countries is about 50% [1]. Nevertheless, a number of these women were already anemic before they became pregnant. According to reports, 26% of ever-married women in Pakistan's metropolitan areas and 47% of rural women suffer from anemia [2]. Anemia is similarly common among metropolitan pregnant women, with rates ranging from 29% [3] to 50% [4, 5] among those who visit antenatal clinics at a big private tertiary hospital in Karachi. Women in developing nations are more likely to experience anemia during pregnancy, and the causes of this condition vary greatly among regions [6]. The physiologic needs of the fetus and the expansion of the mother blood volume during pregnancy exacerbate iron deficiency, which is a result of chronic poor food intake and menstruation and is the main cause of anemia during pregnancy globally [6, 7]. Other variables include hereditary predisposition and inadequate personal cleanliness, both of which might increase the risk of infections and infestations [7]. Anemia has multiple causes, but one of them is a lack of iron in the body, which can happen when women don't eat enough. Iron deficiency is more common in women of childbearing age because of

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menstruation, and it becomes even more of a problem during pregnancy because of the increased metabolic demands and fetal growth. The World Health Organization has suggested that all women and girls in areas where the anemia burden is greater than 20% receive iron supplements as a means of combating the epidemic [8-10]. Despite the fact that various initiatives were able to lessen the worldwide impact of anemia by 12% from 1992 to 2011, these efforts failed to assist WRA residing in LMICs [10]. Further, iron's potential to alleviate anemia among WRA in LMICs is the subject of a plethora of epidemiological investigations, some of which are randomized controlled trials (RCTs). Although some meta-analyses and systematic reviews have synthesized the results of these RCTs, there are certain limitations and gaps in the meta-analyses conducted during the previous decade. Women who were pregnant were not included in this review; however, pregnant women who suffer from anemia throughout pregnancy and need to take extra precautions to prevent the detrimental effects on the mother and unborn child caused by iron deficiency anemia were not included either. On the other hand, non-pregnant women were left out of a different systematic review that was conducted in 2015 [11]. There is some evidence that observational cohort and quasi-experimental studies, which were heavily relied upon in the meta-analysis may have introduced residual and unmeasured confounding into the conclusions regarding the efficacy of iron therapy. Last but not least, a meta-analysis on the effects of iron treatment on women's physical exercise was carried out by Pasricha et al., in 2014, instead of focusing on iron deficiency markers as an outcome [12]. When compared to other South Asian countries, Pakistan has an even smaller percentage of pregnant women who take iron or folic acid supplements [13]. According to the available data, about 3,190 disability-adjusted life years (DALYs) may be prevented in the short and long term if iron supplementation was made available to women in order to reduce the prevalence of iron deficiency anemia [14]. To achieve this goal, first identify the demographics most impacted by iron deficiency anemia and the factors that tend to lead people to take iron supplements. There is a lack of national-level studies on the factors associated with iron consumption among women, especially during pregnancy, and while there is some evidence on the predictors of iron deficiency anemia among Pakistani women [15], our understanding of the factors is very limited overall. Despite research showing that iron supplements can help pregnant women with anemia, no studies in Pakistan have looked at what factors are linked to taking iron supplements while pregnant. This highlights the importance of conducting thorough research into the factors that influence iron consumption in Pakistan. To improve iron intake by pregnant women, it is necessary to have a comprehensive understanding of these factors. Only then can local strategies and specific interventions be developed.

Therefore, the purpose of this research was to examine what factors in Pakistani pregnant women are most likely to use iron supplements for at least 90 days. Furthermore, it was investigated these indicators in both rural and urban areas since it was hypothesized that they may differ depending on where people lived.

METHODS

This Comparative cross sectional study was conducted at Department of Pathology, Laboratory, Liaquat University of Medical and Health Sciences, Jamshoro, Hyderabad. Duration of 6 months, from July 2023-December 2023 with Reference No. LUMHS/REC/-40. A single population percentage sample size calculation formula was used to estimate the prevalence of zinc deficiency. The formula took into account the following factors: a 95% confidence level, a 5% margin of error, a 10% non-response rate, and an expected prevalence of 66.7% of zinc deficiency [23]. Pregnant women with age 17-45 years of rural and urban areas, those provided written consent with no chronic disease in history were included while non pregnant women of gynecological problems, women with diabetic disease or skin infection were excluded from this study. This study was conducted after ethical approval by the ethical review committee of LUMHS and a well-versed written consent was taken from the study patient or next of kin. A structured proforma was used for both cases and comparative group to collect data. A red tip simple tube and Ethylene diamine tetra acetic acid (EDTA) were used to disperse 10 milliliters of blood sample. Cobas 601 was used for the analysis of serum iron. Micro Lab 300 was used for the analysis of zinc and copper. Zinc present in the sample was chelated by 5-Br-PAPS. 2-(5-bromo-2-pyridylazo)-5-(N-sulfopropylamino) -phenol in the reagent. The formation of this complex was measured at a wave length of 560nm. Quantitative determination of iron in human serum are performed on Roche/Hitachi cobas c systems. Serum zinc deficiency was defined as <50 µg/dl and serum iron deficiency was defining as < 11 µg/dl. Data were analyzed by using SPSS version 23.0. Frequencies and percentages were used for categorical variables. T-test was used to compare the difference of outcome variables among (rural/urban) areas. P-value <0.05 was considered as statistically significant.

RESULTS

There were 66 (45.2%) females had age 21-25 years, followed by 32 (22%) cases had age 26-30 years, 28 (19.1%) cases had age 17-20 years and 20 (13.7%) cases had age >30 years (Figure 1).

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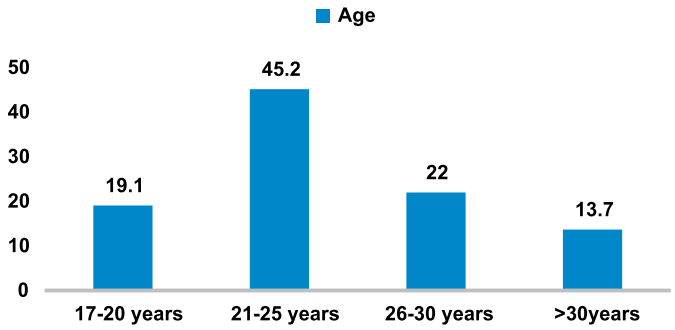

Figure 1: Distribution of study participants according to age ranges

Among all, 61 (41.8%) cases were had third trimester. Frequency of multi-gravidity was found in 95 (65%) cases. There were majority 107 (73.3%) cases had no any miscarriage/abortion history. Majority of the cases 102 (69.8%) were housewives. 112 (76.7%) cases had low socio-economic status. 95 (65.1%) cases had rural residency (Table 1).

Table 1: Demographics of the Pregnant Females (n=146)

Variables	N (%)
Trimester	
First	40 (27.4%)
Second	45 (30.8%)
Third	61 (41.8 %)
Multi-Gravida	
Yes	95 (65 %)
No	51 (35%)
Miscarriage/Abortion History	
Yes	39 (26.7%)
No	107 (73.3%)
Housewives	
Yes	102 (69.8%)
No	44 (30.2%)
Socioeconomic Status	
Poor	112 (76.7%)
Good	34 (23.3%)
Residence	
Rural	95 (65.1%)
Urban	51 (34.9%)

There were 96 (65.8%) cases had history of consuming iron folic acid. There were 67 (45.9%) cases had good meal intake per day (Table 2).

Table 2: Meal Intake and History of Consuming Iron/ Folic Acid (n=146)

Variables	N (%)
Consumption of Iron / Folic Acid	
Yes	96 (65.8%)
No	50 (34.25)
Meal Intake /Day	
Poor	67 (45.9%)
Good	79 (54.1%)

It was found that deficiency of serum zinc was reported in 86 (58.9%) cases. Higher percentage of deficiency was found in women of rural areas 34.2% as compared to urban resident with p value <0.005 (Table 3).

Table 3: Deficiency of Serum Zinc

Variables	Rural	Urban
Serum Zinc N (%)		
Normal	45 (30.8%)	15 (10.3%)
Deficient	50 (34.2%)	36 (24.7%)

Anemia was found in 103 (75.5%) cases (Figure 2).

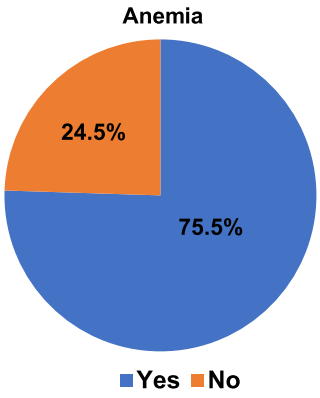

Figure 2: Frequency of Anemia among study participants

Frequency of serum ferritin level was severe low in 44 (42.7%) cases, 49 (47.5%) cases had low serum ferritin level and normal ferritin level was only observed in 10 (9.8%) cases. Significantly higher proportion was seen in women of rural areas with p value <0.05 (Table 4).

Table 4: Association of serum Ferritin Levels with residential status among Pregnant Cases

Variables	Rural	Urban	p-value
Serum Ferritin Level N (%)			
<12ng/mL	30 (29.1%)	14 (13.6%)	0.024
12-30ng/mL	33 (32.03%)	16 (15.5%)	0.018
31-300ng/mL	3 (2.9%)	7 (6.8%)	0.685
Total	66 (64.1%)	37 (35.9%)	0.002

DISCUSSION

Prevalence of anemia in this study was much higher than reported by Agrizzi VT *et al.*, from Tanzania. They reported a prevalence of 18.0% among the pregnant women in their study [16]. Anemia was one of the world's most prevalent prenatal diseases, with dietary iron deficiency being the most common factor. Maternal anemia has been linked to an increased like hood for both maternal and newborn complications. There are several factors that determine maternal nutritional status are multifaceted, and each one's influence changes depending on dietary habits, region, socio-demography, and season. The overall prevalence of anemia among pregnant women in the present study was 70.5% of which the majority of them were from rural settings compared to urban. This finding

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was consistent with findings reported by Kumar A *et al* [17]. Our findings related to the prevalence of anemia among pregnant women are consistent with previous studies carried out in different rural areas of the country, where the prevalence of anemia was reported to be between 41.0% and 77.0 % [18]. In our study, 21–25 years and 26–30 years age groups were found to be the most affected groups and categorized as high-risk groups as the majority of pregnant women with anemia were from this group. These findings are consistent with those reported by Wu S et al [19]. Our study demonstrated that the majority (37.0%) of participants have meat once a week while 27.7% of them never take meat. Another Pakistani study reported that the majority of their participants weren't consuming meat and they found a significant relation between meat consumption status and anemia among pregnant women. iron: heme iron, which was mostly found in foods containing animal flesh, and non-heme iron, which was the only type present in plant-based foods [20]. Moreover, most (52.7%) participants in our study replied that they never consumed green leafy vegetables, and 56.2% replied they take milk and its products on a regular basis. This may be due to the reason that there are two forms of dietary grains and vegetables. Zinc is a mineral that is essential and is recognized to be vital for the regular physiological processes of immune system. Its deficiency during pregnancy has negative effects on the mother as well as the growing fetus [21-23]. The consequences of the eventual delivery is associated with the adverse outcomes. In underdeveloped nations, zinc deficiency is widespread, and earlier studies have linked pregnancy problems to low maternal blood zinc concentrations.

CONCLUSIONS

It was concluded that prevalence of anemia was significantly high among the pregnant women. This prevalence was much higher among the pregnant women residing in rural areas compare to those residing in urban areas.

Authors Contribution

Conceptualization: SA[1]

Methodology: SA[1], KA

Formal analysis: IDU

Writing, review and editing: SA[2], NM, AHC

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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Exploring Variation in Root Canal Morphology of Maxillary Second Premolars: A Cone-Beam Computed Tomography Study in a Pakistani Subpopulation

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ABSTRACT

A comprehensive knowledge of anatomy of roots and root canals was a key for successful treatment outcomes. Maxillary second premolars often display variability in root and canal numbers. Traditional 2-dimensional imaging techniques have limitations in exact diagnosis of dental anatomy, encouraging the practice of Cone Beam Computed Tomography (CBCT) for comprehensive three-dimensional imaging. **Objective:** To explore the variations in the number of roots and root canals in maxillary second premolars using CBCT. **Methods:** The current study was a retrospective and conducted at the Radiology department of Fatima Memorial Hospital College of Dentistry, Lahore. A total of 143 CBCT scans with completely formed roots were included. Data were analyzed using Planmeca Romexis imaging software and statistical analysis was performed using SPSS version 23.0. **Results:** Among 143 individuals, the majority exhibited one root and one canal in maxillary second premolars. In terms of root number, 77% of the 2nd premolars had a single root and 23% had two roots. In relevance of root canals, 62.5% were found to have a single canal and 37.5% had two root canals. However, no any case was found having three roots and canals. Bilateral symmetry in root canal patterns was observed in most cases, with statistically significant differences between genders. **Conclusions:** The findings of this study may contribute to the understanding of variations in dental anatomy in Pakistani population and emphasize the importance of one's treatment approaches for optimal patient care.

INTRODUCTION

The most frequent dental problems for which the patients visit the dental Outpatient Department (OPD) is complaint of painful and carious dentition that may require Root Canal Treatment (RCT) or extraction of a tooth. One of the most considerable causes of root canal failure is missed canal and simple extraction leading to surgical extraction is Broken Down Root (BDR) during extraction [1]. For successful RCT and safe extractions, a comprehensive knowledge of the number of canals and roots is important. In addition to molars, premolars especially maxillary second premolars, are well known for their variability in root and canal numbers [2]. Maxillary 2nd premolars are expected to erupt between 10-12 years of age with roots development completed approximately at the age of 12-14 years. The maxillary second premolars are commonly known to have one canal in one root. However, studies conducted on various populations of the world disclosed that roots and canals in maxillary 2nd premolar may vary from one to three [3]. This variation is not only observed between various populations but also among individuals within the same population. Therefore, accurate knowledge of the root canal system is mandatory to prevent treatment failures [2]. Two-dimensional imagining technique that is routinely used in dental practice may result into challenging situations because of superimposition, distortion, and limited magnification,

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hindering accurate diagnosis and treatment planning [4]. To overcome such situations, Cone Beam Computed Tomography (CBCT) was emerged in 1988. It served as a revolutionary technique that has contributed to precise and accurate three-dimensional imaging of the oral and maxillofacial regions [1]. CBCT has additional advantages over conventional 2-dimentional imaging as it has the ability to reproduce more detailed images with accurate geometrical dimensions having less ionizing radiation exposure [4]. It enables detailed evaluation of pathologies of jaws, periapical lesions, root fractures, joint dysfunctions, and periodontal bone defects. By offering dentists incomparable insights, CBCT helps significantly to prevent the failure of root canal treatment [2, 5]. Therefore, the current study aims to explore the variability in the number of roots and root canals of the maxillary second premolar. This research is designed to enhance our understanding of population-specific variations of Pakistani population. To achieve this, CBCT was employed in this study as an observational tool to precisely identify variations in the number of roots and root canals in the maxillary second premolar.

METHODS

The current study was a retrospective study and it was conducted in the Radiology department of Fatima Memorial College of Dentistry, Shadman, Lahore. This study was approved by the Institutional Review Board of Fatima Memorial Hospital College of Medicine and Dentistry, having reference number FMH-16/05/2024-IRB-1408. The record of previously done CBCTs of the patients who had visited the radiology department of FMH college of Dentistry from October 2022 till March 2023 was taken. This study was retrospective and the collected record was anonymous only having information of gender and age of the patient. Therefore, the consent of the patient was not taken. The data were obtained by simple random sampling technique and sample size was obtained from the following formula: n=p(1-p) (Z/e)2, Effect size = 10%, 1-β at Desired Power of 0.9(90%)=1.28 A at desired level of significance of 0.05 (5%) =1.96, Constant proportion of 2nd root canal = 74.5%. The sample size according to above mentioned formula was 141. Patient selection criteria focused on individuals who had undergone CBCT scans and exhibited fully formed maxillary second premolars. Consequently, participants aged 12 years and above, with maxillary second premolars intact for dental treatment purposes, were included. Exclusions were made for patients lacking maxillary second premolars or falling below the age threshold of 12 years. Imaging procedures relied on CBCT technology calibrated to 90kV and 10 mA, with an exposure duration of 12 seconds. Scan dimensions were standardized to a diameter and volume of 100mm and 80mm, respectively, with a slice thickness of 0.35mm. Images were evaluated using Planmeca Romexis imaging software version 6.0.0.3 on a 24 inches monitor in a dim light. The CBCT images of maxillary premolars were observed in axial, coronal and sagittal planes by all the investigators of this study having interval of few days between the assessments. The proforma documented patient demographics, including age and gender, as well as the number of roots and root canals for both right and left Maxillary 2nd premolars. After the completion of data collection, statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 23.0. Categorical variables were presented as frequencies and percentages to provide a comprehensive overview of the dataset. To assess the significance of differences between genders and between the right and left sides, the Chi-square test was employed. A significance level of 0.05 or lower was considered statistically significant, adhering to standard conventions in hypothesis testing

RESULTS

In the present study, 143 individuals participated, with a mean age of 36 years and standard deviation of 13.83. Among them, five patients lacked a right 2nd premolar, and nine lacked left 2nd premolar, leaving 138 right and 134 left premolars, totaling 272, for analysis. Of the participants, 40% (n=57) were male and 60% (n=86) were female. In terms of root configuration, 77% (n=209) of the 272 maxillary 2nd premolars had a single root, while 23% (n=63) exhibited two roots; none presented with three roots (Table 1).

Table 1: Variation in Number of Roots of Maxillary 2nd Premolar

Root/s	Left N (%)	Right N (%)	Total N (%)
One Root	104 (78)	105 (76)	209 (77)
Two Roots	30 (22)	33 (24)	63 (23)
Three Roots	0	0	0
Total	134	138	272

Upon examination of the root canals of the maxillary 2nd premolar, it was observed that 62.5% (n=170) had a single canal, while 37.5% (n=102) exhibited two root canals. Notably, no instances of three root canals were detected in any of the maxillary 2nd premolars analyzed (Table 2).

Table 2: Variation in Number of Canals of Maxillary 2nd Premolar

Canal/s	Left N (%)	Right N (%)	Total N (%)
One Canal	87 (65)	83 (60)	170 (62.5)
Two Canal	47 (35)	55 (40)	102 (37.5)
Three Canal	0	0	0
Total	134	138	272

While the predominant observation revealed one root and one canal, variations were noted in the presence of one or two canals within a single root (Table 3).

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Table 3: Root Number and Root Canal Pattern in Left and Right Quadrants

Root/s and Canal/s	Left N (%)	Right N (%)	Total N (%)
One Root One Canal	87 (65)	83 (60)	170 (62.5)
One Root Two Canals	18 (13.4)	22 (16)	40 (14.7)
Two Roots Two Canals	29 (21.6)	33 (24)	62 (22.7)
Total	134	138	272

Among the 272 premolars examined, 62.5% (n=170) exhibited one root and one canal, 14.7% (n=40) displayed two canals within a single root (Figure 1),

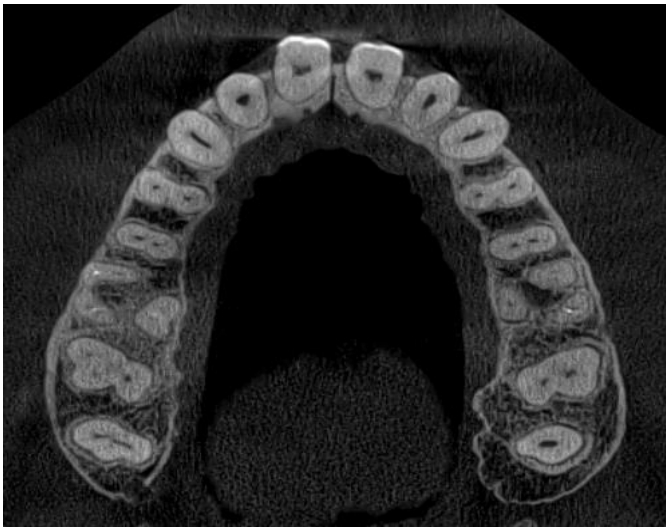

Figure 1: Maxillary Second Premolars Exhibiting a Single Root with Two Canals in Both Quadrants

In the study, 22.7% (n=62) of the maxillary second premolars were found to have two roots, each containing two root canals (Figure 2).

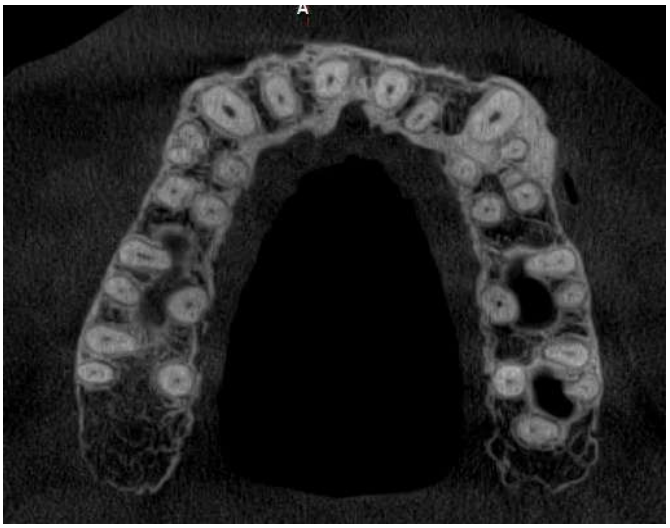

Figure 2: Maxillary Second Premolars Exhibiting Two Roots With Two Canals Each In Both Quadrants

Bilateral variation in root canal patterns was evident in only 14% (n=20) of individuals, with 76% (n=110) exhibiting bilaterally consistent patterns of root canals and root numbers on both sides. A statistically significant p-value of 0.000 was obtained upon comparison of right and left quadrants. The most prevalent pattern observed was one root with one canal in both males and females. Among the 111 maxillary second premolars of males examined, 56% (n=62) featured one root with one canal, 18% (n=20) displayed one root with two canals, and 26% (n=29) exhibited two roots with two canals each. Conversely, among the 161 maxillary second premolars of females, 67% (n=108) had one root with one canal, 12.4% (n=20) had one root with two canals, and 20.4% (n=33) had two roots with two canals. Although not statistically significant (p=0.12), females showed a higher tendency toward a single root with one canal, whereas males exhibited a greater tendency toward two canals in one root and two roots with two canals each (Table 4).

Table 4: Comparison of Root Number and Canal Pattern between Male and Female

Root/s and Canal/s	Male N (%)	Female N (%)	Total N (%)
One Root One Canal	62 (56)	108 (67)	170 (62.5)
One Root Two Canals	20 (18)	20 (12.4)	40 (14.7)
Two Roots Two Canals	29 (26)	33 (20.4)	62 (22.7)
Total	111	161	272

DISCUSSION

Dental morphology and root canal anatomy play a crucial role in dentistry, supplying valuable insights into the complex and diverse anatomy of teeth [6]. The first step in achieving a successful endodontic result was the evaluation of the root canal system and its anatomical variations. Therefore, sufficient knowledge should be there to avoid the failure of root canal treatment and a traumatic extraction. Usually, it was considered that maxillary 2nd premolars have one root and one canal only. But there was probability of this tooth to be having more than one root and canal [7]. The present study was designed to evaluate the prevalence of extra roots and canals in maxillary 2nd premolar among the population of Lahore by using CBCT. In this study, Cone Beam Computed Tomography (CBCT) served as the primary assessment tool for evaluating root canal morphology and numbers. This technology enables detailed visualization of anatomical structures in axial, coronal, and sagittal planes, facilitating more precise observations compared to conventional radiographs. Additionally, CBCT obviates the need for tooth extraction, allowing for comprehensive comparisons of both dental quadrants within individual subjects [8]. Significant variations in root canal morphology and numbers were known to exist among diverse global populations, as well as within specific national demographics. However, limited data regarding these parameters were available for the Pakistani population. Therefore, the present investigation aimed to explore the variability in root and canal configurations within the

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Pakistani subpopulation residing in Lahore. The results of the present study showed that single root was the most common finding (77%) followed by two roots (23%) while no case was found to have three roots. Regarding the number of root canals, 62.5% of the sample population had 1 canal, 37.5% had two canals while no case of three canals in maxillary 2nd premolar was found. These results were in line with another study conducted by Yan Y *et al.*, in 2021 who also reported that a single root was the most prevalent finding, accounting for 94.2% of cases, with only 5.8% of teeth exhibiting two roots. Additionally, they observed that single canals were present in 55.1% of cases, while two canals were found in 44.7% of cases, and three canals were detected in only 0.2% of cases [5]. The finding of three canals is not in line with the current study. The results of another study conducted by Al-Zubaidi SM *et al.*, on Saudi Arabian population in 2021 were also in consistent with the results of present study as they also described that one root was found most frequently in 83.2%, two roots in 15.8% and only 1% sample population had three roots [9]. Similarly, Asheghi B *et al.*, in Brazil in 2019 reported one root in 71.2% of cases, two roots in 28.4% of cases, and three roots in 0.4% of cases using CBCT imaging [10]. Furthermore, Alqedairi A *et al.*, conducted a study in Saudi Arabia in 2018, where 85.2% had one root, 14.5% had two roots, and 0.3% had three roots [11]. Although the results of the above-mentioned studies were consistent with the present study in terms of the most frequent finding. But in many populations, three roots and canals were also found diverging from our results. However, a study by Martins JN *et al.*, in 2018 on the Portuguese population and Felsypremila G *et al.*, in 2015 in India Indian population reported that no cases exhibited three roots, consistent with the findings of the current study [12, 13]. Neither this study nor theirs observed any radiographs with three roots and canals. Abella F *et al.*, in 2015 studied a population in Spain (n=374), where one root was observed in 82.9% of cases, two roots in 15.5% of cases, and three roots in 1.6% of cases [14]. Yang L *et al.*, in their 2014 study on the Chinese population (n=392), found that 86.5% of individuals had one root, 13.5% had two roots, and no cases exhibited three roots, aligning with our findings [15]. The results of the present study showed that males exhibited a higher tendency to have two canals as compared to the females. Similar results were found in Turkey in 2014 by Ok E *et al.*, and one canal was more frequently found on the left side, while two canals were more common on the right side [16]. Many populations worldwide have been assessed for the root number and morphology of the maxillary 2nd premolar, including studies conducted on the Pakistani population. However, variations were observed, particularly concerning the presence of three roots. Although, the most prevalent root number was one root, typically with one canal. But a clear variation was observed in percentage for these entities in Pakistani sub-population. The current study aimed to have knowledge of variation in root number and canals in various populations of the world. However, variation was observed within the Pakistani population. Various areas of Pakistan showed variation in results. For instance, three roots were not found in current study but Shah SA conducted a study in 2023 in Peshawar, reporting that among the study population, 58.27% were single-rooted, 41.35% were two-rooted, and 0.37% were three-rooted [1]. On the other hand, Hanif F *et al.*, conducted a study in Islamabad in 2022, and explored one root as the most common finding and one canal as the most common canal configuration, consistent with the present study [17]. Furthermore, Dil F *et al.*, in 2022 found out that the population in Peshawar had most commonly one canal (54%), followed by two canals (46%) and only 1% had three canals [18]. However, Alkahtany MF *et al.*, studied the number of roots and canals in Peshawar in 2021, reporting that 96.7% of teeth had a single root, 3.3% were two-rooted, and no teeth had three roots. Contrary to the current study, they found a higher prevalence of having two canals instead of one, with 73.3% of teeth having two root canals, while 26.7% had one canal. However, similar to the present study, no maxillary second premolar was found to have three roots or three canals [19]. The findings of a study in Peshawar regarding the prevalence of root canals were comparable to those of Hussain SM *et al.*, in 2020 in Rawalpindi. Both studies observed that the majority of patients, with 150 cases (75%), exhibited a two-canal system, while 50 cases (25%) showed a single canal configuration [20]. Moreover, similar to current study, Nazeer MR *et al.*, conducted a study in 2018 in Karachi, Pakistan, showing that out of 115 cases, one root was observed in 84.3%, two roots in 15.7% and no cases had three rooted premolars. Additionally, they reported one canal in 49.6% of cases, two canals in 48.7% and three canals in 1.7% [21]. Another study in Karachi by Sardar KP *et al.*, in 2006, utilizing the shift cone technique during root canal treatment, found that out of 43 males, 63% had two canals, and out of 57 females, 53% had two canals, with no significant difference between the two groups contradicting the frequent one canal finding in the current study [22].

CONCLUSIONS

Understanding the intricate anatomy of teeth, particularly the root canal system, was essential for successful dental treatments like root canal therapy and extractions. Variability in the number of roots and canals, especially in premolars like the maxillary second premolar, underscores the importance of precise diagnostics. Our study enhances the understanding of root canal morphology in maxillary second premolars, aiding clinicians in providing more precise and effective dental care. This knowledge can help prevent treatment complications and ensure better outcomes for patients undergoing dental interventions.

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Additionally, this study concluded that variations in dental anatomy are not only observed among different populations worldwide but can also be found within the same country's population across different ethnic groups. Specifically, variations were observed in the Punjabi, KPK, and Sindhi populations. Further research with broader population samples and more geographical areas can deepen our understanding of dental anatomy and its clinical implications.

Authors Contribution

Conceptualization: SB
Methodology: SMA, SB
Formal analysis: SB, FS
Writing, review and editing: SMA, NI, AI, MAA, SB

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

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Comparative Effects of Preoperative Carbohydrate Loading and Fasting on Recovery Outcomes in Colorectal Surgery

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ABSTRACT

Preoperative oral carbohydrate treatment improves postoperative recovery. Fasting before surgery increases stress response and insulin resistance. **Objective:** To examine the effects of preoperative oral carbohydrate loading and traditional fasting on gastrointestinal function, independent walking time, and hospital stay after colorectal surgery. **Methods:** A quasi-experiment study with 90 individuals diagnosed by extensive history, clinical examination, and pertinent investigations split patients into Group A and Group B. General Anesthesia was used for all surgeries. Group A had surgery after 6 hours of nil per os, whereas Group B had a clear carbohydrate drink 14 hours before surgery and another 2 hours before anesthesia induction. Up to 72 hours after surgery, bowel noises, first flatus and feces, and time to independent ambulation were monitored. **Results:** The conventional approach in Group A produced a mean time of 51.4 ± 5.2 hours for bowel sounds, 62.9 ± 6.5 hours for first flatus, 77.95 ± 1.00 hours for defecation, 82.73 ± 9.6 hours for independent ambulation, and 5.02 ± 1.4 days for hospital stay. Group B, who received oral carbohydrate loading therapy before surgery, had shorter times for bowel sounds (43.5 ± 9.1 hours), first flatus (54.8 ± 4.6 hours), defecation (67.5 ± 11 hours), and independent ambulation (72.7 ± 6.6 hours), but a similar hospital stay (5.02 ± 1.49 days Hospital stay was not substantially different (p-value = 0.744), but surgical results were (0.000). **Conclusions:** Oral carbohydrate loading before colorectal surgery improves gastrointestinal function, speeds independent walking, and reduces hospital stays.

INTRODUCTION

Preoperative oral carbohydrate therapy shows good postoperative recovery [1]. Preoperative fasting increases the risk of postoperative stress response and postoperative insulin resistance [2]. The stress response is characterized by inflammatory cytokine, pituitary, and sympathetic changes, leading to lipolysis, hyperglycemia, nitrogen loss and postoperative insulin resistance. Peripheral insulin resistance causes less glucose uptake and hyperglycemia; on the other side, hepatic insulin resistance increases gluconeogenesis, leading to "diabetes of injury" [3]. Enhanced Recovery After Surgery (ERAS) perioperative protocols includes a shift from conventional fasting to preoperative oral carbohydrate loading practices [4]. Preoperative carbohydrate loading boosts the immune response, reduces inflammatory cytokine response, and has a good outcome of decreased surgical site infections [5]. Postoperative outcomes are measured in many ways ranging from time to return of GI function, time to first flatus, time to independent ambulation and hospital stay [6]. All these domains are measured and need to be measured to determine surgery and postoperative outcomes [7]. Outcomes are measured to find out the best possible outcome [8]. Preoperative intake significantly influences insulin levels and body

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physiology, whether through oral or intravenous routes. Nil per oral status, indicating no intake, also profoundly impacts body physiology. Preoperative diet or carbohydrate loading effect postoperative recovery; for example, it affects the time to return of GI function, patient if nil per oral or carbohydrate loading, and it is time latency to operation time affects the time to first flatus postoperatively [9]. Same way fasting preoperatively, which is explained as pure nil per oral six hours before surgery [10]. Preoperative fasting induces metabolic stress and insulin resistance, impacting factors like time to independent ambulation and hospital stay, which are influenced by carbohydrate intake timing and route, including nil per oral status [11]. In terms of time to independent ambulation, time to flatus, time of the return of GI function and time of defecation postoperatively and also hospital stay is also strongly affected by carbohydrate loading, time of its intake preoperatively or no carbohydrate intake at all before surgery affects postoperative outcome also affect its postoperative outcomes [12]. Stress-induced high blood sugar levels, common in critically ill patients, influence both preoperative condition and postoperative recovery, irrespective of diabetes, due to the release of counter-insulin hormones. Various colorectal surgeries, including colectomy, hemorrhoidectomy, and others, were performed, with surgical protocols like antibiotic use or carbohydrate loading having significant effects on postoperative recovery, particularly on outcomes such as ambulation, GI function, and defecation [13]. The timing of carbohydrate ingestion in relation to surgery affects postoperative results by affecting inflammatory pathways and interleukin 6 (IL-6) levels. Preoperative carbohydrate loading has been demonstrated in numerous clinical trials to decrease hospital stay, peripheral insulin resistance, and the duration needed for the return of gastrointestinal functions and resumption of work [14,15]. Surgery is a significant process that brings physiological changes in body that prompts metabolic changes. Postoperative insulin resistance contributes to hyperglycemia, which is linked to adverse clinical outcomes, complications, and prolonged hospital stays. To improve perioperative care and outcomes, institutions have developed pathways focusing on managing surgical patients to alleviate physiological stress during procedures [16]. Perioperative dietary approaches encompass fasting or carbohydrate provision, with increasing attention to nutrition. Preoperative carbohydrate loading is advocated by various experts across surgical specialties, showing promising benefits for patient outcomes and mitigating postoperative insulin resistance [17,18].

This study aimed to assess the efficacy of preoperative oral carbohydrate loading and conventional fasting in colorectal surgery in return for gastrointestinal function, time to independent walking and hospital stay.

METHODS

The study, a quasi-experiment study, was conducted at Benazir Bhutto Hospital in Rawalpindi, Pakistan for 6 months from July 2021 to 2022. Patients meeting predefined criteria were selected from the outpatient department after obtaining informed consent. Included were those undergoing open colorectal surgery on elective list and aged between 20 to 65 years old; those detected with stage 4 colorectal malignancy, urgent colorectal surgery, diabetes mellitus, increased risk of gastric content aspiration, immune-modulatory therapy, and history of any drug allergy were excluded from the study. Convenient sampling technique was used. They were divided into two groups, Group A and Group B. Group A underwent surgery after a 6-hour fasting period, while Group B received a clear carbohydrate drink before surgery. General anesthesia was administered for all surgeries, and postoperatively, patients received antibiotics and analgesics. Time to return of bowel sounds, first flatus passage, defecation, independent ambulation, and total hospital stay duration were recorded up to 72 hours post-surgery, with discharge upon tolerating a soft diet. The sample size was determined using the powertwo means analysis of the statistical software Stata [19]. With an alpha threshold of less than 0.05, study power used 80% and 95% confidence levels. With 45 patients in each group, the computed sample size was 90. Attached in Apendix. The findings were displayed as (mean ± SD) values. At the probability level of < 0.05 statistical significance was acknowledged. The paired-t test was used to compare the times for bowel noises, first flatus, defecation, independent walking, and hospital stay days for intergroup comparisons. The Independent t-test was used to compare the groups. All analysis were performed using SPSS version 25.0. Ethical approval was received by the Ethical Review Committee (ERC) Rawalpindi Medical University and Allied Hospitals Rawalpindi under Ref No: 61/REF/RMU/2021.

RESULTS

Figure 2 showed the distribution of gender male and female respectively. Graph shown the 40% female which were 36 in quality and 60% were male which 54 in quantity were.

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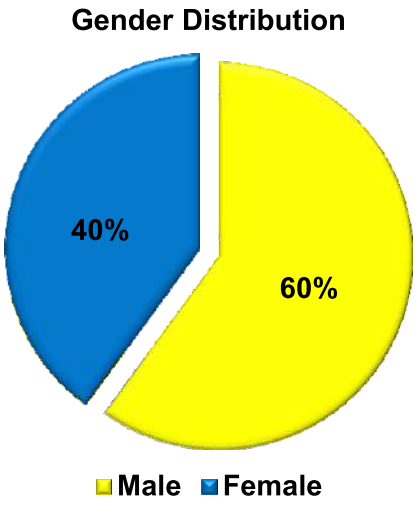

Figure 2: Quantity of Sample Gender Wise Distribution

Table 1 showed the time to first flatus and time to defecation in two groups. It describes the Comparing time to return to bowel sounds (Hours).

Table 1: Comparing Time to Return to Bowel Sounds (Hours) (n=45 per Group)

Outcome Measures	Group	(Mean ± SD)	p-Value
Time to Return to Bowel Sounds	Group A Conventional Fasting	51.48 ± 5.28	0.000
	Group B Preoperative Oral Carbohydrate Loading Therapy	43.53 ± 9.12	
Time to First Flatus	Group A Conventional Fasting	62.93 ± 6.53	0.000
	Group B Preoperative Oral Carbohydrate Loading Therapy	54.80 ± 4.60	
Time to Defecation	Group A Conventional Fasting	77.95 ± 6.745	0.000
	Group B Preoperative Oral Carbohydrate Loading Therapy	67.53 ± 11.104	

Table 2 showed the time to first flatus and time to defecation in two groups. It describes the Gender Stratification and Comparing time to return to bowel sounds (Hours).

Table 2: Gender Stratification and Comparing Time to Return to Bowel Sounds (Hours) (Male (n=27), Female (n=18)

Outcome Measures	Group	Gender	(Mean ± SD)	p-Value
Time to Return to Bowel Sounds	Group A	Male	52.14 ± 6.06	0.311
		Female	50.50 ± 3.79	
	Group B	Male	44.85 ± 11.05	0.239
		Female	41.55 ± 4.63	
Time to First Flatus	Group A	Male	52.14 ± 6.06	0.653
		Female	50.50 ± 3.79	
	Group B	Male	63.29 ± 7.57	0.223
		Female	41.55 ± 4.70	
Time to Defecation	Group A	Male	77.92 ± 6.37	0.972
		Female	78.00 ± 7.45	
	Group B	Male	65.51 ± 13.16	0.138
		Female	70.05 ± 6.15	

DISCUSSION

The average time for the return of bowel sounds was 47.5 ± 8.4 hours, while the mean time for the passage of the first flatus was 58.8 ± 6.9 hours, and defecation occurred at 72.7 ± 10.5 hours postoperatively. Independent ambulation was achieved at 77.7 ± 9.6 hours, and the average hospital stay was 5.07 ± 1.60 days. In the conventional group (Group A), the time for the return of bowel sounds was 51.4 ± 5.2 hours, whereas in Group B, which received preoperative oral carbohydrate loading therapy, it was 43.5 ± 9.1 hours. An independent T-test revealed a significant difference between the two groups in the time for the return of bowel sounds (p-value = 0.000). Previous research suggests that postoperative mortality may decrease with insulin treatment, but similar outcomes can be achieved through strategies like preoperative carbohydrate loading and immune nutrition, indicating the potential benefits of optimizing preoperative nutrition for improved outcomes [20]. In the conventional group, the mean time for the passage of the first flatus was 62.9 ± 6.5 hours, while in Group B, where patients received preoperative oral carbohydrate loading therapy, it was 54.8 ± 4.6 hours. A significant difference was observed between the two groups in the time for passage of the first flatus (p-value = 0.00). Similarly, the mean time for defecation was 77.95 ± 1.005 hours in the conventional group and 67.5 ± 11 hours in Group B, indicating a significant difference (p-value = 0.00). Additionally, the mean time for independent ambulation postoperatively was 82.73 ± 9.6 hours in the conventional group and 72.7 ± 6.6 hours in Group B, with a significant difference between the two groups (p-value < 0.001). This suggests that perioperative dietary supplementation, particularly preoperative oral carbohydrate loading therapy, may positively influence postoperative outcomes in patients undergoing gastrointestinal procedures. Qin PP *et al.*, reported that experimentation included: protein supplementation (preoperative day 30-6), "immunonutrition" (preoperative day 5-1 and postoperative day 1-5) and carb loading surgical or medical procedure day [21]. 90-day postoperative confusion rate, including postoperative irresistible complexities, diminished span from enlistment to medical procedure from 4 weeks to about fourteen days. And it was concluded that blood glucose and other metabolic outcomes of body return back to normal faster in healthy individuals as compared to those diseased and in those who used fluid carbohydrate therapy as compared to those who fasted before surgery. In the conventional group mean time period for hospital stay was found to be 5.13 ± 1.7 days and in group B mean time period for hospital stay was found to be 5.02 ± 1.49. T test showed that no significant difference was seen between two groups in time period for hospital stay with P value of 0.74. Stenberg E et al., reported that carbohydrate fluid were associated with return of bowel sound earlier as

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compared to nil per oral group and these results were in accordance with results of this study [22]. Prior research involved 14 participants assigned to the rehabilitation group and 15 to the control group. Patients undergoing rehabilitation exhibited higher mean levels of complete protein both before surgery (7.4 versus 6.8, p = 0.004) and after surgery (4.9 versus 4.3, p = 0.005). Intraoperative complications were observed in 40% of controls compared to 14.3% in the rehabilitation group, with significantly lower rates of intraoperative blood transfusion in the rehabilitation group (14.3% versus 53.3%, p = 0.027). Despite similar timing of initial ambulation, postoperative complication rates, and length of hospital stay, the study concluded that postoperative recovery occurred more quickly and earlier in healthier individuals with statistical significance.

CONCLUSIONS

Preoperative oral carbohydrate loading therapy has shown early signs of recovery in terms of return of gastrointestinal function, time to independent walking and hospital stay in patients undergoing colorectal Surgery. Gender was also found to impact time to return to first bowel sound and first flatus, with the female gender showing early recovery compared to males.

Authors Contribution

Conceptualization: AM

Methodology: AD, US

Formal analysis: AD

Writing, review and editing: AM, ZA, AS, KZ

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

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Exploring the Efficacy of Ketoconazole versus Ketoconazole Combined with Adapalene in Treating Pityriasis Versicolor: A Comparative Study

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ABSTRACT

Pityriasis versicolor, a fungal infection causing skin discoloration, was commonly treated with antifungal agents like ketoconazole and adapalene, either alone or in combination. **Objective:** To compare the efficacy of ketoconazole alone versus the combination of ketoconazole and adapalene in the treatment of pityriasis versicolor. **Methods:** This study was conducted at Department of Pharmacology, Banu Medical College, Banu from May 2023 to October 2023. Total 90 (45 in each group) adult patients diagnosed with the condition were assigned to either treatment group. Group A was treated with ketoconazole 2% cream monotherapy, while Group-B was given combined therapy with ketoconazole 2% cream and adapalene 1% gel. Both groups underwent treatment for duration of four weeks, with instructions for application provided by the investigators. Treatment outcomes, including lesion clearance rates were evaluated at follow-up. The collected data underwent processing and analysis utilizing IBM SPSS, version 23.0. **Results:** Out of total participants 57(63.3%) were male and 33(36.7%) were females, with a mean age of 30.63 ± 8.38 years. Regarding lesion type, the distribution between hyperpigmented (51.1%) and hypopigmented (48.9%) lesions were relatively balanced. This study depicted a significantly higher proportion of patients in the combination therapy group (n=39, 86.7%) experienced improvement compared to those in the ketoconazole monotherapy group 21 (46.7%) ($p < 0.001$). **Conclusions:** In conclusion, this study demonstrates that the combination of ketoconazole and adapalene exhibits superior efficacy compared to ketoconazole alone in treating pityriasis versicolor.

INTRODUCTION

Pityriasis versicolor, often known as "tinea versicolor," is a prevalent fungal skin disease. Although this condition can be a rather harmless one, the skin's signature appearance of discolored patches is often displeasing and leads to embarrassment in the patients affected by the condition [1, 2]. Therefore, to enhance understanding of pityriasis versicolor by both the healthcare providers and the patients, the causes, morphology, diagnosis, and available treatment options for this condition should be well understood [3]. The cause of this is the yeast malassezia furfur, which is present on everyone's skin inherently [4, 5]. Pityriasis versicolor can occur if this yeast multiplies under certain conditions mainly when there is warm and humid conditions or excessive secretion of sebum. Small round or oval macules are some of the most common complaints in pityriasis versicolor. These patches differ in colour as of brown, white, tan or pink depending on the colour of the skin of the patients. In persons, they manifest more on areas that are normally profusely sweating, including the chest, back, shoulders, and upper arms. Occasionally, the affect area of skin may be associated with modest itching or slight dryness of the skin [6]. Physician usually diagnose pityriasis versicolor usually through visual examination of skin by naked eyes. Sometimes reveals additional information is revealed from skin scrapings or Wood's lamp examination for typical mycological features. They found

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out that pityriasis versicolor must be differentiated from other diseases that exhibit similar symptoms, for example, vitiligo, or eczema to give it the right treatment [7]. A number of therapeutic strategies are generally prescribed for pityriasis versicolor and these include the use of antifungal agents, which can be applied in form of creams, lotions or shampoos. These medications help to get rid of the yeast and allow the normal processes of self-cleaning of the skin flora. A type of systemic antifungal drug commonly employed is ketoconazole, which is well researched in the treatment of pityriasis versicolor [8]. When administered alone ketoconazole exerts its action through suppressing the growth of the aetiologic agent, which is Malassezia furfur. It also comes in the form of creams, shampoos, and oral tablets to suite the extent and areas of infection [9]. Over the last few years, there have been interest towards combination therapy of ketoconazole with adapalene to improve the prognosis of pityriasis versicolor. Adapalene is an anti-inflammatory substance that also contains properties of a keratolytic agent, thus making it compatible with ketoconazole in this regard. Pityriasis versicolor is thus treated by both the fungicidal effect reducing the fungal overgrowth, and the inflammatory and skin turnover effect, trying to manage all the areas affected [10].

The purpose of this study was to establish whether the combination of ketoconazole with adapalene has more effective in the treatment of pityriasis versicolor. In seeking to study this potentially complementary combination therapy, it was aimed to treat both the antifungal and inflammation triggers of the disease to perhaps improve the treatment results. This research could prove to be very useful in expanding the understanding of how to better deal with pityriasis versicolor; thus, providing a broader approach to treat this frequently encountered fungal disorder. Furthermore, the assessment of the efficacy of this combination therapy would help to cover the reported lack of relevant literatures, and contribute to the derationing of evidence-based management of pityriasis versicolor for clinicians.

METHODS

The study was done after getting ethical clearance from the set institutional review body (BMC/IRB/23/37). This study was conducted in the department of pharmacology, Banu Medical College, Banu from May to the end of October in the year 2023. Type of study adopted was experimental study. This research conformed to World Medical Association Declaration of Helsinki, and participants' written informed consent secured beforehand; patient-identifying information was kept confidential and anonymous. A prospective, randomized comparative study design was used. The sample size was determined using WHO calculator (www.openepi.con) assuming improvement with the combination therapy ketoconazole 2% cream and adapalene 1% gel to be (87.5%) compared to ketoconazole alone (47.5%) with a power of 80% and a significance level of 0.05 using a two-sample proportion formula for independent samples [11]. Pityriasis versicolor was identified clinically and verified by microbiological microscopy or culture in adult individuals. Excluded patients had allergies to study drugs or dermatological disorders. Participants were assigned to two treatment groups: Group A was treated with Ketoconazole 2% cream monotherapy, while Group-B was given combined therapy with ketoconazole 2% cream and adapalene 1% gel. Both groups underwent treatment for duration of four weeks, with instructions for application provided by the investigators. Treatment commenced promptly upon diagnosis and continued for 4 weeks. Follow-up assessments were scheduled at 1-month intervals post-treatment initiation to monitor progress and evaluate treatment outcomes. The primary outcome measure was the percentage of participants achieving complete clearance of pityriasis versicolor lesions. Complete clearance of Pityriasis versicolor lesions was defined as the absence of visible lesions upon clinical examination and confirmed by photographic documentation at the end of the treatment period. Specifically, lesions were considered cleared if no signs of scaling, erythema, or hypopigmentation were observed. Clinical evaluation of skin lesions was performed using wood's light lamp by trained dermatologists The infected areas typically exhibit a yellow-green fluorescence under wood's light [22]. Compliance was monitored through regular follow-ups, and any mild irritation or redness at the application site was documented as an adverse effect. The assessment of adverse effect mild irritation was labeled as slight discomfort or redness at the application site, noticeable but not interfering significantly with daily activities or requiring specific treatment. Satisfaction levels were categorized into "well satisfied" for strong positive feedback, "moderately satisfied" for mixed responses, and "unsatisfied" for negative feedback, based on patient self-reports. The data were analyzed using the statistical software SPSS version 23.0. The mean and standard deviation were employed to analyzed quantitative data such as age and duration of disease. Qualitative factors (gender, type of lesion, improvement yes/no, side effects yes/no, patients satisfaction) were analyzed to determine their frequency and percentage. Chi-square tests and unpaired t-test were employed to assess the comparative effectiveness of the treatments in the two groups. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

The baseline characteristics of the participants were

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summarized in table 1. Many participants i.e. 57 (63.3%) were male, with an average age of 30.63 ± 8.38 years. Most patients fell within the age group of 18-30 years 58 (64.4%), and the duration of the disease varied, with a substantial proportion 31 (34.4%) experiencing symptoms for 1-2 months. Regarding lesion type, the distribution between hyperpigmented (51.1%) and hypopigmented (48.9%) lesions was relatively balanced.

Table 1: Baseline Characteristics of Study Participants

Variables	N (%) / Mean ± SD
Gender	
Female	33 (36.7)
Male	57 (63.3)
Age Groups (Years)	
18-30	58 (64.4)
31-50	32 (35.6)
Age (Years)	30.63 ± 8.38
Less than 1 Month	30 (33.3)
1-2 Months	31 (34.4)
More than 2 Months	29 (32.2)
Type of Lesion	
Hyperpigmented	46 (51.1)
Hypopigmented	44 (48.9)

Table 2 presented a comparison between the two treatment groups concerning baseline characteristics. No statistically significant differences were observed between the groups in terms of gender, age distribution, age mean, duration of disease, or type of lesion.

Table 2: Comparison between the Treatment Groups Regarding Baseline Data

Variables	Group A	Group B	p-Value
	N (%) / Mean ± SD	N (%) / Mean ± SD	
Gender			
Female	16 (35.6)	17 (37.8)	0.827[a]
Male	29 (64.4)	28 (62.2)	
Age Groups (Years)			
18-30	28 (62.2)	30 (66.7)	0.660[a]
31-50	17 (37.8)	15 (33.3)	
Age (Years)	31.4 ± 8.46	29.9 ± 8.32	0.402[b]
Duration of Disease			
<1 month	16 (35.6)	14 (31.1)	0.905[a]
1-2 month	15 (33.3)	16 (35.6)	
>2 month	14 (31.1)	15 (33.3)	
Type of Lesion			
Hyperpigmented	21 (46.7)	25 (55.6)	0.399[a]
Hypopigmented	24 (53.3)	20 (44.4)	

[a]Chi square test; [b]Unpaired t-test

The efficacy of the treatment regimens was evaluated based on the improvement observed in the patients. As depicted in Table 3, a significantly higher proportion of patients in the combination therapy group (n=39, 86.7%) showed improvement compared to those in the Ketoconazole monotherapy group 21(46.7%)(p<0.001).

Table 3: Comparison of Improvement between Treatment Groups

Improvement	Group A	Group B	p-value
	N (%)	N (%)	
Yes	21 (46.7)	39 (86.7)	< 0.001[a]
No	24 (53.3)	6 (13.3)	

[a] Chi square test

Regarding side effects and patients' satisfaction, the combination therapy group reported a higher incidence of mild irritation (n= 16, 35.6%) compared to the Ketoconazole monotherapy group (n=3, 6.7%) (p < 0.001). However, patients in the combination therapy group also exhibited higher satisfaction levels, with 55.6% reporting being well satisfied, compared to 31.1% in the monotherapy group (p = 0.048)(Table 4).

Table 4: Comparison between the Treatment Groups Regarding Side Effects and Patients' Satisfaction

Treatment	Group A	Group B	p-Value[a]
	N (%)	N (%)	
Side Effects (Mild Irritation)	3 (6.7)	16 (35.6)	<0.001
Patients Satisfaction			
Well Satisfied	14 (31.1)	25 (55.6)	0.04
Moderately Satisfied	20 (44.4)	15 (33.3)	
Unsatisfied	11 (24.4)	5 (11.1)	

[a] Chi square test

DISCUSSION

Pityriasis versicolor, a common fungal infection of the skin, presents with characteristic discolored patches that can cause discomfort and self-consciousness. Ketoconazole, a widely used antifungal medication, has been a mainstay in the treatment of this condition, effectively targeting the underlying fungal overgrowth. Nonetheless, new studies show that ketoconazole increases adapalene, an anti-inflammatory compound, leading to better results in sufferers of pityriasis versicolor. Thus, the purpose of this work was to compare the effectiveness of ketoconazole used alone and in combination with adapalene, which will help in determining the further approach to the treatment of this dermatological lesion [12, 13]. Similar to Jha S findings, this study observed a higher prevalence of males, with 63.3%males and 36.7% females. Participants mean age 30.63 (SD =8. 38) was quite comparable to Jha S in participant's age of 31.1 (SD =9. 22) Likewise, participant's age distribution especially in younger age group of 18 to 30 years confirm both this study finding and that of Jha S [14]. Additionally, while this study noted variability in the duration of the disease, ranging from one to two months in a substantial proportion of patients (34. 4%), Mohankar's findings corroborate the notion of a relatively short duration of symptoms, with an average duration of three months (range: (First time users – 1 to 6 months) [15]. The outcomes of this study corroborate the research of Hameed S *et al.*, in 2022, namely, the higher efficacy of combination therapy as opposed to monotherapy for pityriasis versicolor. In the present study, a significantly

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higher proportion of patients in the combination therapy group 39 (86.7%) showed improvement compared to those in the ketoconazole monotherapy group 21 (46.7%) ($p < 0.001$) [16]. The present study established the results same as Tawfik KM *et al.*, in 2022 who established that in the frequency of improvement, a combination of drugs fared much better than Ketoconazole [17]. Shi TW *et al.*, in 2015 conducted the study on the effectiveness of different concentrations of adapalene in treating acne and established that combined therapy with ketoconazole 2% cream and adapalene 1% gel has been shown to increase the ratio of the patients who felt improvement compared to the control group (92% vs 72%; P= 0. 0009), which was in parallel to this findings [18, 19]. Further, the findings of this research were in harmony and line with other research carried out by Gobbato AA *et al.*, in 2015. The results of the present study were in line with those of Bakr E *et al.*, in 2020, who found that 93.3% of patients in the combination group and 83.3% in the monotherapy group both showed substantial improvement; this sample size was similar to that of the former [20, 21]. Results of present study were consistent with the results of other studies thus strongly support the conclusion that combining medications was more effective than using a single therapy for treating pityriasis versicolor [19-22]. Lack of long-term follow-up limits assessment of treatment durability. Future research should consider larger sample sizes and longer-term follow-up to evaluate treatment sustainability and relapse occurrence.

CONCLUSIONS

In conclusion, this study demonstrates that the combination of ketoconazole and adapalene exhibits superior efficacy compared to ketoconazole alone in treating pityriasis versicolor, highlighting the potential of combination therapy as a preferred treatment approach for this dermatological condition. These findings contribute to the optimization of therapeutic strategies, ultimately improving patient outcomes and quality of life.

Authors Contribution

Conceptualization: SH, SA
Methodology: SH, SZ, GS, SA
Formal analysis: AM, SF
Writing, review and editing: SZ, GS, SA

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

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Impact of Letrozole on Mature Follicle Rate in Treatment of Subfertility Due to Polycystic Ovarian Syndrome

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ABSTRACT

Letrozole was an aromatase inhibitor that has gained prominence as an alternative to the clomiphene citrate for ovulation induction in females with Polycystic Ovarian Syndrome (PCOS). **Objective:** To assess the frequency of mature follicle rate as a result of letrozole treatment in subfertility due to PCOS. **Methods:** This interventional study was performed at Obstetrics and Gynecology Department, Combined Military Hospital, Multan, over a period of 6 months, from March 1, 2023 to September 1, 2023. The study included 322 cases aged between 20–40 years, who reported infertility for longer than a year, had Body Mass Index (BMI)<28, and had subfertility due to PCOS. All study participants were subjected to letrozole treatment. Development of mature follicles was observed utilizing transvaginal ultrasound starting from the 10th day of treatment. **Results:** The mean age of patients was 32.82 ± 4.30 years. The mean weight was 61.74 ± 7.35 kg, whereas the mean height was 1.61 ± 0.069 m. The mean BMI was 23.68 ± 2.96 kg/m^2. Among the participants, 161 (50.0%) patients had primary infertility, and 161 (50.0%) had secondary infertility. After receiving letrozole treatment, 237 (73.6%) patients had mature follicles on ultrasonography. **Conclusions:** Letrozole seems to improve the rate of follicle maturation in women with subfertility due to PCOS, thereby increasing the likelihood of pregnancy. Based on these findings, letrozole can be regarded as a suitable alternative to first-line therapies such as clomiphene citrate, providing favorable outcomes and minimal side effects, specifically in patients with clomiphene citrate resistance.

INTRODUCTION

Polycystic Ovarian Syndrome (PCOS) is the most frequently occurring endocrine dysfunction in females, affecting approximately 4-18% of reproductive age women all over the world [1]. The prevalence of PCOS is higher among Pakistani women (33.3%) compared to Western women (20-25%) [2, 3]. It is identified as irregular menstrual cycle, manifestation of overabundance of androgen such as acne and hirsutism, and the presence of multiple small cysts in the ovaries, as seen on USG [4]. Although it is one of the many paramount reasons of infertility in women of reproductive age, its cause is still undetermined and its management is complex [5, 6]. Recent studies have demonstrated that PCOS is linked with anovulatory infertility and the induction of ovulation is the primary goal in managing PCOS-induced infertility. Weight reduction, lifestyle modifications, and several pharmacological agents such as metformin and clomiphene citrate are various strategies for managing PCOS [7]. Aromatase inhibitors, specifically letrozole, were introduced by Mitwally and Casper in 2001 for the induction of ovulation [8]. It is a potential non-steroidal agent that functions by reducing the conversion of androstenedione and testosterone into estrogen [9]. By diminishing the body levels of estrogen, letrozole alleviates the negative feedback on the hypothalamus and pituitary gland. This causes raised Follicle-Stimulating Hormone (FSH) and

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Luteinizing Hormone (LH) levels, which stimulate the ovarian follicle development [10]. Letrozole exhibits a mono-follicular response and does not cause adverse effects on endometrium and mucosa of cervix, due to its lack of estrogen receptor blockage. Also, it is cleared from circulation more quickly due to its shorter half-life (2 days) [11]. Compared to other similar drugs, it has a lower risk of multiple pregnancies, ovarian hyperstimulation syndrome, and congenital fetal malformations [12, 13]. The main side effects of this drug are headache, gastro-intestinal disturbances, joint ache, flushing, and sweating [14]. Due to presence of evidence regarding safety and efficacy of letrozole, it has been approved by the US Food and Drug Administration for first line treatment [15, 16]. Several studies have reported a varied impact of letrozole in treating subfertility in women with PCOS. A study reported that mature follicles rate (≥17 mm in size) was 38% in patients receiving letrozole treatment [6]. Another systematic review reported that the possibility of ovulation was much higher in letrozole [17]. Another study reported the ovulation rate was 86.7% following the administration of letrozole [18].

Given the dearth of local evidence and the contrasting results from global data regarding the number of mature follicles, the rationale of this study was to determine the frequency of mature follicles in patients receiving letrozole for the treatment of subfertility due to PCOS. If this study finds a higher number of mature follicles, it could possibly result in considering letrozole as a first-line therapy in the future. Moreover, letrozole is a safer drug and can effectively substitute the first-line drugs for ovulation induction in patients with PCOS.

Thereby, it could be regarded as a feasible first-line treatment option for inducing ovulation in these cases.

METHODS

The interventional study was carried out at Obstetrics and Gynecology department, Combined Military Hospital, Multan, for 6 months from 1st march to 1st September 2023. Sample size of 322 was measured utilizing 95% confidence level, 5% margin of error and expected percentage of mature follicles in the group getting letrozole as 70.21% [19]. Consecutive sampling technique was utilized to gather the data. Patients aged between 20–40 years, reporting infertility for longer than a year, having body mass index <28 kg/m^2, and having subfertility owing to PCOS (absence of ovulation, symptoms of increase in androgen in the blood such as hirsuitism and acne, and the raised levels of testosterone in the blood) were included in the study. Patients having tubal patency on hysterosalpingography, abnormal follicle stimulating hormone, luteinizing hormone, prolactin, progesterone, estrogen, and testosterone levels or patients whose husbands had abnormal semen analysis report were excluded from the study. The study proposal was submitted to the institutional ethical committee of Combined Military Hospital, Multan for review and approval. The Committee examined the adherence of the study to ethical standards, including participant safety, privacy, and the risk-benefit ratio and the approval was granted on 1st Jan, 2023 with the reference number (ERC No. 24/2024). Informed consent was obtained from all patients before including them in the study. Detailed information regarding the objectives, procedures, possible risks, and benefits of the study was given to patients through a written consent form. It was designed to ensure that patients had ample and appropriate information to make an informed decision about their inclusion in the study. Data were then taken from each patient meeting the inclusion criteria. All cases were diagnosed for subfertility and PCOS using Rotterdam criteria [20]. Initial dose of 2.5 mg letrozole was given to all patients, and then the dose was escalated up to 5 mg per day for 5 consecutive days beginning from the day 3 of the menstruation, as recommended in the literature [9, 18]. Each woman continued to receive metformin 500 mg thrice a day, as recommended in the previous studies [21]. Development of mature follicles was observed utilizing transvaginal ultrasound starting from the 10th day of treatment. A subcutaneous injection of 10,000 IU of Human Chorionic Gonadotropin (hCG) was given to activate ovulation as soon as at least one mature follicle having a mean diameter ≥18 mm was seen on TVUS. All data was collected by researcher herself. All data was entered and analyzed utilizing Statistical Package for Social Sciences (SPSS) version 23.0. Quantitative data such as age, weight, height, and body mass index were presented as mean ± standard deviation. Categorical data like type of infertility and number of mature follicles were presented as frequencies and percentages. Chi-square test was utilized to compare the number of mature follicles following letrozole treatment with respect to age, body mass index and type of infertility.

RESULTS

A total of 322 patients were included in the study. Baseline characteristics were explained in table 1. Mean age of patients was 32.82 ± 4.30 years, with a range of 20 years. Mean weight of the patients was 61.74 ± 7.35 kg whereas the mean height was 1.61 ± 0.069 m. Mean BMI was 23.68 ± 2.96 kg/m^2. Among these patients, 161(50.0%) patients had primary infertility and 161(50.0%) had secondary infertility.

Table 1: Baseline Parameters of Patients Having Subfertility due to PCOS (n = 322)

Variables	(Mean ± SD) / N (%)
Age* (Years)	32.82 ± 4.30
Weight* (Kg)	61.74 ± 7.35
Height* (m)	1.61 ± 0.069
BMI* (Kg/m^2)	23.68 ± 2.96

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Type of Infertility	
Primary	161(50.0)
Secondary	161(50.0)

PCOS = polycystic ovarian syndrome; n = number of study participants; % = percentage of study participants; kg = kilogram; m = meter; BMI= Body mass index; kg/m^2 = kilogram per meter square; * = mean ± standard deviation was used to explain the data.

Figure 1 illustrated the frequency of mature follicles in patients with PCOS treated with letrozole for subfertility. Among these patients, 237(73.60%) had mature follicles on ultrasonography after receiving letrozole treatment.

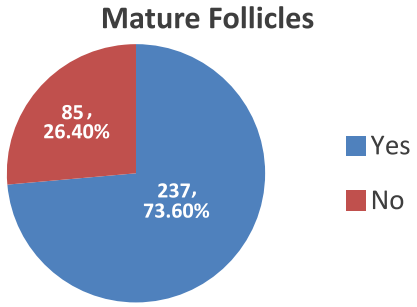

Figure 1: Frequency of Mature Follicles in Women with PCOS Treated with Letrozole for Subfertility

Table 2 showed the comparison of mature follicle rate following administration of letrozole with respect to age, body mass index, and type of infertility. Results demonstrated that patients who belonged to 20-30 years age group responded better to letrozole in terms of follicular maturation (p = 0.004). Similarly, patients who were underweight had a significantly higher number of mature follicles following letrozole treatment (p = 0.028), as compared to over-weight individuals. Letrozole showed more beneficial impacts in patients having primary infertility (p <0.000).

Table 2: Comparison of Mature Follicle Rate Following Administration of Letrozole With Respect to Age, Body Mass Index and Type of Infertility (n = 322)

Variables	Description	Mature Follicle N (%)			p-Value*
		Yes	No	Total	
Age Groups (Years)	20–30	85 (84.16)	16 (15.84)	101 (100.0)	0.004
	31–40	152 (68.78)	69 (31.22)	221 (100.0)	
BMI (Kg/m^2)	Underweight	4 (100.0)	0 (0.0)	4 (100.0)	0.028
	Normal Weight	148 (69.16)	66 (30.84)	214 (100.0)	
	Over Weight	85 (81.73)	19 (18.27)	104 (100.0)	
Type of Infertility	Primary	133 (82.61)	28 (17.39)	161 (100.0)	0.000
	Secondary	104 (64.60)	57 (35.40)	161 (100.0)	

n = Number of study participants; BMI= Body mass index; kg/m^2 = kilogram per meter square; * = Chi-square test was utilized to calculate p-value and p≤0.05 was taken significant.

DISCUSSION

PCOS was the most frequently encountered female endocrine dysfunction responsible for subfertility among women of reproductive age [22]. Safe and effective induction of ovulation was crucial for women with infertility [18]. So, this study was executed to assess the frequency of mature follicle rate as a result of Letrozole treatment in subfertility due to PCOS. In this interventional study, 322 women with subfertility were included. All patients received Letrozole treatment for follicular maturation. In the present study, mature follicular development was reported in 237 (73.60%) cases in response to Letrozole treatment. In a study by Bansal S *et al.*, mature follicular development was observed in 68.47% patients who received Letrozole treatment [18]. In another study conducted by Hegde R *et al.*, it was reported that mono-follicular development was higher as a result of Letrozole therapy (86.9%). Ovulation rate was also greatly enhanced following Letrozole treatment (92.0%) [23]. Likewise, Javeria M *et al.*, reported that the successful ovulation was achieved in 81% in patients taking Letrozole [24]. A clinical trial carried out by Gupta E *et al.*, revealed that the number of follicles ≥18 mm for the Letrozole group was 1.11 ± 0.43 and 2.53 ± 1.10 for the Clomiphene Citrate group (P<0.001). Letrozole group also had a higher endometrial thickness than the group taking Clomiphene Citrate (P<0.001). Higher ovulation rate was also observed in the letrozole group (P = 0.047), compared to the findings of the present study [25]. Various other studies documented the similar results. In an Indian study, it was found out that ovulation rate was 73% in patients who received a combination of letrozole in comparison to 38% in those who received Letrozole alone (p = 0.003) [6]. Similarly, a Bangladeshi study also reported that mono-follicular development was higher in Letrozole group (p = 0.004) [12]. Another study conducted by Zeba D *et al.*, showed that 65% of patients had ovulation following Letrozole administration [5]. However, an RCT reported that patients who received the combination of letrozole and Clomiphene citrate had a higher ovulation rate (77%) than those who received letrozole alone (43%) this study has several limitations [9]. First, the interventional nature of the study restricts the ability to determine the long-term effects and causality of Letrozole treatment. Secondly, no control group was included in the study, limiting the ability to compare the effects of Letrozole against a baseline or alternative treatments.

CONCLUSIONS

Letrozole seems to improve the rate of follicle maturation in women with subfertility due to PCOS, thereby increasing the likelihood of pregnancy. Based on these findings, letrozole can be regarded as a suitable alternative to first-line therapies such as clomiphene citrate, providing favorable outcomes and minimal side effects, specifically in patients with clomiphene citrate resistance.

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Authors Contribution

Conceptualization: MJ
Methodology: MJ, SH
Formal analysis: AH
Writing, review and editing: LN, UT, QUAH, SH, AH

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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Ambulatory Sedation in Pediatric Dentistry "Knowledge and Practice of Dental Graduates of Karachi" A Cross Sectional Study

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ABSTRACT

Ambulatory sedation in pediatric dentistry is crucial for managing anxiety and pain, ensuring effective treatment. Assessing the knowledge and practice of dental graduates regarding this technique is essential for improving pediatric dental care. **Objective:** To evaluate the knowledge and practice of dental graduates in Karachi regarding ambulatory sedation in pediatric dentistry. **Methods:** A cross-sectional survey was conducted from July 2023 to December 2023 among dental graduates in Karachi using a simple random sampling technique. Data were collected through a structured, self-administered questionnaire, which included 5 demographic questions, 14 knowledge questions, and 3 practice questions. The knowledge questions were scored, with each correct answer allocated 1 point, and the total score categorized into poor (0-4), good (5-9), and excellent (10-14) knowledge levels. Data were analyzed using SPSS version 25.0, with descriptive statistics and Chi-square tests employed for analysis. **Results:** Out of 200 respondents, 45% demonstrated excellent knowledge, 40% had good knowledge, and 15% had poor knowledge regarding ambulatory sedation in pediatric dentistry. The practice assessment revealed that 60% of the graduates regularly used ambulatory sedation techniques, while 40% reported occasional use. Significant associations were found between knowledge levels and years of practice ($p<0.05$). **Conclusions:** The study indicates that while a substantial proportion of dental graduates in Karachi have excellent knowledge of ambulatory sedation, there is a need for continued education and training to ensure consistent practice. Enhancing knowledge and practice through targeted programs can improve pediatric dental care outcomes.

INTRODUCTION

Children can be difficult during dental work due to the fear and anxiety that comes with it [1]. There are several unique challenges to pediatric dentistry. This fear and anxiety often results in incomplete procedures being done or the parents refusing to let their kids receive necessary treatments which they need [2]. In light of this problem, dental professionals have come up with different methods for dealing with young patients. One of these methods involves giving them drugs that make them sleepy but not unconscious known as ambulatory sedation. The dentist administers medications which depress the central nervous system while still being able to talk with the child. Through experience it has been shown that this method creates an environment where the kid is more comfortable and willing to corporate thus making the treatment process smoother [3, 4]. Common medications used by dentists to aid sedation in children who are visiting the dental office for serious procedures are midazolam and Propofol. They prefer these because they work well and are safe if given by someone who knows what they're doing [5]. The American Academy of Pediatric Dentistry (AAPD) and other top medical organizations support the use of sedation therapy during office-based treatment where children have their teeth looked at, noting advantages like affordability, simplicity, and early care access among others [6]. Even with these developments, there is still a great deal of unknown about the proper use of sedation by dentists in pediatric dentistry, especially in areas such as Karachi. With the goal of improving chair side efficiency, lowering visit frequency, and improving patient comfort, this study

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examines outpatient sedation practices and advancements in pediatric dentistry settings. The goal of the study is to enhance juvenile dental care procedures by addressing these important factors. Level of knowledge and practice of ambulatory sedation among dental professionals in Tanzania, Majority of dentist have enough knowledge of sedation in dentistry, it's been reported that only one in ten have had proper training on sedation [7]. The requirement of sedation for dental treatments is more in preschool patients in the city of Cuenca. Ambulatory sedation plays a vital role in situations where it is impossible to use operating rooms. This study concluded that the knowledge is inadequate about the procedure and conditions of giving sedatives [2]. Individual adjustments should be made to the appropriate amount of sedation in order to properly balance the demands of the patient, the operator, and the procedure's safety. The amount of time spent on surgery is crucial for the recovery stages, and it may be significantly impacted by the patient's cooperation or interruptions of the surgeon [8]. Oral sedatives have historically been the primary source of pediatric dental sedation; however, new developments have led to the introduction of innovative drugs and techniques that are producing outstanding outcomes [9]. Experts in sedation must anticipate the negative consequences of sedation, which is why carefully chosen patients under precise therapeutic guidelines are needed to prevent the as-yet-undetermined potential neurological repercussions. The prevalence of pediatric dental diseases makes it likely that sedation will be required in the near future. By utilizing the right medications and delivery methods and fine-tuning the behavioral evaluation criteria, this scenario will improve the effectiveness of sedation [10]. Following dental treatment under GA, a number of the children experienced relapses; 24–59% acquired new caries lesions and 6.5–87% needed further restorative dental care. Dental practitioners should put more of an emphasis on prevention rather than the conventional strategy of treating the symptoms of oral disorder [11]. The use of general anesthesia and sedation in dentistry offices is not well documented throughout Latin America. During the COVID-19 confinement period in Ecuador, mobile anesthesia became essential as it was nearly difficult for children to receive dental care in a hospital setting [12]. Children's anatomical, pharmacokinetic, and psychological characteristics are always changing; thus, sedation attempts to preserve safety, relieve pain, lessen anxiety, and regulate behavior so that the intended intervention may be carried out. Since deep sedation or general anesthesia are necessary to safely develop dental treatment due to factors like the child's extensive treatment needs, age, acute situational anxiety, limited cognitive functioning, long intervention times, physical disability, or medical conditions, minimal pharmacological or non-pharmacological interventions are frequently insufficient to achieve adequate comprehensive care in pediatric dentistry [13]. Ambulatory sedation is used to relieve anxiety, pain and discomfort in a broad spectrum of patients during many types of diagnostic or therapeutic procedures. Number of students who have obtained a recognized qualification in dentistry in a given years are dental graduates. Among those are Fresh Graduates, Post Graduates and Dental practitioners. No previous study has been conducted so far in Karachi to Assess the Knowledge and Practice about the Ambulatory Sedation in Pediatric Patients. This study will help to lessen the feeling of pain during dental treatments, which will contribute to the development of trust and a positive relationship between the pediatric patient and the dentist, as well as the elimination of fear and anxiety and the promotion of a positive patient attitude towards dental care.

METHODS

The Cross-sectional design was used in this study. The study settings were dental OPDs of dental colleges and clinics in Karachi. Study duration was 6 months (July 2023 to December 2023) after approval of synopsis from IRB Ref. No. IRB/D-000070/23. Study population was Dental house officers, FCPS/MCPS/ MDS trainees, Post Graduates and Clinical faculty members and sample size was calculated using online software. Inclusion criteria was dental graduates and post graduates, practicing dentist, male / female dentist, age above 20 years. Exclusion criteria was dental graduates who have not practiced in the last year, dental graduates who are currently not residing in Karachi; dental graduates who did not consent to participate in the study. A simple random sampling technique was used to ensure that every dental graduate in Karachi had an equal chance of being included in the study, minimizing bias and ensuring a representative sample. A structured, self-administered questionnaire was developed for data collection. The questionnaire was pre-tested on a small group of dental graduates to ensure clarity and validity. It consisted of three main sections: Demographic Information: 5 questions assessing the demographic characteristics of the dental graduates. Knowledge Assessment: 14 questions, each correct answer allocated 1 point, assessing the knowledge regarding ambulatory sedation in pediatric dentistry. The questions were developed and validated based on previous studies by Sales N *et al.*, and Li SF *et al.*, [3, 14]. Practice Assessment: 3 questions assessing the practice of dental graduates regarding ambulatory sedation. The total score for the knowledge assessment ranged from 0 to 14. Based on the scores, the knowledge levels were categorized as follows: poor knowledge: 0-4 points, good knowledge: 5-9 points and excellent knowledge: 10-14 points. Data were analyzed using SPSS software version 25.0. Descriptive statistics, including frequencies and percentages, were used to

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summarize the demographic characteristics and knowledge levels of the respondents. Inferential statistics were used to identify associations between demographic variables and knowledge levels. Specifically: The Chi-square test was used to assess associations between categorical variables. Mann-Whitney U test was used to compare knowledge scores between two independent groups when the data did not follow a normal distribution. However, this test was not used in the results section, indicating a need for reconsideration of its application. A p-value of <0.05 was considered statistically significant.

RESULTS

Results revealed that the majority of participants were aged between 25-35 years, with a relatively equal distribution of male and female participants. Most respondents were dental graduates practicing in private settings, with more than five years of experience (Table 1).

Table 1: Sociodemographic Characteristics of study Participants

Category	Frequency (%)
Age	
25-35 Years	150 (61%)
36-45 Years	80 (32.5%)
>45 Years	16 (6.5%)
Gender	
Male	130 (52.8%)
Female	116 (47.2%)
Level of Dental Education	
Graduates	200 (81.3%)
Post Graduates	46 (18.7%)
Settings	
Private	180 (73.2%)
Government	66 (26.8%)
Years of Experience	
<5 Years	90 (36.6%)
>5 Years	156 (63.4%)

A significant proportion of participants believed that sedation can reduce patient anxiety. Many participants correctly identified midazolam as a sedative agent, while recognizing that local anesthetic agents like lidocaine and articaine are not sedatives. Participants were aware that propofol is a sedative administered intravenously, and nitrous oxide is used as an inhalation gas sedative. A considerable number of respondents correctly answered questions related to the pharmacological effects of sedative agents, such as midazolam's impact on neuromuscular transmission and the comparative properties of diazepam and midazolam (Table 2).

Table 2: Knowledge Assessment among study participants

Questions	Yes N (%)	No N (%)
Can Sedation Reduce Patient's Anxiety?	210 (85.4%)	36 (14.6%)
Can a Sedative Drug Be Used To Replace A Local Anesthetic Agent?	186 (75.6%)	60 (24.4%)
Is Midazolam A Sedative Agent?	230 (93.5%)	16 (6.5%)
Is Lidocaine A Sedative Agent?	26 (10.6%)	220 (89.4%)
Is Propofol A Sedative Agent?	198 (80.5%)	48 (19.5%)
Is Articaine A Sedative Agent?	20 (8.1%)	226 (91.9%)
Is Nitrous Oxide A Sedative Agent?	202 (82.1%)	44 (17.9%)
Is Diclofenac A Sedative Agent?	16 (6.5%)	230 (93.5%)
Can Diazepam Be Administered By Nasal Spray?	140 (56.9%)	106 (43.1%)
Is Nitrous Oxide Administered Only As Inhalation Gas?	178 (72.4%)	68 (27.6%)
Does Midazolam Affect Neuromuscular Transmission?	162 (65.9%)	84 (34.1%)
Does Diazepam Have A Greater Amnesic Effect Than Midazolam?	126 (51.2%)	120 (48.8%)
Does Midazolam Have A Longer Duration Of Action Than Diazepam?	186 (75.6%)	60 (24.4%)
Is It True That Propofol Is Both An Analgesic And A Sedative That Is Administered Through Intravenous Route?	214 (87.0%)	32 (13.0%)

Out of 200 respondents, 45% demonstrated excellent knowledge, 40% had good knowledge, and 15% had poor knowledge regarding ambulatory sedation in pediatric dentistry (Figure 1).

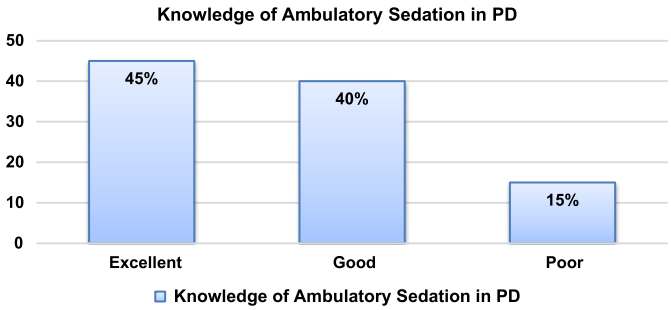

Figure 1: Distribution of Knowledge Levels among Respondents

A notable percentage of participants reported practicing sedation in children. Reasons for not practicing sedation included a lack of training, cost concerns, and perceived patient (Table 3).

Table 3: Practice of Sedation among study participants

Practice of sedation	Yes (%)	No (%)
Are you practicing sedation in children?	(19%)	(81%)
The reason for not practicing sedation		
Due to lack of training	(67%)	(33%)
Due to cost	(23%)	(77%)
Due to risk factors of patients	(10%)	(90%)
Recommendation of sedative dose in a child		
Pain	(45.5%)	(54.5%)
Anxiety	(60.2%)	(39.8%)
Other	(30.9%)	(69.1%)

DISCUSSION

The outcomes of this cross-sectional study shed light on dental practitioners' knowledge and practices regarding ambulatory sedation in pediatric dentistry in Karachi. The

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research examined a number of topics, including sedative use, expertise evaluation, and sociodemographic traits. The sample size for the study was 246 people, including postgraduates and graduates in dentistry. The majority of participants were dental graduates with over five years of experience, which shows that they have some knowledge and expertise with pediatric dental operations [1=7]. The study's knowledge evaluation component found important facts about dental practitioners' understanding of ambulatory sedation. The majority of participants correctly recognized sedation's ability to lower patient anxiety as a significant benefit of pediatric dental treatment. In a similar vein, many individuals seem to have a good grasp of the pharmacological elements of sedation as they know that sedatives may be employed in place of local anaesthetics [14]. Also, the volunteers clearly knew their way around the various sedatives, including propofol and midazolam, and how to administer them. There were significant knowledge gaps on certain drugs, such lidocaine and articaine, which are local anaesthetics and not sedatives. The need for more knowledge and training in differentiating between anesthetics used in dental treatments is highlighted by this [2]. Sedation has been found to be a promising trend in pediatric patients. Many respondents indicated that they often gave children drugs for sedation and this could mean a willingness to use drug-induced sleep more frequently for the benefit of the patient. However, others said that they did not use sedation because they were not trained on it, considered it as expensive or feared that the patient would be at risk. By using these obstacles as targets for interventions and teaching campaigns, dentists can increase their utilization of these methods. In keeping with established principles of pediatric dental sedation, most comments revolved around the best time to administer relaxants in order to alleviate pain and fear in children. The results of the survey showed that these surveyed practitioners are aware that thorough pain and anxiety assessments should be performed so as to make dental visits positive experiences for both child [4]. According to recent research by Wiener RC *et al.*, in 2022, dental practitioners today have a better grasp of sedation procedures than they had in the past. This has led to improved support for sedation treatments and an awareness of the hazards connected with them. It was shown that less anxious patients had more frequent dental checkups and improved overall dental health [15]. According to a study of 2024, ambulatory sedation is a substantial substitute for general anesthesia in pediatric dentistry treatment cases when research shows it to be more beneficial [16]. The technique should be selected with the patient's unique qualities in mind. For juvenile patients, both ambulatory and general anesthesia have advantages, but they shouldn't be used as the main tools for behavior control. It is important that dentists have a thorough grasp of various sedation methods in order to provide the best possible dental treatment [17,18]. In Kuwait, parents and dentists' knowledge and use of nitrous gas sedation were assessed in 2024 by Alkandari SA *et al.*, despite their willingness to use it based on their dentist's prescription, the majority of parents still know very little about nitrous oxide sedation as a Behavior Management Strategy (BMT). The study does, however, also show that a sizable percentage of these dentists are devoid of the knowledge and tools required to properly provide sedation. This emphasizes how important it is for dentists to have greater access to the right instruments and improved training programs in order to administer nitrous gas sedation to children [19]. Li SF *et al.*, in 2013 conducted an examination of dental practitioners' knowledge, attitude, and practice regarding conscious sedation in children. The findings indicated that although the majority of dental professionals were aware of the practice, they frequently lacked practical experience in administering appropriate dosages. According to their survey, 15% of dental practitioners did not employ the oral route of sedative administration, whereas 85% liked it [14]. In their evaluation of the elements needed to create an efficient sedative, Hazara R emphasized the need of blending many medicines into a single formulation. The technique of choice, the patient's characteristics, and the expectations of healthcare practitioners and patients all have a role in the selection of sedative medications. As a result, there is still no clear answer in the literature on the best drug to take in a given situation [20].

CONCLUSIONS

The study concludes by identifying dental practitioners in Karachi who are presently engaged in ambulatory sedation and areas where they need improvements most. Findings revealed that the respondents knew what sedation need to be given to patients thus making them more comfortable, and they could mention some of the various drugs which can be used as sedatives and how to give them properly. This indicates that there is a need for an improved and expanded pharmacological education as there exists a significant knowledge gap between sedatives and local analgesics. However, despite these gaps, several participants reported routinely administering sedation to pediatric patients suggesting a positive attitude towards utilizing sedative techniques to enhance patient care. Strengthening the quality of pediatric dentistry care can be achieved in future through standardization of sedation protocols, continuous education and training programs, comprehensive training courses among others. For safe and effective operations involving sedations it is necessary for dental organizations, educational institutions, and regulatory bodies work together. This will lead to better outcomes and experiences for patients in pediatric dentistry. Dental professionals' sedation knowledge and

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practices can be improved through future research that focuses on long-term impacts of sedation methods and treatments.

Authors Contribution

Conceptualization: IA
Methodology: M, RK
Formal analysis: M, AH
Writing, review and editing: RK, AF, UZ, AF, TA

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

Conflicts of Interest

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Impact of Trainees Involvement on Surgical Outcomes of Abdominal and Laparoscopic Myomectomy in Tertiary Care Hospital

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ABSTRACT

Myomectomy was one of the most frequently performed gynecologic procedures. It was a core competency of training in the field of Obstetrics and Gynecology internationally and was increasingly performed. **Objective:** To find the impact of trainee's involvement on surgical outcomes of abdominal and laparoscopic myomectomy in tertiary care hospital. **Methods:** This retrospective study was conducted at Iqra National University Department of Allied Health Sciences Peshawar from May 2022 to January 2023. Data were collected from 245 patients who had undergone abdominal and laparoscopic myomectomy in tertiary care hospital. Data were collected by using questionnaire which include all the information related to demographic, socioeconomic status of patients, trainee's information, operative details, preoperative measures, postoperative measures, length of hospital stay, blood loss during surgery. **Results:** Data were collected from 245 patients from hospital records. Mean age in group A was 42.01 ± 8.23 years and group B 41.76 ± 9.09 years. Mean uterine size in trainee involved group was 10.2 ± 2.1cm and in group B was 10.5 ± 2.3 cm. In simple abdominal myomectomy, procedures performed with trainees took longer compared to those without trainees, with a mean operative time of 110 ± 20 minutes versus 90 ± 15 minutes, respectively ($p < 0.05$). **Conclusions:** It was concluded that trainee involvement in abdominal and myomectomies surgeries create a significant but negative impact on surgical outcomes due to increased operative time and complications.

INTRODUCTION

Myomectomy is one of the most frequently performed gynecologic procedures. It is a core competency of training in the field of Obstetrics and Gynecology internationally and is increasingly performed in a minimally invasive fashion. However, myomectomies are complex surgical procedures, with the risk of blood transfusion as high as 10%. It is therefore prudent that we understand the impact of trainee's involvement on outcomes of myomectomy to balance education with patient safety [1]. To our knowledge, whether trainee's involvement is associated with surgical outcomes of myomectomy is unknown. Furthermore, no studies have evaluated the impact of an abdominal versus (vs) laparoscopic approach to myomectomy. Surgical trainees play a pivotal role in the delivery of surgical care, contributing to patient outcomes through their participation in various procedures [2]. Abdominal and laparoscopic myomectomy, commonly performed to treat symptomatic uterine fibroids, represent intricate surgical interventions that require skillful execution and precise technique [3]. The impact of trainee involvement in these procedures on surgical outcomes, including safety, efficacy, and patient recovery,

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has garnered significant interest in the medical community. Treatment systems for uterine leiomyoma can incorporate medical choices, (for example, oral contraceptives, progesterone, gonadotropin-delivering chemical agonist (GnRHa), particular progesterone receptor modulators, or the blend of relugolix-estradiol-norethisterone), careful mediations (like hysterectomy, laparoscopic myomectomy, and hysteroscopic myomectomy), and non-careful choices (uterine artery embolization) [4]. Uterine artery embolization is a helpful strategy to save the uterus if a patient encounters significant dying [5]. Notwithstanding potential confusions associated with uterine artery embolization, the primary concern is harm to the ovarian vascular stockpile [6]. The myomectomy can protect richness and keep up with the physical trustworthiness of the pelvic floor. Patients are progressively choosing laparoscopic myomectomy on account of the fast headway of negligibly intrusive methods. Nonetheless, utilizing a fibroid morcellator and different issues limit the utilization of this methodology [7]. The laparoscopic electric fibroid morcellator has been generally utilized in laparoscopic myomectomy since the U.S. Food and Medication Organization (FDA) endorsed its clinical use in 1995. It might likewise prompt the scattering of sores, for example, parasitic leiomyomata, iatrogenic endometriosis, and disease movement [8]. Freeman AH *et al.*, reflectively reviewed the data of 4478 patients going through laparoscopic myomectomy, and the incidence of uterine sarcomas was 0.54%. Uterine sarcoma incidence in individuals matured 50 to 60 years was pretty much as high as 10/375 (2.6%), and utilizing a fibroid morcellator expanded the gamble of harmful growths spreading to the abdominopelvic cavity [9]. Consequently, the FDA expressed the use of fibroid morcellator and alerts in 2014, restricting the use of laparoscopic myomectomy. Tertiary care hospitals serve as vital centers for surgical training, providing trainees with opportunities to develop their surgical skills under the guidance of experienced mentors [10]. The involvement of trainees in abdominal and laparoscopic myomectomy procedures offers valuable hands-on experience, facilitating skill acquisition and professional development [11]. However, the extent to which trainee participation influences surgical outcomes, such as operative time, intraoperative complications, blood loss, length of hospital stay, and postoperative morbidity, remains a subject of investigation and debate [12].

The main objective of the study is to find the impact of trainee's involvement on surgical outcomes of abdominal and laparoscopic myomectomy in tertiary care hospital.

METHODS

This quasi-experimental study was conducted at Iqra National University Department of Allied Health Sciences Peshawar from May 2022 to January 2023. Data were collected from 245 patients after calculating sample size using the Open Epi calculator. The calculation included a 95% confidence level, 80% study power, an anticipated effect size of 0.3, and the prevalence of outcomes based on pilot data (0.2). Adjustments were made to account for the quasi-experimental design and division into two groups. Data collection was conducted after obtaining informed consent from the patients. Patients who had undergone surgery in hospital and willing to participate in the study were included. Those who were not willing to provide data were excluded from the study. Data were divided into two groups: Group A: cases where trainee participated in the surgery procedure, Group B: cases where no trainee present and surgery were done by attending surgeon. Data were collected by using designed questionnaire which include all the information related to demographic, socioeconomic status of patients, trainees information, operative details, preoperative measures, postoperative measures, length of hospital stay, blood loss during surgery. The reliability of questionnaire was tested by using SPSS version 29.0. Cronbach alpha for questions was between 0.70 to 0.85. The validity of the data was checked by expert from surgery departments from Iqra National University, department of Allied health sciences. The primary outcome measures were operative time and transfusion rate. Secondary outcomes were length of hospital stay, major and minor complications after surgery. Trainee involvement and intraoperative participation were also recorded. Data were then entered into SPSS. We conducted bivariate analysis to compare the two groups using Chi-square tests for categorical variables and independent t-tests for continuous variables. For mean differences between the two groups, independent t-tests were applied. Percentage differences between the groups were analyzed using Chi-square tests. P value <0.05 were considered as significant. Ethical approval was received by the Ethical Review Committee (ERC) Iqra National University, Peshawar under Ref No: INU/AHS/286-22.

RESULTS

Among the 120 cases involving trainees, 67% (n=80) had trainees assisting in the surgery, 17% (n=20) had trainees leading the surgery, and 17% (n=20) were observing only. This distribution indicates that the majority of trainee involvement was in supportive roles, with a smaller proportion taking on leadership or observational roles. The data reflects a significant focus on hands-on training through assistance, while leadership and observation offer

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opportunities for different levels of engagement in surgical procedures (Figure 1).

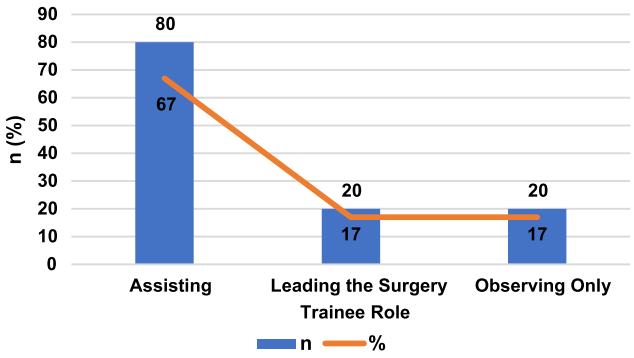

Figure 1: Distribution of Trainee Roles in Surgeries

Data were collected from 245 patients from hospital records. Table 1 showed that the mean age in group A was 42.01 ± 8.23 years and group B 41.76 ± 9.09 years. Mean uterine size in trainee involved group was 10.2 ± 2.1cm and in group B was 10.5 ± 2.3 cm. BMI was slightly lower in the Trainee-Involved Group (25.5 ± 3.2 kg/m^2 vs. 26.0 ± 3.5 kg/m^2). Hypertension (60% vs. 50%), diabetes mellitus (30% vs. 34%), and other comorbidities (10% vs. 16%) were somewhat more prevalent in the Trainee-Involved Group. The uterine size was slightly smaller in the Trainee-Involved Group (10.2 ± 2.1 cm vs. 10.5 ± 2.3 cm), with a higher median number of fibroids (4 (3-6) vs. 3 (2-5)). Myoma locations showed minor differences, with 40% fundus, 35% body, and 25% cervix in the Trainee-Involved Group compared to 45% fundus, 30% body, and 25% cervix in the Attending Surgeon-Only Group. Preoperative anemia was present in 20% of the Trainee-Involved Group and 18% of the Attending Surgeon-Only Group (Table 1).

Table 1: Demographic Data of Patients (n=245)

Variables	Trainee-Involved Group (Mean ± SD) / N (%)	Attending Surgeon Only Group (Mean ± SD) / N (%)	p-Value
Age (Years)	42.01 ± 8.23	41.76 ± 9.09	0.25
Socioeconomic Status*			
Low	48 (40%)	44 (35%)	0.12
Medium	54 (45%)	63 (50%)	0.25
High	18 (15%)	19 (15%)	0.55
BMI (Kg/m^2)	25.5 ± 3.2	26.0 ± 3.5	0.005
Comorbidities			
Hypertension	72 (60%)	63 (50%)	0.12
DM	36 (30%)	43 (34%)	0.35
Others	12 (10%)	20 (16%)	0.35
Uterine Size (cm)	10.2 ± 2.1	10.5 ± 2.3	0.3
Myoma Location			
Fundus	48 (40%)	56 (45%)	0.45
Body	42 (35%)	38 (30%)	0.65
Cervix	30 (25%)	31 (25%)	0.55
Preoperative Anemia	Yes: 24 (20%)	Yes: 22 (18%)	0.002
	No: 96 (80%)	No: 103 (82%)	
Fibroid Number	Median (IQR)	4 (3-6)	1.15 (1.05-1.30)
Previous Abdominal Surgery	36 (30%)	31 (25%)	0.4
Type of Surgery			
Abdominal	84 (70%)	100 (80%)	-
Laparoscopic	36 (30%)	25 (20%)	-
Use of Morcellation			
Yes	54 (45%)	50 (40%)	-
No	66 (55%)	75 (60%)	-
Uterine Weight (g)	300.09 ± 50.12	280.98 ± 60.01	0.05
Blood Transfusion Rate	18 (15%)	13 (10%)	0.25

* Low SES: This typically refers to individuals or groups with lower income, less education, and jobs that may be less secure or lower in status; Middle SES: This group includes individuals or groups with moderate income, higher education levels, and more stable or prestigious jobs compared to the low SES group; High SES: This category includes individuals or groups with higher income, advanced education, and high-status or highly secure jobs.

Mean operative time in trainee involved group was higher (150 ± 30 min) as compared to other group (130 ± 25 min). Mean blood loss in group A was 300 ml and in group B was 250 ml, p value was <0.05 which was non-significant. Length of hospital stay were also increased 3 (IQR: 2-5) days in trainee involved group (Table 2).

Table 2: Comparative Analysis of Operative Parameters

Variables	Trainee-Involved (Mean ± SD)	Attending Surgeon Only (Mean ± SD)	p-Value
Operative Time (minutes)	150 ± 30	130 ± 25	0.001
Blood Loss (mL)	300 (IQR: 200-400)	250 (IQR: 150-350)	0.001
Length of Hospital Stay (Days)	3 (IQR: 2-5)	2 (IQR: 1-3)	0.002

This study compares the mean operative time between surgeries involving trainees and those performed solely by attending surgeons, assessing the impact of trainee involvement on procedural efficiency (Figure 2).

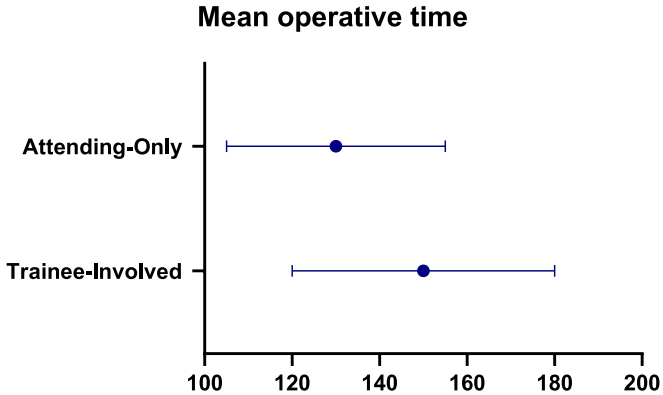

Figure 2: The Comparison of Mean Operative Time in Trainee-Involved Group and Attending Surgeon-Only Group

In simple abdominal myomectomy, procedures performed with trainees took longer compared to those without trainees, with a mean operative time of 110 ± 20 minutes versus 90 ± 15 minutes, respectively (p < 0.05). Similarly,

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complex abdominal myomectomies and laparoscopic procedures also exhibited prolonged operative times when trainees were involved, with mean times of 180 ± 30 minutes and 150 ± 25 minutes, respectively, compared to procedures without trainees ($p < 0.01$ and $p < 0.05$, respectively)(Table 3).

Table 3: Operative Time According to type of Myomectomy and Trainee Involvement

Types of Myomectomy	Involvement	Mean Operative Time (Minutes) (Mean ± SD)	p-Value
Simple Abdominal	Trainee-Involved	110 ± 20	0.002
	Attending Surgeon-Only	90 ± 15	
Complex Abdominal	Trainee-Involved	180 ± 301	0.01
	Attending Surgeon-Only	50 ± 25	
Laparoscopic	Trainee-Involved	150 ± 25	0.011
	Attending Surgeon-Only	120 ± 20	

Pre-operative data includes the size of the fibroids, the number of fibroids, and preoperative hemoglobin levels. Both groups were comparable with no significant differences in these variables(Table 4).

Table 4: Preoperative Data

Preoperative Data	Trainee Involvement Group (Mean ± SD)	Attending Surgeon Only Group (Mean ± SD)	p-Value
Size of Fibroids (cm)	6.5 ± 2.1	6.3 ± 2.0	0.42
Number of Fibroids	3.2 ± 1.5	3.0 ± 1.6	0.30
Preoperative Hemoglobin (g/dL)	11.8 ± 1.2	11.9 ± 1.1	0.55

When trainees were present, a higher percentage of cases experienced surgical site infections (30% vs. 20%), hemorrhage (16% vs. 10%), wound dehiscence (8% vs. 6%), and urinary retention (6% vs. 4%) compared to cases without trainees. These differences were found to be statistically significant with p-values less than 0.05 for surgical site infection, wound dehiscence, and urinary retention, and less than 0.01 for hemorrhage (Table 05). In abdominal myomectomy, trainee involvement was not significantly associated with surgical site infection ($p = 0.108$) or wound dehiscence ($p = 0.294$)(Table 5).

Table 5: Post-Operative Complications

Post-Operative Complications	Involvement	Number of Cases N (%)	p-Value
Surgical Site Infection	Trainee-Involved	15 (30%)	0.108
	Attending Surgeon-Only	10 (20%)	
Hemorrhage	Trainee-Involved	8 (16%)	0.021
	Attending Surgeon-Only	5 (10%)	
Wound Dehiscence	Trainee-Involved	4 (8%)	0.294
	Attending Surgeon-Only	3 (6%)	
Urinary Retention	Trainee-Involved	3 (6%)	0.020
	Attending Surgeon-Only	2 (4%)	

DISCUSSION

The study demonstrated that surgeries involving trainee participation resulted in longer operative times, greater blood loss, and a higher incidence of both intraoperative and postoperative complications compared to those performed solely by attending surgeons. These outcomes align with existing literature, which frequently reports extended procedure durations and increased complication rates when trainees are involved [13]. Several factors may explain these differences. Trainees, especially those early in their training, may lack the technical proficiency and decision-making skills of experienced attending surgeons [14]. The increased complexity of procedures and the learning curve associated with laparoscopic techniques could further impact the outcomes of surgeries involving trainees. Barber et al. highlighted that the surgical approach influences how trainee involvement affects perioperative complications, with operative time serving as a key, potentially modifiable factor in this relationship [15]. Kim et al. also emphasized that the impact of trainee involvement on surgical outcomes varies based on the procedure, the skills required, and the training paradigms in place [16]. Interestingly, the study found that the majority of trainee involvement (67%) was in a supportive role, with fewer trainees taking on leadership (17%) or observational roles (17%). This suggests a significant emphasis on hands-on training through assistance, while leadership and observation offer opportunities for different levels of engagement during surgical procedures. Trainee involvement in laparoscopic myomectomy was associated with an increase in operative time. This may be due to the advanced technical skills required for laparoscopic procedures, which are often performed by more senior trainees or with more significant involvement from the attending physician [17]. Another potential factor is the use of robotic assistance, as robotic skills are generally acquired more rapidly than laparoscopic skills, potentially influencing trainee participation and operative efficiency. A cross-sectional study using ACS-NSQIP data supported this, finding that trainee involvement in common procedures like laparoscopic appendectomy, laparoscopic cholecystectomy, and open inguinal hernia repair significantly increased operative time, regardless of trainee seniority [18]. The association between trainee involvement and complication rates likely varies depending on the procedure, the skills required, and the training paradigms in place [19, 20]. For instance, when comparing resident and fellow involvement in abdominal myomectomy, no significant difference in operative time was found between groups. However, there was a higher rate of blood transfusions and complications in procedures involving fellows, possibly because fellows, as more senior and skilled trainees, were more likely to be involved in more complex cases.

CONCLUSIONS

Procedures involving trainees had longer operative times compared to those performed by attending surgeons

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alone. The trainee-involved group experienced slightly higher blood loss and longer hospital stays. These differences were statistically significant for primary outcomes such as operative time and blood loss. The presence of trainees was significantly associated with an increased risk of hemorrhage, although no significant associations were found for surgical site infections or wound dehiscence. While the trainee involvement may lead to longer procedure durations and a higher likelihood of certain complications, its effect on primary surgical outcomes was minimal. It was suggested that to make optimizing protocols for trainees to ensure safe and efficient surgical procedures.

Authors Contribution

Conceptualization: IAK, NK

Methodology: IAK, AN, HB, NK

Formal analysis: SK, AN, HB, IA

Writing, review and editing: SK, AN, HB, NK, IA

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

Conflicts of Interest

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Original Article

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Evaluating the Diagnostic Accuracy of C-Reactive Protein in Diagnosing Pneumonia in Children Using Blood Culture as the Gold Standard

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ABSTRACT

C-Reactive Protein (CRP) is important in identifying and evaluating bacterial infections as a conventional biomarker. **Objective:** To determine the diagnostic accuracy of CRP in diagnosing pneumonia keeping blood culture and radiological findings as a gold standard. **Methods:** A descriptive cross-sectional study was conducted in the Department of Pediatrics at Lady Reading Hospital, Peshawar Pakistan from December 2022 to December 2023. After selecting 246 patients who satisfied the required inclusion criteria for pneumonia, an immunoturbidimetric assay was utilized to quantitatively measure CRP levels. To compare the results to those of the gold standard of blood culture, patients with both positive and negative cultures were included. Among the 246, the mean age of the children was 9±2.73 years. There were 136 males (55%) and 110 females (45%), with male to female ratio of 1.24:1. **Results:** Results were true positive in 207 (84.15%), true negative in 7 (2.85%), false positive in 9 (3.66%) and false negative in 23 (9.35%). Diagnostic accuracy was analyzed as CRP had a sensitivity of 87.77%, specificity of 52.94%, Positive predictive value of 96%, negative predictive value of 24.32%, and overall diagnostic accuracy was 85.36%. **Conclusions:** Clinicians and laboratory professionals face difficulties in making a precise and prompt diagnosis of pneumonia. However, by conducting a single, inexpensive, and rapid test using CRP as a qualitative estimator, physicians can prevent the unnecessary use of antibiotics with an accuracy of 85.36%.

INTRODUCTION

Community-acquired Pneumonia (CAP) is a significant source of illness in developed nations and a crucial cause of morbidity and mortality in underdeveloped nations [1].CAP impacts 0.3%–1.5% of children every year in Western nations [2]. The current conventional treatment approach in international guidelines for CAP involves administering 7–10 days of oral amoxicillin, irrespective of the etiology [3]. Viruses, either alone or in mixed infections with bacteria, dominate as the primary cause of CAP in children below the age of 5 years [4]. Studies have established that Mycoplasma pneumoniae contributes to over 50% of cases in children above 10 years of age, but the efficacy of antibiotics in such cases remains unclear [5]. Streptococcus pneumoniae is the most significant bacterial pathogen in all age groups [6]. Overlapping symptoms, non-specific physical exam findings, and limited access to diagnostic tests are challenges in diagnosis of pneumonia, in low-resource settings. Chest X-rays and blood cultures are still thought to be the gold standards for diagnosis [7]. However, these methods are not always feasible or affordable in such settings, which highlights the need for a rapid, accurate, and affordable diagnostic tool for pneumonia, especially in low-resource settings. Tillet and Francis discovered C-Reactive Protein (CRP) in 1930, which is a homopentameric protein that is highly conserved in plasma. CRP is an acute-phase inflammatory agent that shows increased expression in inflammatory conditions such as cardiovascular disease,

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and rheumatoid arthritis, infection. Inflammatory disorders cause the CRP levels in plasma to deviate by at least 25% [8]. Recent meta-analyses have highlighted the variability in diagnostic approaches and the effectiveness of CRP in distinguishing between bacterial and viral pneumonia in pediatric populations. Such analyses have provided the need for improved diagnostic algorithms for pneumonia diagnosis in resource-limited environments [9, 10]. CRP is important in identifying and evaluating bacterial infections as a conventional biomarker. Among the several tests available, CRP's role in pneumonia has been extensively studied which indicates its high sensitivity and specificity in diagnosing bacterial infections in children with pneumonia.

This study aimed to assess the diagnostic accuracy of C-Reactive Proteins (CRP) in diagnosing pneumonia by utilizing radiological findings and blood cultures as the gold standard. Although pneumonia is a prevalent disease worldwide, it can be difficult to diagnose the illness early and accurately. Studies that have already been conducted have shown conflicting results about the validity of CRP as a stand-alone marker. Some of these studies have not included a thorough comparison with gold-standard diagnostics, or they have given inconsistent information about the predictive usefulness of CRP. By carefully measuring CRP levels in addition to using recognized diagnostic techniques, this work fills up these gaps. In doing so, it hopes to provide light on whether CRP can serve as a trustworthy early indicator of pneumonia, facilitating prompt clinical decision-making. In the end, the results may contribute to a decrease in the overuse of antibiotics, and enhance patient outcomes.

METHODS

A descriptive, cross-sectional study was carried out at the Department of Pediatrics at Lady Reading Hospital, Peshawar Pakistan from December 2022 to December 2023. The study was conducted after obtaining the necessary approvals from the Department of Pediatrics at Lady Reading Hospital, Peshawar (Reference No. 422/CBW/LRH). The sample size was 246 patients, using 95% sensitivity, 45% specificity, and 52% proportion of pneumonia with a margin of error for sensitivity as 3.2% and specificity as 8% using Raosoft software for diagnostic accuracy. The sensitivity value of 95% was selected based on existing literature indicating that CRP has a high potential to correctly identify true positive cases of pneumonia [11]. Specificity was set at 45% to account for the possibility that CRP, while sensitive, may also be elevated in other conditions, reflecting a moderate ability to exclude non-pneumonia cases. The proportion of pneumonia was estimated at 52% based on local epidemiological data, providing a realistic reflection of the prevalence of pneumonia in the pediatric population studied. A non-probability purposive sampling technique was followed. All children from 2 to 14 years of age with high suspicion of pneumonia were involved in the study. Pneumonia was suspected when children had a fever of more than 100°F at the time of presentation and tachypnea upper limit according to age. Children with a history of surgical intervention, renal insufficiency (serum urea level of>50mg/dl and creatinine level of >1.1mg/dl), and trauma were excluded from the study. The exclusion criteria was set to eliminate factors that could confound CRP levels and affect the accuracy of the study. Patients with a history of surgical intervention and trauma were excluded due to the potential for surgery-induced or trauma-induced inflammation, which could falsely elevate CRP levels. Children with renal insufficiency were excluded because renal dysfunction can alter CRP metabolism, leading to inaccurate measurements. An explanation was provided to the parents of the child regarding the purpose and benefits of the study. They were reassured of the study's objectives and advantages, informed of any associated risks, and made aware that the study was solely conducted for research and data publication. Once the parents agreed to participate, written consent was obtained. A thorough clinical examination was conducted on all children, and a brief history was obtained from their parents. To detect pneumonia, 5cc of blood was collected from each child using strict aseptic techniques and sent to the hospital laboratory for CRP testing. An immunoturbidimetric assay was utilized to quantitatively measure CRP levels, with a threshold of 5mg/dL. The same blood specimen was also sent for complete blood culture analysis in the same laboratory to confirm the presence of pneumonia. Additionally, a chest X-ray was performed for the results in the meantime. The laboratory investigations were conducted under the supervision of a microbiologist who had a minimum of five years of experience. A pre-designed form was used to record all the relevant information. To ensure control of confounders and bias in the study results, strict exclusion criteria were followed. The collected data were analyzed using SPSS version 24.0, with numerical variables such as age calculated for mean and standard deviation. Categorical variables, including qualitative CRP and blood culture results were presented as frequency and percentages. Furthermore, sensitivity, specificity and negative, and positive predictive values for CRP in identifying children with blood culture and x-ray-proven pneumonia were also computed.

RESULTS

In this study, 246 patients with pneumonia were included. The mean age of the children was 9 ± 2.73 years. There were 136 males (55%) and 110 females (45%), with male to female

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ratio of 1.24:1. Results were true positive in 207 (84.15%), true negative in 7 (2.85%), false positive in 9 (3.66%) and false negative in 23(9.35%)(Table 1).

Table 1: Total Accuracy of CRP in Diagnosis of Pneumonia(n=246)

Blood Culture Sensitivity and X-Ray Diagnosis					
CRP levels	**Positive**	**Negative**	**Total**	**False Positive (%)**	**False Negative (%)**
Positive	207	9	216	84.15%	2.85%
Negative	23	7	30	3.66%	9.35%
Total	230	16	246	87.81%	12.19%

Diagnostic accuracy was analyzed as CRP had a sensitivity of 87.77%, specificity of 52.94%, Positive predictive value of 96%, negative predictive value of 24.32% and overall diagnostic accuracy was 85.36% (Table 2). To align with the study objectives, the results demonstrate a high diagnostic accuracy of CRP in diagnosing pneumonia, keeping blood culture and radiological findings as the gold standard. Specifically, CRP exhibited a high sensitivity (87.77%) in identifying true cases of pneumonia, which supports its effectiveness as a diagnostic tool. However, the 9 false positives and 23 false negatives observed in the study indicate potential limitations in CRP diagnostic accuracy. Moreover, the lower specificity (52.94%) indicates that while CRP is useful in detecting pneumonia, it may not be sufficient as a standalone marker.

Table 2: Validity and Predicted Outcomes of CRP

Diagnostic Test	(%)
Sensitivity	87.77%
Specificity	52.94%
Positive Predictive Value	96%
Negative Predictive Value	24.36%
Accuracy	85.36%

DISCUSSION

Pneumonia remains a significant cause of morbidity and mortality, particularly in the developing world where its incidence was significantly higher. The delay in diagnosis and initiating therapy were the main reasons for high mortality. Diagnostic tests for pneumonia may include chest X-rays, blood tests, sputum analysis, and sometimes a CT scan. Starting from the early 1990s, the World Health Organization (WHO) has suggested using quantitative tachypnea to identify children who may need antibiotic treatment for potential Pneumonia [12]. However, this technique relies on subjective assessment. Blood culture and chest x-ray were still considered as a gold standard for diagnosis. Among the different tests used to diagnose pneumonia, the role of CRP in the diagnosis of pneumonia has been vastly considered. Based on the results, there were 246 total children, of which 84.15% (207 children) were classified as true positive for pneumonia based on CRP results, and 9.35% (23 children) were classified as false negative. This means that the CRP test correctly identified the majority of cases of pneumonia, but missed a small number of cases. The efficacy of CRP in identifying pneumonia in children was also reported by previous studies [9, 13, 14]. Studies should also explore its effectiveness in diverse clinical settings, especially where advanced diagnostics were limited. Additionally, examining CRP role in monitoring treatment response and disease progression could be beneficial for clinical practice. A similar study was conducted by Barek-Corren Y *et al* in 2021 [15]. In that study, 835 children with CSP were examined, out of which 87 had viral pneumonia and 89 had invasive bacterial pneumonia. According to the study, the viral pneumonia group exhibited lower levels of PCT and CRP in the absence of malaria parasites compared to the invasive bacterial pneumonia group. PCT and CRP cut-offs were determined at 0.72 ng/ml (with a sensitivity of 94.6% and specificity of 74.2%) and 20.9 mg/l (with a sensitivity of 95% and specificity of 54.2%), respectively. Wrotek A *et al.*, also compared prolactin and CRP and showed similar results [16]. Another study by Dudognon D *et al.*, which included 586 children under 5 years of age with severe clinical pneumonia, also yielded similar results [17]. The positive bacterial culture (BC+) group comprised all children with bacteremia, while a random selection of other children was placed in the negative bacterial culture (BC-) group. The results indicated that at a sensitivity of 95%, the specificity of CRP was 45%, similarly, at a sensitivity of 85%, the specificity of CRP was 57%. The Area under the curve for evaluating BC+ was 0.79 for CRP, slightly lower than the AUC of 0.80 for Procalcitonin. However, the difference between the two markers was not statistically significant (P = 0.617). The meta-analysis by Gunaratnam LC *et al.*, Tsou PY *et al.*, and Gentilotti E *et al.*, also comply with these results [10, 18, 19]. Gunaratnam LC *et al.*, aimed to evaluate the effectiveness of various biomarkers in diagnosing bacterial pneumonia in children, particularly in resource-poor settings. The study analyzed 31 observational studies and found that CRP and procalcitonin were the most effective in distinguishing bacterial from viral pneumonia. Their results demonstrated moderate accuracy with the though their accuracy was moderate, with sensivities from 60% to 85% and specificities from 76% to 83%. CRP slightly outperformed procalcitonin. The study concluded that while CRP and PCT were useful diagnostic tools [10]. Another study by Tarhani F *et al.*, evaluated the diagnostic accuracy of CRP level for pneumonia in children presenting at an emergency department [20]. Of the 687 children, 286 went through CRP measurement and chest radiography and 148 had pneumonia. The study found that higher CRP levels were related to a higher proportion of pneumonia and that CRP level was independently associated with pneumonia, even after adjusting baseline characteristics. However, low CRP levels did not exclude pneumonia. The study suggests that CRP could have a diagnostic significance for pneumonia in children and prompts further evaluation in primary care settings.

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CONCLUSIONS

The study's radiological findings suggested that CRP can be a useful tool for clinicians to accurately diagnose pneumonia and avoid unnecessary antibiotic use with an accuracy of 85.36%, as they have difficulty in making an accurate and timely diagnosis of pneumonia. However, CRP alone cannot be relied upon to definitively diagnose pneumonia, as it has limitations. It should be used in conjunction with other diagnostic tests and clinical assessments to make an accurate diagnosis.

Authors Contribution

Conceptualization: NA
Methodology: AI[1], IU, IK, IM
Formal analysis: IU
Writing, review and editing: NA, AI[1], AI[2], IK, IM

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

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Effect of Dexamethasone Versus Triamcinolone Acetonide on Postoperative Complications after Impacted Third Molar Surgery

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ABSTRACT

In the area of maxillofacial surgery, taking out of impacted teeth, particularly third molars represents a common practice. Corticosteroids play a substantial role in reducing edema and have been found to have anti-inflammatory belongings. **Objective:** To compare the outcome of Dexamethasone vs. Triamcinolone Acetonide after impacted third molar surgery. **Methods:** A quasi-experimental study was organized at the Department of Oral and Maxillofacial Surgery, Liaquat University of Medical and Health Sciences, Jamshoro/Hyderabad. A total of 288 patients with Mesioangular impaction of mandibular 3rd molar tooth were placed into two groups at random. Group-A (Dexamethasone Injection) 4mg was injected instantly into the submucosal at about 1cm above the surgical area and in Group-B (Triamcinolone Acetonide Injection) 4mg was also injected immediately at the same place. Measurements were made on the mouth opening, severity of pain, and swelling. **Results:** The mean pain score was significantly lower in group B than in group A on the 7th postoperative day ($p = 0.0005$). Mean facial swelling size was not statistically significant between groups at 2nd day but it was significantly low in group B as compared to group A at 5th and 7th postsurgical days. Mean mouth opening was also significantly higher in group B than in group A at the 5th and 7th postoperative days ($p = 0.0005$). **Conclusions:** Submucosal applying corticosteroid medication may be a very painless, effective, cheap, less hazardous, simpler technique for both the patient and the doctor, and its systemic effect is limited.

INTRODUCTION

The obstructed tooth declines to explode into its appropriate place at the period of emission and it is the last tooth to erupt in permanent dentition [1]. It is categorized radio graphically using angulations categorization based on the inclination to the long axis of the second molar i.e; Mesioangular (37.4%), Vertical (32.8%), Distoangular (16.6%), Horizontal impaction (11.2%), among the types of impaction. Mesioangular impaction is the most common type of mandibular impaction [2, 3]. The surgical process to take out third molars frequently includes incision, flap reflection, and bone removal to expose the socket is associated with postoperative complications [4]. Due to the anatomical location of submerged mandibular third molars, both soft and hard tissue trauma occurs and causes post-operative complications [5]. The impacted mandibular third molar tooth is on the point of the inferior alveolar vessels, so the surgical area is very highly vascular leading to postoperative complications [6, 7]. These

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complications interfere with the patient's comfort and social life. Many clinical studies investigate drug therapy to improve clinical results with minimization of postoperative complications of impacted mandibular third molar surgery using antiseptic mouthwash, antibiotics, muscle relaxants, corticosteroid treatment, and physiotherapy [8-10]. Amongst steroids are useful in surgery for decreasing chemical mediators of inflammatory tissues, by falling transudation of fluids and decreasing edema, pain, and trismus; Betamethasone, Triamcinolone Acetonide, Prednisolone, Hydrocortisone, Dexamethasone, Methylprednisolone [11-13]. The long-standing production of dexamethasone is un-justifiable because of half-life is 36-48 hours, so its duration of action is up to the 2nd day but not on the 7th day [14]. Another study shows that 63% of dexamethasone was slightly affected by post-operative pain and only 21.6% of dexamethasone experienced moderate to severe pain. Some authors showed the ability to reduce swelling by 42-50% and another study shows 73.7% mouth opening improved in 72% after using the dexamethasone [15]. The purpose of this study is to compare the efficacy of dexamethasone and triamcinolone acetonide on postsurgical complications after impacted third molar surgery. It may reduce post-operative morbidity and complications like pain, swelling, and trismus. The study was beneficial for clinicians/ surgeons to have a better treatment choice and for patients to have good treatment protocols.

This study aimed to compare the outcome of Dexamethasone vs Triamcinolone Acetonide after impacted third molar surgery.

METHODS

A quasi-experimental study was conducted at the Department of Oral and Maxillofacial Surgery, Liaquat University of Medical and Health Sciences, Jamshoro/ Hyderabad by employing a non-probability consecutive sampling technique in the time frame of six months (from 11-10-2019 to 10-03-2020) with approval of research ethics committee (LUMHS/REC/336) after getting the written consent from the patients. The epitools online calculator was applied to calculate the sample size. The study reported a mean reduction in pain, swelling, and trismus on the outcome variable on day 7 Dexamethasone group (1.23 ± 3.01, 0.22 ± 0.51 and 3.46 ± 6.24 respectively) compared to current outcome variable on day 7. Triamcinolone Acetonid (0.42 ± 1.65, 0.08 ± 0.10 and 2.53 ± 3.90 respectively) [9, 10]. Considering 95% confidence interval, considering power as 80% is 288 with 144 patients in each group. Patients with mesioangular impaction mandibular 3rd molar tooth diagnosed clinically and on radiographic examination, having age from 18 to 45 years, either gender and good oral hygiene in terms of healthy, functionally and esthetically stable mucosa, were included and patients on steroid therapy, immunocompromised patients like; AIDS, Diabetics Mellitus, Alcoholism, Malnourished and patients with Acute Severe Pericoronitis were excluded from the study. The impacted tooth was diagnosed by history, clinical assessment, and radiographs like periapical and panoramic radiographs. The demographics age, gender, and clinical parameters like swelling, pain, and mouth opening were recorded. SPSS version 26.0 was employed for data analysis. The Mean and Standard deviation were counted for age. Frequency and percentage were figured for age, and gender. Comparison of facial swelling, pain, and trismus among groups was conducted by independent t-test. The p-value was measured as significant ≤ 0.05. The surgical procedure to remove the third molar was made with local anesthesia by giving a conventional inferior nerve block also anesthetizing the lingual nerve and buccal nerve by injecting xylocaine 2% with epinephrine 1:100000. Surgical blade no.15 was used for incision. An envelope mucoperiosteal flap was lifted to uncover the third molar. Before the start surgical process, all patients were given Clorohexidine mouth wash for at least two minutes. A Standardized surgical procedure was under taken as a means of to disclose the impacted mandibular third molar, the cortical bone at the buccal side, around with slow speed handpiece for the alveolotomy under continuous irrigation of 0.9% normal saline solution, then the tooth was exposed and extracted after taking away of a tooth any sharp bone was smoothened by same round bur and the socket was washed with 0.9% normal saline. The flap was repositioned and sutured with vickryl 3-0 in both groups. Submucosal injection of single dose dexamethasone (4mg) or Triamcinolone Acetonid was immediately injected at about 1cm above the surgical area following the surgical mandibular impacted third molar [8]. The pressure pack was placed for thirty minutes [3]. Post-operative directions consist of a soft diet, and maintaining oral hygiene via mouthwash, antibiotics, and analgesics three times a day for five days [6]. Analgesic Ibuprofen 600mg three times a day for five days. Antibiotic Amoxicillin with clavulanic acid 1 gram twice daily for five days. The sternness of pain was assessed by using a Visual Analog Scale. The extent of swelling was calculated by facial size through Amin and Laskin's criteria which was measured in millimeters. Normal inter-incisal distance is 35 to 45mm, less than 35 mm distance is considered as limiting mouth opening, which can be measured by ruler. Mouth aperture was considered by interincisal distance through a ruler (35-45mm normal value). All the data were documented on the 2nd, 5th, and 7th day by the clinician.

RESULTS

A sum of 288 participants were integrated for this study,

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the gender distribution shows male preponderance 168 (58.3%) were male and 120 (41.7%) were female. The greater part of the sample was aged between 31-40 years old (47.56%) followed by 21-30 years (29.51%) and a large amount of the patients have primary level education (32.63%) and bulk of the extractions were from the right side (52.08%) of the lower 3rd molar (Table 1).

Table 1: Demographic Status of Participants

Characteristics	Group A	Group B
Age		
18-20	12 (4.17)	18 (6.25)
21-30	39 (13.54)	46 (15.97)
31-40	75 (26.04)	62 (21.53)
>40	18 (6.25)	18 (6.25)
Mean ± SD	32.45 ± 7.81 Years	
Gender		
Male	85 (59.02)	83 (57.64)
Female	59 (40.98)	61 (42.36)
Site of Extraction		
Right	74 (51.39)	76 (52.78)
Left	70 (48.61)	68 (47.22)
Educational Status		
Illetrate	48 (16.67)	33 (11.46)
Primary	51 (17.71)	43 (14.93)
Matriculation	14 (4.86)	20 (6.94)
Intermediate	24 (8.33)	33 (11.46)
Graduate and Above	7 (2.43)	15 (5.21)

The mean pain score of the patients on different days it was not statistically significant between groups at 2nd and 5th postoperative days however mean pain score was significantly low in group B than group A at 7th postoperative day (p=0.0005) (Table 2).

Table 2: Comparison of Pain Between the Groups

Pain	Group A	Group B	p-Value
	Mean ± SD	Mean ± SD	
2nd day	4.59 ± 0.97	4.68 ± 0.85	0.402
5th day	3.33 ± 0.87	3.17 ± 1.06	0.170
7th day	1.27 ± 0.73	0.53 ± 0.59	0.0005

The comparison of facial size that was measured on 2nd, 5th and 7th days after impacted 3rd molar surgery. Likely mean facial swelling size was not statistically significant between groups at 2nd days but it was significantly low in group B as compare to group A at 5th and 7th postoperative day (Table 3).

Table 3: Comparison of Facial Size Swelling Between Groups

Facial size (mm)	Group A	Group B	p-Value
	Mean ± SD	Mean ± SD	
2nd day	1.42 ± 0.27	1.46 ± 0.26	0.177
5th day	1.20 ± 0.26	1.05 ± 0.39	0.0005
7th day	1.14 ± 0.22	0.73 ± 0.25	0.0005

The mouth opening size measured on 2nd, 5th, and 7th day mouth opening was significantly high in group B than group A on 5th and 7th postoperative days (p=0.0005) (Table 4).

Table 4: Comparison of Mouth Opening Size Between Groups

Mouth Opening (mm)	Group A	Group B	p-Value
	Mean ± SD	Mean ± SD	
2nd day	23.47 ± 5.46	22.36 ± 6.58	0.120
5th day	25.28 ± 5.28	39.74 ± 10.04	0.0005
7th day	31.11 ± 11.03	40.28 ± 10.37	0.0005

DISCUSSION

The highest percentage of individuals with at least one impaction had lower third molars accounting for 33% of cases. Third molars are often impacted due to skeletal deficiency in the area of eruption. Sagittal growth of mandible finished earlier than eruption of the third molar in many cases leading to impaction. Subtraction of impacted third molar is allied with postsurgical obstacles. Since corticosteroids have anti-inflammatory attributes, they are frequently used to treat these side effects [16-18]. Complications related to impacted teeth removals are not irrelevant and their improvement is conditioned via local and general elements inclusive of tooth position, age, and fitness popularity of the affected person, understanding and experience of the surgeon, and surgical device. Unlike the research conducted by Grossi *et al.*, and Graziani *et al.*, the current investigation discovered statistically significant differences between the DEX and TA groups on the seventh postoperative day [18, 19]. In comparison to the current study, high extent of patients older than 40 years were observed in a study that could be due to lack of oral health attentiveness leading to holdup in treatment [20]. While it is a minor surgical method, the common sequelae, which are pain, swelling, and trismus, can harshly influence patients' quality of life through the post-operative phase Both steroidal and non-steroidal anti-inflammatory drugs are extensively utilized to manage pain and inflammation [21-23]. In present study, the age ranges from 18 to 45 years with an average age 32.45 ± 7.81 years. In contrast to another study, age was counted from 20 to 50 years [15]. This age disparity can be because of a diversity of reasons like rational differences, or delayed reports by the patients at the hospitals. In current study out of 288 patients, there were 168 (58.3%) male and 120 (41.7%) female. In a comparable study by Tegginamani and Prasad 58% of the patients were male and 42% female thus demonstrating male dominance [16]. Comparably, a study carried out in India by Srinivasulu *et al.*, revealed that 45.33% of the patients were men and 54.67% of the patients were women [14]. This gender gap may be a result of specific social, environmental, and geographic factors. There were statistically significant differences between the two groups on the 7th day of the postsurgical time. The mean pain score was not statistically significant between groups at 2nd and 5th postoperative days however mean pain score was significantly low in group B (triamcinolone acetonide) than group A at 7th postoperative day (p = 0.0005). Similarly

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mean swelling facial size was not statistically significant between groups at 2nd days but it was significantly low in group B as compare to group A at 5th and 7th postoperative day. Mean mouth opening was also significantly high in group B than group A at 5th and 7th postoperative days (p = 0.0005). On the second and fifth postoperative days, there were no statistically significant differences between the DEX and TA groups for the assessment of pain. Triamcinolone acetonide works postoperatively, and its effect on trismus and pain was better than that of other groups, according to Srinivasulu *et al.*, comparison of the effectiveness of submucosal injection of dexamethasone and triamcinolone acetonide on postoperative pain, swelling, and occurrence following impacted mandibular third molar surgery in 150 patients [14]. Because of its greater local potency, a longer period of action, and lesser systemic absorption, trimetinone is a superior corticosteroid for intralesional injection.

CONCLUSIONS

The present study showed that administration of submucosal dexamethasone and TA produced similar effects in reducing edema, pain, and trismus after third molar surgery on day 2 to 5 postoperatively but on 7th postoperative day, TA was found to be more potent and effective. It may reduce the post-operative morbidity and complications like pain, swelling, and trismus. The study was beneficial for clinicians/surgeons to have a better treatment choice and for patients to have good treatment protocols.

Authors Contribution

Conceptualization: IBK

Methodology: IBK, THS, SS

Formal analysis: IBK

Writing-review and editing: AAK, MHZ, SUB, KAC

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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Exploring Hypertension Knowledge and Identifying Determinants of Inadequate Knowledge Among Non-Hypertensive Adult Pakistanis

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ABSTRACT

Hypertension was a serious global health issue, with over half of the adults in underdeveloped nations remained undiagnosed. Given its prevalence and associated repercussions, non-hypertensive people continue to have low awareness of hypertension. **Objective:** To assess Knowledge of hypertension and identify determinants of inadequate Knowledge among non-hypertensive adult Pakistanis. **Methods:** A cross-sectional survey was conducted from January to May 2024. A sample of 500 non-hypertensive adults was recruited using the snowball sampling technique. The information was gathered using an online survey based on the Hypertension Knowledge-Level Scale (HK-LS). Data analysis was performed using SPSS version 26.0, and chi-square tests were applied to identify determinants of inadequate Knowledge. **Results:** The research project comprised 265 males (53%) and 235 females (47%), averaging 35.2 years. According to the total knowledge score, only 33.64% of participants had the necessary hypertension information, while 66.36% did not comprehend it. Knowledge about medication compliance, medical care, and hypertension problems was shown to have significant gaps. Age, educational attainment, and a family history of hypertension were among the demographic characteristics that significantly influenced Knowledge ($P<0.05$). Higher education levels and a family history of hypertension were associated with better knowledge levels among participants. **Conclusions:** In Pakistan, the non-hypertensive population is largely unaware about hypertension. In order to reduce hypertension and increase awareness, targeted outreach initiatives were necessary. Enhancing health literacy through media, healthcare providers, and family health communication can bridge the knowledge gap.

INTRODUCTION

Global sociodemographic shifts toward aging, fast urbanization, and the expansion of sedentary lifestyles promote tobacco use, excessive salt intake, weight gain, and inactivity, which raises the risk of noncommunicable diseases, particularly hypertension [1, 2]. According to numerous studies, hypertension is the leading cause of premature mortality and is a serious medical condition that primarily affects the kidneys and brain and increases the risk of cardiovascular disease [1, 3]. The prevalence of hypertension is the same in high-income and middle-income nations. On the other hand, hypertension is a serious health risk in low- and middle-income nations [4, 5]. Southeast Asia contributes to 80% of all cardiovascular disease deaths in those with poorly managed blood pressure [6]. Researchers have found that various factors influence understanding of hypertension, including socioeconomic level, lifestyle decisions such as high salt intake, medication adherence concerns, and gaps in

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clinical practice adherence to guidelines [7, 8]. Studies were out in poor nations found a correlation between high blood pressure and a lack of Knowledge about hypertension. The research highlights the need for all-encompassing health education initiatives that prioritize lifestyle modifications [9-11]. Similarly, a mixed-methods study conducted in Tanzania revealed a high prevalence of hypertensive disease (28%); remarkably, almost half of the participants (48%) acknowledged having hypertension but found it difficult to control because of various obstacles, including inadequate access and care from unqualified medical personnel [8]. The latter situation reflects issues within health service delivery systems that hinder effective care [12]. Another study conducted in Saudi Arabia investigated hypertension patients' Knowledge of their blood pressure measurements; despite higher educational levels only 74.4% were aware of their target blood pressure readings [13]. Later studies pinpoint a wide range of factors that lead to non-hypertensive individuals' low Knowledge of hypertension. It is widely accepted that early adulthood is the best time to start primary prevention, early detection, and blood pressure control. By highlighting gaps and increasing awareness, Knowledge of HTN in hypertension patients is crucial to controlling modifiable risk factors and reducing burden. Studies in Africa Asia revealed that good awareness of HTN is connected with higher rates of blood pressure control, medication adherence, and reduced morbidity and death [1, 7, 14, 15]. Furthermore, Nadeem MK *et al.*, examined hypertension-related Knowledge among Pakistanis, demonstrating a gap between Knowledge and appropriate management. Although the people had relevant information about hypertension (79%), only 64.8% could maintain their blood pressure [11]. To the best of the researcher's Knowledge, no study has used the standard Hypertension Knowledge-Level Scale (HK-LS) to assess Knowledge status and identify causes of low awareness among non-hypertensive adult Pakistanis [14]. Our study's objectives were to evaluate adult Pakistanis without hypertension's understanding of the condition and identify the factors contributing to this ignorance.

METHODS

A cross-sectional survey was carried out in 2024 between January and May. Open Epi software version 3.0 was used to calculate the sample size using the statistical approach n= [DEFF*Np(1-p)]/ [(d2/Z21-α/2*(N-1)+p*(1-p)] [16]. Based on the 40.7% prevalence of hypertension among participants from the prior study, the sample size was calculated, with a 5% margin of error and a 95% confidence interval, yielding a sample size 525. Nevertheless, we manage to assemble a 500-person sample size with a 95.2% response rate [3]. The snowball technique (Figure 1) was used to select participants who fulfilled the following requirements: they had to be Pakistani citizens who had been in the country for more than five years, not have a history of hypertension, be at least eighteen years old (regardless of gender), able to understand and write in English, have given written consent to participate, and be able to use electronic devices with a basic understanding of computers in order to complete the survey. The RLKU Medical College, Lahore Institutional Review Board (IRB) granted ethical permission before the research investigation could begin (Reference Number: RLKU.IRB-003/12/23). People gave their informed consent in writing before enrollment. Thirty volunteers helped validate the questionnaire. More than 0.7 is regarded as an appropriate value for a Cronbach's alpha coefficient in a survey used to gather data. Three knowledgeable researchers assessed the validity of the complete form. For every question, the item-objective congruence index was more significant than 0.5, which was considered satisfactory. The Hypertension Understanding Level Scale (HK-LS), an instrument designed by Erkoc SB *et al.*, to measure Turkish adults' comprehension of hypertension, comprises 22 items in Section 2 [14]. Six subdomains were created from the twenty-two components, including definition of illness, medical treatment, medication adherence, lifestyle, food, and repercussions. The number of questions that the research volunteers answered correctly indicated whether or not their level of knowledge was appropriate. The participant was asked to indicate whether the supplied assertion was true, false, or unknown for each item, which consisted of a whole sentence." For every accurate response, one point was given; 'do not know' or erroneous responses yielded zero points. At least 75% of the right answers were required for a satisfactory level of knowledge (17 or more of 22). Should the percentage of correct answers stay below 75% (17 out of 22), the participant considered their knowledge to be insufficient. An online, self-administered, closed-ended survey made with the Google Forms platform was used to collect the research data. The SPSS version 26.0 was used to analyze the data. Frequencies and percentages were used to represent different types of variables. The mean and standard deviation were used to express the overall and subdimensional results of the HK-LS.

RESULTS

The Shapiro-Wilk test was utilized to confirm the normality of the data. Using Chi-Square, the factors that lead to inadequate knowledge were discovered. Every test was deemed significant when the P-value was less than 0.05. Arc GIS software displayed the participants' geographic locations (Figure 1).

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Figure 1: Geographical Distribution of Study Participants

The dataset provides an insightful glimpse into various demographic and socio-economic characteristics of non-hypertensive adults in Pakistan (Table 1), focusing on their awareness and Knowledge of hypertension. The sample consists of 500 individuals, with a slight male majority (265 males, or 53%, and 235 females, or 47%). The mean age of participants is 35.2 years, with a standard deviation of 5.1 years. Age distribution reveals that 31.25% were between 18 and 30 years old, 33% were between 31 and 40 years, 14.43% fall within the 41 to 50 years range, 11.57% were aged between 51 and 60 years, and 9.75% were over 60 years old. Participants come from various provinces in Pakistan, with Punjab being the most represented (42.50%), followed by Sindh (23.25%). Education levels vary, with most having completed bachelor's degrees (38.50%) or master's degrees (36%). Secondary education was reported by 20.25%, and 5.25% have a PhD. According to socioeconomic level, 42.75% of people have balanced financial conditions, 34.50% occasionally face financial difficulties, 12% frequently experience financial difficulties, and 10.75% have financial difficulties all year round. The nearly equal distribution of genders guarantees that both the views of men and women were taken into account. The need of focusing awareness campaigns on younger individuals was underscored by the prevalence of younger age groups, particularly those between the ages of 31 and 40. The necessity for region-specific tactics was seen in the strong presence of Punjab. Given the high proportion of married people, family-based therapies may be successful. The noteworthy percentage of individuals possessing advanced education suggests the possibility of utilizing academic accomplishments in health awareness initiatives. The socioeconomic data emphasize the financial difficulties experienced by many participants, and the varying job status emphasizes the necessity for customized methods based on various employment conditions.

Table 1: Socio-Demographics Characteristics of the Participants (n=500)

Variables	Category	Frequency (%)
Gender	Male	265 (53)
	Female	235 (47)
Age (Years)	18–30	155 (31.25)
	31–40	165 (33)
	41–50	72 (14.43)
	51–60	58 (11.57)
	>60	49 (9.75)
Age (Mean ± S.D)	-	35.2 ± 5.1
Province	Sindh	115 (23.25)
	Punjab	213 (42.50)
	Gilgit Baltistan	36 (7.25)
	KPK	78 (15.5)
	Balochistan	58 (11.50)
Marital Status	Single	146 (29.25)
	Married	308 (61.50)
	Separated / Divorced	46 (9.25)
Education Level	Secondary	101 (20.25)
	Bachelors	193 (38.50)
	Masters	180 (36.00)
	PhD	26 (5.25)
Employment Status	Employed	204 (40.75.5)
	Self-Employed	84 (16.75)
	Looking for a Job	74 (14.75)
	Housewife	36 (7.25)
	Student	82 (16.50)
	Retired	20 (4)
Socio-Economic Status	Insufficient Funds for the Whole Year	54 (10.75)
	Insufficient Funds for Some Time	172 (34.50)
	Balance	214 (42.75)
	Sufficient Funds for Most of the Times	60 (12)
	Yes	88 (17.50)
	No	230 (46)
	Don't Know	182 (36.5)
Source of Information about HTN	Media	157 (31.5)
	Healthcare Workers	96 (19.25)
	Friends and Family Members	202 (40.25)
	Others	45 (9)

The assessment of participants' Knowledge regarding hypertension (Table 2), evaluated through the Hypertension Knowledge Level Scale (HK-LS), reveals varying levels of understanding across different sub-dimensions of Knowledge. Participants' responses indicate significant gaps in Knowledge about hypertension, its treatment, and its complications. Regarding the definition of hypertension, 51.04% correctly identified that increased diastolic blood pressure indicates increased blood pressure, while 50.37% correctly noted that high diastolic or systolic blood pressure indicates increased blood pressure.

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Table 2: Assessment of Participant's Knowledge through the Hypertension Knowledge Level Scale

Sub-Dimensions of Knowledge	Variables	Correct Responses Frequency (%)
Definition	Higher diastolic blood pressure suggests high blood pressure	255 (51.037)
	Elevated diastolic or systolic blood pressure demonstrates a higher blood pressure	250 (50.37)
Drug Compliance	There is no need to change your lifestyle if your blood pressure medication can control it	153 (30.63)
	Aging causes high blood pressure; thus, treatment is unnecessary	198 (39.62)
	Individuals with elevated blood pressure can avoid therapy by changing their lifestyle	160 (32.15)
	People with high blood pressure can eat salty meals as long as they take their medications regularly	130 (26.07)
Medical Treatment	Medications for High Blood Pressure need to be Used Daily	154 (30.88)
	Individuals with elevated blood pressure Should only take their medicine when they are feeling not well	207 (41.39)
	Those with high blood pressure must take their medicine throughout their lives	230 (46.96)
	People with elevated blood pressure levels Should take their medicine in a way that makes them feel well	183 (36.63)
Complications	If not addressed, high blood pressure may result in premature death	196 (39.25)
	Untreated high blood pressure can lead to cardiac disease, including heart attacks	160 (31.96)
	If not treated, high blood pressure can lead to strokes	96 (19.24)
	Untreated high blood pressure might lead to renal failure	175 (35.06)
	Untreated high blood pressure might cause vision problems	164 (32.78)
Diet	White meat is ideal for those with high levels of blood pressure	168 (33.67)
	People with high blood pressure benefit most from red meat	124 (24.81)
Lifestyle	People with high blood pressure may drink alcoholic beverages	108 (21.77)
	People with high blood pressure should avoid cigarettes	157 (31.13)
	Individuals with high blood pressure should consume fruits and vegetables frequently	165 (32.91)
	For people with high blood pressure, frying is their preferred cooking method	182 (36.45)
	The optimum cooking techniques for people with high blood pressure are boiling or grilling	94 (18.73)
Total Knowledge Score	Adequate Knowledge	168 (33.64)
	Inadequate Knowledge	332 (66.36)

Among adult Pakistanis who were not hypertensive, sociodemographic factors related to several subdomains of hypertension knowledge exhibit some noteworthy relationships (Table 3). The Hypertension Knowledge Level Scale (HK-LS), which has subdomains for Disease Definition, Medical Treatment, Drug Compliance, Lifestyle, Diet, and Complications, was used to convey the data. According to residency areas, although the difference was not statistically significant, urban inhabitants have slightly better knowledge of disease definition (2.98 ± 1.64) than rural residents (1.97 ± 1.35). There were no appreciable disparities between residents of urban and rural areas in other subdomains. Another factor was family history of hypertension; individuals with a positive history demonstrated slightly more Knowledge of Medical Treatment (3.44 ± 0.88) and Complications (4.65 ± 1.87) than those with a negative history. Complications has a p-value of 0.004, which suggests a significant difference. Overall, the total knowledge score indicates significant gaps in hypertension knowledge among the participants, with education and family history being strong determinants. These findings suggest that targeted educational interventions focusing on these sociodemographic factors could help improve hypertension awareness and management among non-hypertensive adults in Pakistan.

Table 3. Association of Sociodemographic Determinants with the Subdomains of Hypertension Knowledge Level Scale (HK-LS)

Variables	HK-LS Subdomens (Mean ± SD)					
	Disease Definition	Medical Treatment	Drug Compliance	Lifestyle	Diet	Complications
	Min-Max	Min-Max	Min-Max	Min-Max	Min-Max	Min-Max
	0–3	0–4	0–4	0–5	0–2	0–4
Sex						
Male	1.62 ± 1.21	2.14 ± 1.24	3.44 ± 1.55	5.36 ± 2.27	1.21 ± 042	2.31 ± 1.52
Female	1.66 ± 1.31	2.51 ± 1.15	3.31 ± 1.24	5.25 ± 2.21	1.11 ± 0.70	2.60 ± 1.46
p-Value[a]	0.876	0.003	0.324	0.075	0.631	0.301
Age Group						
18–30	1.50 ± 1.38	1.78 ± 1.33	2.26 ± 1.54	5.10 ± 2.00	0.78 ± 0.63	2.59 ± 1.59
31–40	1.58 ± 1.36	1.13 ± 1.25	2.35 ± 1.53	5.24 ± 1.73	1.04 ± 0.68	2.51 ± 1.55
41–50	1.48 ± 1.26	2.42 ± 1.41	2.54 ± 1.26	5.42 ± 1.28	1.38 ± 0.72	3.56 ± 1.71

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51–60	1.87 ± 1.34	2.38 ± 1.46	2.77 ± 1.22	5.42 ± 1.33	1.22 ± 1.35	2.63 ± 1.292
>60	1.75 ± 1.44	1.85 ± 0.83	2.62 ± 1.37	4.51 ± 1.42	1.44 ± 1.85	3.87 ± 1.23
p-Value[b]	0.650	0.034	0.094	0.185	0.229	0.732
Educational Level						
No Formal Education	1.41 ± 0.45	1.65 ± 1.24	1.81 ± 1.49	4.83 ± 1.46	0.79 ± 1.34	1.84 ± 1.76
Primary	2.17 ± 1.28	1.47 ± 1.35	2.67 ± 1.26	5.27 ± 2.56	1.56 ± 0.95	2.76 ± 1.45
Intermediate	1.34 ± 1.25	2.47 ± 0.89	1.37 ± 1.87	5.41 ± 2.55	1.29 ± 0.69	2.63 ± 1.97
Secondary	1.78 ± 1.38	1.41 ± 1.45	2.49 ± 1.49	5.44 ±1.78	0.75 ± 0.92	2.67 ± 1.93
Higher Education	1.30 ± 1.26	2.78 ± 1.39	2.76 ± 1.56	5.78 ± 1.78	1.37 ± 1.93	1.78 ± 1.07
p-Value[b]	<0.002	0.004	<0.002	0.001	0.204	0.090
Residency Area						
Urban	2.98 ± 1.64	1.23 ± 1.28	2.42 ± 1.36	5.47 ± 1.81	2.34 ± 1.10	3.68 ± 2.87
Rural	1.97 ± 1.35	2.57 ± 1.07	2.87 ± 1.33	5.87 ± 1.22	2.45 ± 1.21	3.56 ± 2.23
p-Value[a]	0.751	0.304	0.325	0.786	0.5633	0.344
Family History of HTN						
Negative	1.76 ± 1.55	3.56 ± 1.24	3.65 ± 1.33	5.41 ± 1.67	1.61 ± 0.94	4.54 ± 1.567
Positive	1.66 ± 0.87	3.44 ± 0.88	3.67 ± 2.34	5.67 ± 1.89	1.22 ± 0.89	4.65 ± 1.87
p-Value[a]	0.359	0.046	0.531	0.235	0.543	0.004
Source of Information about HTN						
Media	2.56 ± 1.34	2.78 ± 1.65	3.45 ± 1.63	5.34 ± 1.82	2.13 ± 0.53	2.65 ± 1.87
Healthcare Workers	2.56 ± 1.36	1.78 ± 1.97	2.72 ± 1.72	5.56 ± 1.97	1.87 ± 0.76	2.53 ± 1.65
Friends and Family Members	1.89 ±1.461.3	2.76 ± 1.34	3.87 ± 1.72	5.67 ± 1.76	1.86 ± 0.32	2.63 ± 1.47
Others	2 ± 1.67	2.67 ± 1.32	1.24 ± 1.62	5.53 ± 1.85	1.42 ± 1.53	3.13 ± 1.67
p-Value[b]	0.635	0.045	0.256	0.374	0.546	0.087
Total	1.68 ± 1.45	1.89 ± 1.73	2.987 ± 1.53	6.01 ± 1.23	1.12 ± 1.40	3.86 ± 1.95

DISCUSSION

This study aimed to explore the Knowledge of hypertension and identify determinants of inadequate awareness among non-hypertensive adult Pakistanis. The findings reveal significant gaps in hypertension knowledge, with various sociodemographic factors influencing the levels of understanding across different subdomains of hypertension knowledge. Our analys was shows that overall hypertension knowledge was inadequate among most participants. Only 33.64% demonstrated adequate Knowledge, while 66.36% had inadequate Knowledge. These findings align with previous studies conducted in similar contexts, which have also reported low levels of hypertension awareness in developing countries [1, 16, 17]. The study showed that there are slight differences in men's and women's knowledge levels. In the subdomains of Disease Definition, Lifestyle, Diet, Drug Compliance, and Complications, there were no statistically significant variations between the performance of males and females. Women outperformed men significantly in the Medical Treatment subdomain (mean score: 2.51 ± 1.15 versus 2.14 ± 1.24, p-value = 0.003). This suggests that women could know more about the medical aspects of managing hypertension. Gender differences in hypertension knowledge have also been observed in previous research conducted in low-income countries; these studies typically attribute women's greater awareness to their more frequent interactions with the healthcare delivery system [7, 11, 15]. The study discovered that participants who were younger (18-30 years) had poorer knowledge scores in Medical Treatment (mean score: 1.78 ± 1.33) and Drug Compliance (mean score: 2.26 ± 1.54). Participants aged 41-50 demonstrated the highest Knowledge in the Complications subdomain (mean score: 3.56 ± 1.71). Age substantially impacts Knowledge in the Medical Treatment subdomain, as indicated by the p-value of 0.034. The results suggest that older persons may be more knowledgeable or interested in understanding the effects of hypertension and available treatment options. Similar findings were made by K Mohanty S *et al.*, in 2021 and Cissé K *et al.*, in 2021: older adults in low- and middle-income nations are more knowledgeable about hypertension because of their higher risk and more frequent encounters with the illness. [18, 19]. Level of schooling was a significant predictor of hypertension knowledge. Respondents without formal education scored the lowest in Drug Compliance (mean score: 1.81 ± 1.49) and Complications (mean score: 1.84 ± 1.76). The results presented highlight the importance of education in promoting health literacy. Similarly, India (2020) and Sri Lanka (2020) revealed a favorable association between educational achievement and hypertension knowledge in Asian populations [20, 21]. The studies discovered no substantial differences in hypertension knowledge between urban and rural populations across all subdomains. This contrasts with

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prior studies, indicating that metropolitan inhabitants generally have better access to health information and services, resulting in greater Knowledge [22, 23]. This study's lack of significant variations could be attributed to a balanced mix of urban and rural participants and similar exposure to hypertension information across Pakistan's varied resident areas. Due to direct or indirect encounters with family members, individuals with a history of hypertension were more likely to be aware of the disease's treatment and complications. This result was in line with studies conducted in Uganda and India [10, 19], which showed how family history affects hypertension awareness and treatment. With a mean score of 3.87 ± 1.72, the participants who depended on friends and family exhibited greater knowledge of the Drug Compliance subdomain. These variations show the value of reliable sources in disseminating health information, even though none were statistically significant. Prior research has highlighted the contribution of social media and the media to raising public health awareness, especially in areas where access to healthcare was scarce [24, 25]. Limitation of the study was it was started with a cross-sectional design, which may offer a basic knowledge of hypertension and its origins. It was advised to do longitudinal research to gain a deeper understanding of the influence of each factor and how it interacts with different situations.

CONCLUSIONS

The study focuses on the variables affecting adult Pakistanis who were not hypertensive in their hypertension awareness. The Hypertension Knowledge Level Scale provides different degrees of understanding for different information sub-dimensions. The replies from the participants reveal significant ignorance of the causes, symptoms, and treatment of hypertension. Better health outcomes for Pakistan will result from addressing these variables through targeted educational initiatives that increase understanding of hypertension and its management.

Authors Contribution

Conceptualization: SH, SAB

Methodology: SH, SAB, SMW, JA, PP, DP

Formal analysis: SH, SAB, JA

Writing, review and editing: SH, SAB, SMW, JA, PP, DP

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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The Impact of Malocclusion Severity on Self-Confidence and Facial Appearance among Orthodontic Patients

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ABSTRACT

Malocclusion was a group of dental deviations that have a particular psychological influence on the society. **Objective:** To assess the correlations between malocclusion severity and its effects on self-confidence and facial appearance in patients seeking orthodontic treatment. **Methods:** The hospital-based study was performed at Orthodontic Department, Institute of Dentistry of Liaquat University of Medical and Health Sciences, Jamshoro. Participants aged 7 to 30 years who were diagnosed with varying degrees of malocclusion, were included in the study while those with congenital or traumatic facial deformities unrelated to malocclusion were excluded from the study. Data were collected via questionnaires (Rosenberg Self Esteem and Dental Aesthetic Index) and clinical assessments. Correlation analysis was used as data analysis. **Results:** The research comprised of 383 individuals, with 110 (28.7%) were males, and 273 (71.3%) females. 361 (94.3%) participants having aesthetics problem, 19 (5.0%) reported with Functional issues, and 3 (0.8%) had found with Temporomandibular Joint (TMJ) complications. There were moderate to strong negative correlations between malocclusion severity and self-confidence ($r=-0.45$, $p<0.05$) and between the impact on facial appearance and self-confidence ($r=-0.52$, $p<0.05$) A positive correlation was observed between malocclusion severity and facial appearance impact ($r=0.65$, $p<0.05$) (Table 5). **Conclusions:** The study found that malocclusion significantly impacts self-confidence and facial appearance, with 71% of participants reporting negative effects on appearance and 47.3% experiencing reduced self-confidence.

INTRODUCTION

Malocclusion exerts influence on the dental health, psychological well-being, and social well-being of the patients. The most common repercussions of malocclusion include unaesthetic facial appearance; difficulty in speech, chewing, or cleaning; high prevalence of caries; low self-esteem; low self-confidence; and poor emotional and social health [1]. The consequences of facial aesthetics vary across the genders, age groups, social and economic groups, and in accordance with cultural backgrounds, which required considerable significance in understanding the treatment needs. Therefore, in order to enhance the preference for pursuing the orthodontic treatment procedures in order to enhance natural beauty and overall appearance reflects a substantial and legitimate demand [2, 3]. However, it has been observed that women are often demonstrated greater concerns regarding their attractiveness, beauty, and facial appearance; therefore, malocclusion usually noticed earlier by them and made women much more anxious than men [4]. The current medical approach is gradually evolving towards a "bio-psycho-social" model that takes into considerations the subjective feelings and psychological conditions of patients. Moreover, there is an emerging trend toward enhancing the psychosocial status and quality of life of patients [1]. Therefore, in order to improve quality of life related matters appropriate

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diagnosis and need for treatment has paramount importance. It has been found usually that the most frequently cited reasons for seeking orthodontic or orthodontic surgical treatment included aesthetic concerns, functional issues, headaches, temporomandibular disorders, and factors usually associated with self-confidence and facial attractiveness [1]. However, the percentages of reported motivating variables vary significantly between studies [5]. The Psychosocial factors, cultural norms, overall treatment expenses, patients age, sexes and expected treatment results can significantly have an effect on motivation and treatment seeking [6]. It has also been shown that patients' personal motivations for conventional orthodontic treatment orthognathic surgical interventions may considerably varies from patient understandings regarding recommendations [6, 7]. Moreover, patients' personal point of views on the requirement for orthodontic treatment may vary from assessments made by specialists [8]. Generally, women are more likely than males to seek treatment for malocclusion and to experience more deleterious influences as a result of malocclusion [6]. When it comes to oral health, many people supposed that diseases of the mouth didn't cause much of a problem. As a result, their psychological and societal consequences were underestimated [9]. Dental health is now widely acknowledged as a significant factor in overall health, and how people observe their own health and quality of life [10]. Malocclusion also effects on patient's mental well-being. People are concerned about their teeth's alignment and appearance, and as a result, the dentition plays a significant role in facial attractiveness [11]. Facial attraction is important in social interactions, as discussed in many studies. Facial appearance is markedly affected by malocclusion. Bullying and teasing are more common in people who have significant anterior teeth crowding or a midline diastema [12]. In addition, because orthodontic treatment improves both functional and aesthetic aspects, it can boost people's self-esteem and overall quality of life [13]. In a latest survey, timely orthodontic treatment during childhood or adolescence improves mental and social well-being. However, since all studies in the previously reported systematic review are based on observation, the interpretation of their findings is limited [14].

Therefore, this study was conducted to explore the effects of malocclusion on self-confidence and facial appearance on patients seeking orthodontic treatment.

METHODS

This research was a cross-sectional study which employed a non-probability consecutive sampling technique, conducted at the Department of Orthodontics, Liaquat University Hospital Hyderabad, and the Institute of Dentistry Jamshoro. The sample size of 383 patients was determined using the Open Epi sample size calculator, taking anticipated frequency as 50% with 5% margin of error and 95% confidence interval. The study was approved by Ethical Review Committee of LUMHS, vide letter no. No. LUMHS/REC/-912. The duration of study was 1 year, starting from Oct 2020 to Sept 2021. Participants aged 7 to 30 years who were diagnosed with varying degrees of malocclusion, as confirmed by clinical examination and orthodontic assessment, and who provided written informed consent to participate, were included in the study. While individuals with congenital or traumatic facial deformities unrelated to malocclusion with significant medical conditions affecting facial appearance or self-confidence, and those already undergoing orthodontic treatment, were excluded from the study. Data were collected via questionnaires and clinical assessments. Clinical assessments included orthodontic examinations to determine the severity of malocclusion and facial aesthetic evaluations based on clinical photographs and expert assessments. Self-confidence was measured in terms of self-esteem through the Rosenberg Self Esteem questionnaire, which consists of 10 items on a four-point: Likert scale, ranging from Strongly Agree to Strongly Disagree, that measure global self-worth by evaluating positive and negative feelings about oneself. Scores were calculated by summing the responses, with higher scores indicating higher self-esteem [15]. The impact of malocclusion on facial appearance was measured via Dental Aesthetic Index (DAI) which involved subjective evaluation where the aesthetic impact of dental conditions was judged based on standardized photographs or direct clinical observation [16]. The DAI score ranges from 0 to 100, with higher scores reflecting a greater perceived aesthetic impact. Specifically, a DAI score between 0 and 25 indicates minimal concerns while scores ranging from 26 to 30 signify some aesthetic concerns but not severe. A score between 31 and 35 reflects that the malocclusion has a more noticeable aesthetic impact. Scores from 36 to 45 suggest a significant malocclusion. A score of 46 or above denotes a substantial effect on the individual's self-esteem and social interactions. Descriptive statistics were used to summarize demographic data, malocclusion severity, self-confidence scores, and facial appearance perceptions. Correlation analysis was performed using Pearson coefficient to explore relationships between malocclusion severity, self-confidence, and facial appearance perceptions. Analysis was done using SPSS version 24.0, at significance level of $p < 0.05$.

RESULTS

The mean age of participants was 19.4 ± 4.612 years with 110 (28.7%) being male and 273 (71.3%) female. 361 participants (94.3%) reported with aesthetic concerns, 19 participants (5.0%) cited functional problems and 3 participants (0.8%) mentioned issues related to temporomandibular joint.

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Regarding the effect to the Distribution of the effects of malocclusion on Self-Confidence, 28 (7.3%) participants were Confident, 181 (47.3%) participants were Less Confident, and 174 (45.4%) participants were Un-affected. Regarding the subjective effect to the Malocclusion on Facial Appearance, 272 (71.0%) of participants were experiencing some sort of Effect on Facial Appearance, whereas 111 (29.0%) did not feel any effect on Facial Appearance (Table 1).

Table 1: Participant Subjective Responses and Impact of Malocclusion

Response	Frequency (%)
Aesthetic Concerns	361 (94.3%)
Functional Problems	19 (5.0%)
Temporomandibular Joint Issues	3 (0.8%)
Confident	28 (7.3%)
Less Confident	181 (47.3%)
Un-Affected	174 (45.4%)
Experiencing Effect	272 (71.0%)
No Effect	111 (29.0%)

Participants reported a diverse range of malocclusion severities. The largest group, 28.7%, perceived their malocclusion as "None," while 22.2% classified it as "Minimal." A significant portion, 20.1%, described their condition as "Moderate." "Severe" malocclusion was reported by 15.2% of participants, and 13.8% considered their malocclusion as "Extreme" (Table 2).

Table 2: Subjective Severity of Malocclusion

Severity of Malocclusion	Frequency (%)
None	110 (28.7%)
Minimal	85 (22.2%)
Moderate	77 (20.1%)
Severe	58 (15.2%)
Extreme	53 (13.8%)

Self-confidence / Self-esteem among participants varied considerably. A total of 15.7% of individuals scored in the "Low" range (10-20), indicating lower self-confidence. The majority reported "Moderate" self-esteem, with 32.6% falling in the 21-30 range. Almost as many, 32.4%, had "High" self-esteem (31-40), while 19.3% achieved "Very High" self-esteem scores (41-50) (Table 3).

Table 3: Self-Confidence Scores

Self-Esteem	Frequency (%)
Low (10-20)	60 (15.7%)
Moderate (21-30)	125 (32.6%)
High (31-40)	124 (32.4%)
Very High (41-50)	74 (19.3%)

Similarly, the impact of malocclusion on facial aesthetics was notably significant. A substantial 31.3% of participants experienced a "Minimal Effect," while 24.8% reported "Some Effect." The study found that 20.6% observed a "Noticeable Effect," 14.1% faced a "Significant Effect," and 9.2% felt a "Substantial Effect" on their facial appearance (Table 4).

Table 4: Effect of Malocclusion on Facial Appearance

Effect on Facial Appearance	Frequency (%)
Minimal Effect (DAI 0-25)	120 (31.3%)
Some Effect (DAI 26-30)	95 (24.8%)
Noticeable Effect (DAI 31-35)	79 (20.6%)
Significant Effect (DAI 36-45)	54 (14.1%)
Substantial Effect (DAI 46+)	35 (9.2%)

There were moderate to strong negative correlations between malocclusion severity and self-confidence ($r=-0.45$, $p<0.05$) and between the impact on facial appearance and self-confidence ($r=-0.52$, $p<0.05$) A positive correlation was observed between malocclusion severity and facial appearance impact ($r=0.65$, $p<0.05$) (Table 5).

Table 5: Correlation Analysis Summary

Variables Pair	Correlation Coefficient (r)	Significance (p-Value)
Malocclusion Severity and Self-Confidence	-0.45	<0.05
Facial Appearance Impact and Self-Confidence	-0.52	<0.05
Malocclusion Severity and Facial Appearance Impact	0.65	<0.05

DISCUSSION

The apprehension of dental irregularities and their unfavorable influences on dental aesthetics can significantly affect social interactions, self-confidence, and psychological well-being. According to the findings of the psychological attractiveness study, the perception of one's own physical appearance was frequently related to anxieties about other people's response and a negative body concept [17]. It has been observed that the patient's personal motivations for orthodontic / orthognathic surgery may differ from their discernment of recommendations [17]. Previously several studies in different areas of Pakistan had been conducted to extensively explore the reasons for seeking treatment for malocclusions. While this study's findings cannot be anticipated to the entire population of Pakistan, they offer perceptions of patients into malocclusion trends and its impact on patient's self-confidence and facial appearance in orthodontic patients reported at OPD in Hyderabad and Jamshoro districts. Patients receiving orthodontic treatment were chosen according to the inclusion criteria to complete a questionnaire, which investigated treatment objectives, its influence on self-esteem and on patient's self-appearance among individuals aged 7-30 seeking care at LUMHS Jamshoro and ADCC Hyderabad. All participants were willing and actively engaged throughout the research, demonstrating a clear understanding of its purpose. Notably, the study observed a significantly higher prevalence of orthodontic treatment among women

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compared to men, aligning with previous research findings. This discovery also aligns with prior studies indicating a higher likelihood of girls seeking orthodontic treatment compared to males [18, 19]. The results of this research also showed that out of the 361 participants, (94.3%) reported with aesthetic concerns, 19 participants (5.0%) cited functional problems, and 3 participants (0.8%) mentioned issues related to temporomandibular joint. While, regarding the effect to the Distribution of the effects of malocclusion on Self-Confidence, 28 (7.3%) participants were Confident, 181 (47.3%) participants were Less Confident and 174 (45.4%) participants were Un=affected. It have also been observed that according to the effect of Malocclusion on Facial Appearance, 272 (71.0%) of participants were experiencing some sort of Effect on Facial Appearance, whereas 111 (29.0%) did not feel any effect on Facial Appearance. Various studies have persistently inquired the desire to enhance the facial appearance as the primary motivation which was driving patients to seek orthodontic and orthodontic-surgical treatments. [20, 21] Skeletal malocclusion in patients directly influences their facial appearance, making it a crucial factor that can exert effects on their contentment and drive throughout orthodontic and orthognathic surgical treatments [22]. As with increasing awareness of the impact of dent facial influences on social and psychological well-being of the individuals, Orthodontists make out that achieving aesthetically pleasing teeth and associated soft tissue enhances both self-confidence and social well-being [13, 23]. Therefore, the primary duty of caregiver's was to appropriately assess the requirements for treatment, taking into consideration not only the child's dental health but also their overall cosmetic needs and subjective perception of concerns for orthodontic care [24]. It was also necessary to investigate the psychological influence of malocclusion in order to better understand the potential interventions desired at enhancing overall personal well-being. Any interventions should impart to improve the oral health-related quality of life (OHRQoL), physical health, self-esteem, and psychological personality of well-being [25]. The present study therefore underscores the importance of integrating orthodontics into the curricula of both public and private educational institutions. It also emphasizes ongoing discussions on appropriate treatment options and advocates the need for substantial research advancements in this field.

CONCLUSIONS

This study suggested that malocclusion has a significant effect on both self-confidence and facial appearance. A substantial majority of participants (71%) reported a negative impact on their facial appearance, while nearly half (47.3%) experienced reduced self-confidence due to their malocclusion. Notably, only a small percentage of participants (7.3%) reported feeling confident, highlighting the profound influence of malocclusion on self-perception. The results also indicate that aesthetics concerns (94.3%) far outweigh functional issues (5.0%) and TMJ complications (0.8%) as the primary motivation for seeking orthodontic treatment. Overall, this study underscores the importance of addressing malocclusion to improve not only oral health but also psychological well-being and self-esteem.

Authors Contribution

Conceptualization: AMZ

Methodology: AMZ, MSK, EQ, AJ, SS, AM

Formal analysis: AMK

Writing, review and editing: AMZ, MSK, EQ, AJ, SS, AM

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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Exclusive Breastfeeding Practice and Associated Factors among Mothers of Infants under 6-Months of Age

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ABSTRACT

The consequences of poor feeding practices might exhibit in the form of poor nutritional status in the early part of life whereas delayed mental as well as motor developmental disorders are some most commonly exhibited long term consequences. **Objective:** To determine the prevalence and associated factors of exclusive breastfeeding (EBF) among mothers of infants below six months of age. **Methods:** This cross-sectional study was done at the Department of Pediatrics, Sheikh Khalifa Bin Zayed Al Nahyan Hospital, Rawlakot, Azad Kashmir, Pakistan from August 2022 to January 2023. **Results:** In a total of 237 mothers, the mean age was 27.15 ± 3.87 years. The EBF was reported by 151 (63.7 %) mothers. High socio-economic status (adjusted odds ratio=5.87, p=0.003), having fewer than 4 antenatal visits (adjusted odds ratio=4.15, p<0.001), cesarean delivery (adjusted odds ratio=5.57, p<0.001). the absence of postnatal advice on EBF (adjusted odds ratio=3.06, p=0.004), and children aged 4-6 months (adjusted odds ratio=8.58, p<0.001) had significantly higher odds of absence of EBF. **Conclusions:** It was concluded that the exclusive breastfeeding was practiced by 63.7% mothers. High socio-economic status, fewer antenatal visits, cesarean section, absence of postnatal advice on exclusive breastfeeding, and relatively older age of the infant were associated with lack of exclusive breastfeeding practices.

INTRODUCTION

Suboptimum breastfeeding, particularly nonexclusive breastfeeding, has profound consequences on child health especially among infants living in developing countries [1, 2]. Globally, rates of exclusive breastfeeding have reached around 48% and very close to reaching the global goal of 25% by 2025 [3]. Data from the developing world revealed that only 52% of children aged below 6 months had exclusive breastfeeding (EBF) [4]. Data from Pakistan revealed that only around 38% of the babies are exclusively breastfed [5]. The consequences of poor feeding practices might exhibit in the form of poor nutritional status in the early part of life while infectious morbidity and metabolic disorders are some of the other concerns among non-exclusively breast fed infants [6, 7]. Therefore, promoting optimal breastfeeding practices during the critical early parts of life is essential for ensuring the health and well-being of children and future generations. In regions like South Asia where stunting prevalence rates are high [8], inappropriate feeding practices need significant interventions to reduce the related infantile morbidity and mortality. A study conducted in Germany revealed that infants who were exclusively breastfed for first six months had a lower incidence of gastroenteritis compared to those breastfed for less than four months [9]. A cohort study in the United States found that infants exclusively breastfed for more than six months had a reduced risk of pneumonia

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and recurrent otitis media compared to those breastfed for 4-6 months [10]. The "World Health Organization (WHO)" recommends exclusive breast-feeding from birth until six months of age, advising that mothers receive counseling and support for exclusive breast-feeding during each postnatal visit [3]. Arif *et al.*, performed a secondary analysis on data from Pakistan Demographic and Health Survey (PDHS) for the year, and shared that 81 % of mothers aged between 30-34 years were having EBF for at least first six months of age [1]. The present study was planned to fill this research gap.

This research aimed to determine the prevalence and associated factors of EBF among mothers of infants below six months of age.

METHODS

This cross-sectional study was performed at the Department of Pediatrics, Sheikh Khalifa Bin Zayed Al Nahyan Hospital, Rawlakot, Azad Kashmir, Pakistan, from August 2022 to January 2023. Approval from "Institutional Ethical Committee" was acquired for this research (604/SKB2/CMH RKT). Informed and written consents were sought from mothers explaining them the aims of this research. A sample size of 237 was calculated taking the anticipated proportion of EBF by mothers among infants below six months of age as 81 % [1], with 95 % confidence level and 5 % margin of error. Mothers aged between 18 to 35 years who gave birth to a single baby in the past 6 months, and willing to participate in this research were included. Mothers who had any contraindication to EBF were excluded. Mothers who did not show consent to be part of this research were also excluded. Adherence to exclusion criteria was observed to avoid confounders. At the time of enrollment, demographic factors (age of the mother, marital status, residence, socio-economic status, educational level and number of alive children), maternal factors (birth order, antenatal care visits frequency, delivery mode, delivery place and postnatal advice about the EBF by healthcare professional) and infant factors (gender, age, initiation of breastfeeding within first hour) were noted on a specially formed questionnaire. Interview was planned at a quiet room in the pediatric unit after taking permission from the mothers. The verbal interview method was used to labeled EBF and it was defined as baby below 6 months of age who was fed only by breast milk in the past 24 hours as described by the mother [11]. Socio-economic status was labeled as low if family monthly income was below 18,000 PKR, middle 18,000 to 40,000 PKR, or high if >40,000 PKR [12]. Residential status was labeled as urban if living in a city above or equal to district level, or rural if living in a city/town below district level. For the data analysis, IBM-SPSS Statistics, version 26.0 was used. Descriptive statistics were applied for the representation of the data. Chi-square test was applied to compare categorical data. The multivariable binary logistic regression analysis was performed considering independent variables that had p-value below 0.200. Adjusted odds ratio (AOR) with 95 % confidence interval (CI) were calculated and factors with p-value below 0.05 were considered statistically significant.

RESULTS

In a total of 237 mothers, the mean age was 27.15 ± 3.87 years, ranging between 18-35 years. Socio-economic status was low among 130 (54.9 %) mothers. There were 61 (25.7 %) mothers who were illiterate. Mode of delivery was reported to be vaginal delivery among 152 (64.1 %) mothers. Post-natal advice about EBF was provided to 144 (60.8 %) mothers. The mean age of the children at the time of enrollment of mothers was 3.24±1.41 months (ranging between 1 to 6 months). Initiation of breastfeeding in the 1st hour following delivery was reported by 108 (45.6 %) mothers. The EBF was reported by 151 (63.7 %) mothers. Univariate analysis revealed EBF to have significant association with maternal age (p<0.001), socio-economic status (p<0.001), birth order (p=0.029), number of antenatal visits (p<0.001), postnatal advice of EBF (p<0.001), child's age (p<0.001), and initiation of breastfeeding in the 1st hour following delivery (p=0.026). Details about the comparison of study variables with respect to EBF practice are stated in table 1.

Table 1: Comparison of Study Variables with Respect to Exclusive Breastfeeding Practice (N = 237)

Study Variables		Exclusive Breastfeeding		p-Value
		Yes (n=151)	No (n=86)	
Maternal Age (Years)	18-29	100 (66.2 %)	75 (87.2 %)	<0.001
	30-35	51 (33.8 %)	11 (12.8 %)	
Marital Status	Married	141 (93.4 %)	83 (96.5 %)	0.539
	Divorced	5 (3.3 %)	2 (2.3 %)	
	Widowed	5 (3.3 %)	1 (1.2 %)	
Residence	Urban	47 (31.1 %)	35 (40.7 %)	0.136
	Rural	104 (68.9 %)	51 (59.3 %)	
Socio-Economic Status	Low	91 (60.3 %)	39 (45.3 %)	<0.001
	Middle	50 (33.1 %)	25 (29.1 %)	
	High	10 (6.6 %)	22 (25.6 %)	
Educational Level	Illiterate	38 (25.2 %)	23 (26.7 %)	0.789
	Literate	113 (74.8 %)	63 (73.3 %)	
Family Size	≤4	98 (64.9 %)	65 (75.6 %)	0.088
	>4	53 (35.1 %)	21 (24.4 %)	
Birth Order	1-2	63 (41.7 %)	51 (59.3 %)	0.029
	3-4	45 (29.8 %)	20 (23.3 %)	
Antenatal Visits	>4	43 (28.5 %)	15 (17.4 %)	<0.001
	<4	46 (30.5 %)	60 (69.8 %)	
	≥4	105 (69.5 %)	26 (30.2 %)	
Delivery Mode	Cesarean	35 (23.2 %)	50 (58.1 %)	<0.001
	Vaginal	116 (76.8 %)	36 (41.9 %)	
Delivery Place	Home	36 (23.8 %)	18 (20.9 %)	0.607
	Hospital	115 (76.2 %)	68 (79.1 %)	

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Postnatal Advice of Exclusive Breastfeeding		108 (71.5 %)	36 (41.9 %)	<0.001
Child's Gender	Boy	92 (60.9 %)	51 (59.3 %)	0.806
	Girl	59 (39.1 %)	35 (40.7 %)	
Child's Age (Months)	<4	118 (78.1 %)	25 (29.1 %)	<0.001
	4-6	33 (21.9 %)	61 (70.9 %)	
Initiation of Breastfeeding in the First Hour Following Delivery		77 (51.0 %)	31 (36.0 %)	0.026

High socio-economic status significantly increased the odds of lack of EBF (AOR=5.87, p=0.003). Having fewer than 4 antenatal visits significantly increased the odds of lack of EBF (AOR = 4.15, p<0.001). Cesarean delivery significantly increased the odds of lack of EBF (AOR = 5.57, p<0.001). The absence of postnatal advice on EBF significantly increased the odds of not practicing EBF (AOR=3.06, p=0.004). Children aged 4-6 months had significantly higher odds of absence of EBF (AOR=8.58, p<0.001). Details about the multivariate binary logistic regression analysis showing factors associated with lack of EBF are shown in table 2.

Table 2: Multivariate Binary Logistic Regression Analyzing Factors Associated with Lack of Exclusive Breastfeeding

Study Variables		p-Value	Adjusted Odds Ratio	95% Confidence Interval	
				Lower	Upper
Maternal Age (Years)	18-29	0.632	1.29	0.45	3.71
	30-35	Reference			
Residence	Urban	0.149	1.79	0.81	3.95
	Rural	Reference			
Socio-Economic Status	Low	Reference			
	Middle	0.186	0.57	0.25	1.32
	High	0.003	5.87	1.861	8.54
Family Size	≤4	Reference			
	>4	0.529	1.73	0.31	9.60
Birth Order	1-2	Reference			
	3-4	0.368	2.45	0.351	7.19
	>4	0.491	1.79	0.34	9.43
Antenatal Visits	<4	<0.001	4.15	1.92	8.99
	≥4	Reference			
Delivery Mode	Cesarean	<0.001	5.57	2.251	3.80
	Vaginal	Reference			
Absence of Postnatal advice of Exclusive Breastfeeding		0.004	3.06	1.42	6.59
Children's Age (Months)	<4	Reference			
	4-6	<0.001	8.58	3.931	8.75
No initiation of Breastfeeding in the first hour following delivery		0.851	1.08	0.47	2.50

*Reference Category

DISCUSSION

This study was conducted to evaluate EBF practices among mothers belonging to Azad Jammu Kashmir District of Pakistan. This research revealed that 63.7 % mothers were practicing EBF in infants aged up to 6 months. Studies from other developing countries like Ethiopia, Ghana, and Uganda have shown relatively higher EBF rates of 60.4 %, 70 %, and 62.3 %, respectively [13-15]. As per "World Health Organization", only 37.7 % of mother practice EBF among infants aged below 6 months of age [16]. Data from this study reported much higher EBF rates that what have been reported from India (49 %) [17], Mexico (28 %) [18], and China (30 %) [19]. There seems to be a clear variation in patterns of EBF practice so it is imperative to study the factor contributing to these trends in specific population. Our research found that high socio-economic status significantly increased the odds of lack of EBF (AOR = 5.87, p = 0.003). Current findings are in accordance to the published data that there exists a significant relationship between socio-economic status and mother's motivation to EBF [20]. Mothers belonging to higher socio-economic status may prefer buying formula milk than just providing EBF to their babies. Likewise, mothers belonging to low socio-economic status may not have the option to buy formula milk due to its higher price in a country like Pakistan. In this study, relatively higher number of antenatal visits were linked with significantly higher EBF rates. These findings are in accordance to the established beliefs and strengthening antenatal care and delivery at healthcare facilities are thought to improve EBF practices among mothers [21]. The present study highlighted cesarean section to be significantly associated with lack of EBF practices. Mod of delivery has been documented to an important factor influencing EBF practices. The possible explanation could be the negative impact of cesarean section on the physiology of lactation and challenges hindering mother's physical contact with the newborns [22]. Some authors have proved maternal affiliation from rural areas to positively impact EBF but we did not observe any significant differences among rural and urban areas [23, 24]. The present study is perhaps the first one from Azad Jammu Kashmir Region of Pakistan analyzing EBF practices among mothers of infants up to 6 months of age. Single stud center and a relatively modest sample size reduce the generalizability of this research and warrants further research. Most of the study data were based on recall ability of the mothers which might post some bias.

CONCLUSIONS

Exclusive breastfeeding was practices by 63.7% mothers. High socio-economic status, fewer antenatal visits, cesarean section, absence of postnatal advice on exclusive breastfeeding, and relatively older age of the infant were associated with lack of exclusive breastfeeding practices.

Authors Contribution

Conceptualization: SI, SMB, RIA
Methodology: SC
Formal analysis: CR, DC
Writing-review and editing: ME

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

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Frequency of Middle Mesial Canal in Mandibular Molars

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ABSTRACT

Being the most difficult to detect unusual canal in mandibular molars, creating greater anatomical complexity and thereby variability, it is important that careful investigation aids in successful endodontic treatments. **Objective:** To evaluate the incidence and features of MMC in mandibular molars; to study demographic parameters and dental factors that may have an effect on its detection. **Methods:** A cross-sectional study was performed at Shahida Islam Medical College (SIMC), Lodhran from September 2023 to March 2024, and contained a total of 148 patients. Data was assessed for the presence of MMC in first, second and third mandibular molars. Two expert dental radiologists evaluated the results of the X-ray films. **Results:** The prevalence of MMC was 18%, with complete and partial compartments seen in more than half the patients (77%). It was shown that MMCs were most commonly observed in 51-65 age group (21.28%); however, there were non-significant differences based on patient's age and gender or tooth type and position accompanying OAC site. **Conclusions:** In present study, MMC was noted in 18% patients. Statistically insignificant demographic or dental predictors for MMC were identified.

INTRODUCTION

For successful endodontic treatments, complexity of root canal anatomy plays very crucial role. For the understanding of presence and configuration of root canals, like middle mesial canal (MMC) in lower mandibular molars, is important for achieving successful treatment [1]. MMC located between the mesiobuccal and the mesiolingual canals, is often difficult to be identified and treated because of its complex and hidden position [2]. New diagnostic imaging modalities like CBCT and micro-CT scanning have immensely contributed to our understanding of MMC, particularly in terms of 3D images that are essential for accurate analysis regarding canals [3]. The incidence of MMC as reported in the literature varied widely, like a Saudi study reported frequency of MMC in only 2.6% of 1st mandibular molars and 0.2% of 2nd mandibular molars [4]. The frequency of MMCs and their detection may vary according to age, gender and specific tooth characteristics. The detection or identification of MMCs can be difficult, requiring sophisticated imaging, thorough clinical assessment and the use of magnification to guarantee that indolent lesions are found [5, 6]. Studies on prevalence of MMCs in Pakistan is scarce. Bhatti *et al.*, found MMC in only 7.7% patients and Rehman *et al.*, found MMCs in 9 patients out of 189 patients [7, 8]. The aim of this study was to evaluate the cases in which MMC were diagnosed on mandibular molars, and also discuss their

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clinical difficulties encountered by either being hidden or related with complex location. Knowledge of the prevalence and clinical characteristics of MMC in Pakistani population may help improving diagnosis, practice patterns, treatment outcomes associated with endodontic management.

This study aimed to enrich local data and current global knowledge on MMC, towards the creation of better tailored endodontic protocols.

METHODS

From September 1, 2023, to March 30, 2024, this cross sectional study was conducted at Department of Dentistry, Shahida Islam Medical College, Lodhran. Ethical approval was taken from ethical review committee of the hospital (Approval No. SIMC/H.R./7720/23). We enrolled 148 patients, either male or female having age between 18-65 years, presented for routine dental examinations or treatment and required dental radiographs for diagnostic or treatment planning purposes. Patients with fully erupted mandibular 1st, 2nd or 3rd molars were eligible for the study. We exclude patients with history of endodontic treatment, significant dental anomalies, or systemic conditions impacting dental morphology. Informed consent was obtained from all participants. The sample size of 148 selected patients was calculated using frequency of 10.79% of MMC, 95% confidence level and 5% margin of error [9]. Radiographic assessment was done by using initial digital panoramic radiographs (Planmeca ProMax® 3D Classic) for the assessment of general dentition and check for retained mandibular molars. This was followed by targeted periapical radiographs by using Kodak 6100 Digital Radiography System to focus on the mandibular molars of interest. MMCs were confirmed on x-ray by using periapical radiographs which were very important for evaluating any ambiguous cases based on visual discernment of additional canal spaces within the mesial root of mandibular molars. For the purpose of radiographic analysis, images demonstrating both the presence and absence of MMCs were included to illustrate the variable occurrence of this anatomical feature. This was instrumental in supporting the study's findings and providing clear evidence of MMC identification. The primary variable of this study was the presence of MMCs in mandibular molars. Secondary variables included patient demographics and specific tooth characteristics such as age, gender, molar type (first, second, or third), position (right/left side), and treatment history. These variables were analyzed to determine their potential association with the presence of MMCs. The data collected were analyzed with SPSS version 26.0. Means and standard deviations were used to describe age, whereas frequencies with percentages described categorical variables including the presence of MMC (yes/no), gender (male/female), tooth type (first molar/ second molar /third molar), tooth position (left/right) and treatment history (treated/ untreated). Stratification of the data was done according to age, sex, type of retained tooth correction (tooth number or teeth group), position in dental arch and history of orthodontic treatment. The association of MMC location with categorical variables was assessed using chi-square tests in a post-stratification fashion. A p-value ≤0.05 was determined as statistically significant.

RESULTS

In the current study, the average age of the participants was 42.34 years, with a standard deviation of 13.31 years, highlighting a broad age range among the sampled individuals. Notably, the middle mesial canal (MMC) was detected in 26 of the 148 patients, accounting for 18% of the study population (Figure 1).

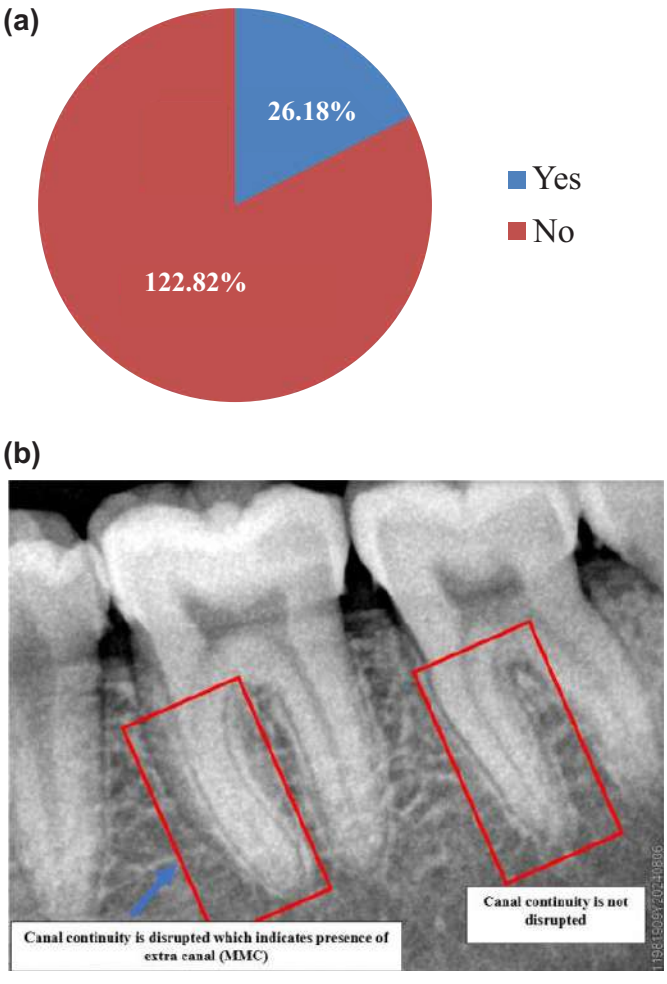

Figure 1: Part A Showed Frequency of MMC Found in Our Study, Part B Showed Radiograph for The Presence and Absence of MMC

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The examination of MMC across different age brackets revealed the highest prevalence in the 51-65 age group, where 10 out of 47 patients (21.28%) exhibited this anatomical feature. This represents 31.76% of the total study cohort. Conversely, the 41-50 age group showed the lowest incidence, with only 4 patients (10.26%) demonstrating MMC out of the same group size. Although these variations were notable, the chi-square test confirmed that they were not statistically significant (P=0.2891), suggesting that age may not be a primary factor in MMC presence (Table 1).

Table 1: Association of Middle Mesial Canal with Age Groups

Age Groups	Middle Mesial Canal		Total N (%)	P value
	Yes N (%)	No N (%)		
18-30 Years	7 (17.95%)	32 (82.05%)	39 (26.35%)	0.2891
31-40 Years	5 (21.74%)	18 (78.26%)	23 (15.54%)	
41-50 Years	4 (10.26%)	35 (89.74%)	39 (26.35%)	
51-65 Years	10 (21.28%)	37 (78.72%)	47 (31.76%)	
Total	26 (17.57%)	122 (82.43%)	148 (100.00%)	

Gender comparison showed a slightly higher occurrence of MMC in males (15 out of 70; 21.43%) than in females (11 out of 78; 14.10%). However, statistical analysis indicated that this difference was not significant (P=0.2413), implying that gender does not critically influence the presence of MMC (Table 2).

Table 2: Association of Middle Mesial Canal with Gender

Gender	Middle Mesial Canal		Total N (%)	P value
	Yes N (%)	No N (%)		
Male	15 (21.43%)	55 (78.57%)	70 (47.30%)	0.241
Female	11 (14.10%)	67 (85.90%)	78 (52.70%)	
Total	26 (17.57%)	122 (82.43%)	148 (100.00%)	

When classified by tooth type, second molars were most commonly associated with MMC (12 out of 59; 20.34%), followed by third molars (8 out of 47; 17.02%) and first molars (6 out of 42; 14.29%). Despite these findings, the statistical tests showed no significant differences (P=0.8223), suggesting that the type of tooth does not significantly dictate the likelihood of MMC occurrence (Table 3).

Table 3: Association of Middle Mesial Canal with Tooth Type

Tooth Type	Middle Mesial Canal		Total N (%)	P value
	Yes N (%)	No N (%)		
First Molar	6 (14.29%)	36 (85.71%)	42 (28.38%)	0.822
Second Molar	12 (20.34%)	47 (79.66%)	59 (39.86%)	
Third Molar	8 (17.02%)	39 (82.98%)	47 (31.76%)	
Total	26 (17.57%)	122 (82.43%)	148 (100.00%)	

Analysis based on tooth position revealed that MMC was more frequently observed in right mandibular molars (15 out of 72; 20.83%) than in left mandibular molars (11 out of 76; 14.47%). Despite this apparent disparity, it was not statistically significant (P=0.3475), indicating that the side of the mandible was not a determining factor for MMC detection (Table 4).

Table 4: Association of Middle Mesial Canal with Tooth Position

Tooth Position	Middle Mesial Canal		Total N (%)	P value
	Yes N (%)	No N (%)		
Left	11 (14.47%)	65 (85.53%)	76 (51.35%)	0.347
Right	15 (20.83%)	57 (79.17%)	72 (48.65%)	
Total	26 (17.57%)	122 (82.43%)	148 (100.00%)	

Interestingly, MMC was more prevalent in patients with previous dental treatments (17 out of 80; 21.25%) compared to those without such history (9 out of 68; 13.24%). However, the lack of statistical significance (P=0.2891) suggests that past dental interventions do not markedly affect the identification of MMC (Table 5).

Table 5: Association of Middle Mesial Canal with Treatment History

Treatment	Middle Mesial Canal		Total N (%)	P value
	Yes N (%)	No N (%)		
Treated	17 (21.25%)	63 (78.75%)	80 (54.05%)	0.2891
Not-treated	9 (13.24%)	59 (86.76%)	68 (45.95%)	
Total	26 (17.57%)	122 (82.43%)	148 (100.00%)	

DISCUSSION

The complexity of anatomy in mandibular molars was highlighted in the search for the middle mesial canal (MMC). Our study identified an MMC rate of approximately 18% in a cohort of 148 patients, which aligns with the variability reported in international studies and underscores certain anatomical peculiarities unique to this study population. This rate contrasts with previously reported rates in Pakistan where Bhatti *et al.*, found a 7.7% prevalence and Rehman *et al.*, observed MMCs in about 4.76% of mandibular molars examined using CBCT [7, 8]. The notably higher prevalence found in our study could be attributed to several factors: first, the utilization of more advanced CBCT technology allowing for better visualization and detection of MMCs compared to traditional imaging methods possibly used in earlier studies; second, our sample might represent a demographically distinct subset of the Pakistani population with potential anatomical variations; and finally, variations in the rigorousness of the radiographic analysis performed by different researchers could also contribute to discrepancies in prevalence rates. Talabani *et al.*, reported MMC prevalence 14.7% and 19.3% respectively on right and left side which was slightly higher than our results. This might suggest anatomical discrepancies or variations in detection techniques [10]. In a Brazilians study, Barros-Costa *et al.*, found MMC in 11.1% patients, lower than our findings that could indicate regional anatomic differences [11]. Azim *et al.*, reported frequency of MMC as 46.2%, demonstrating the power of high magnifications and resolution in uncovering some features missed by conventional techniques [12]. Nosrat *et al.*, and Yang *et al.*, studies highlighted age-related developmental constraints in MMC formation, arguing for an individualized diagnostic strategy [13, 14]. In a study by

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Iqbal *et al.*, conducted in India, authors found MMC in 21.8% patients, indicating that ethnic or genetic factor might be responsible for formation of MMC [15]. In an Iranian study by Hosseini *et al.*, conversely a lower MMC rate was reported i.e. 9%, maybe due to an infrequent use of modern diagnostic tools [16]. Kuzekanani *et al.*, found that 8.1% of the patients had MMCs visible on CBCT technology, indicating the significance of advanced imaging in locating complex root canal systems [17]. Hatipoğlu *et al.*, reported in their study that there was a considerable impact of demographic factors on the prevalence of MMC. They reported substantial variations in MMC detection rates by countries [18]. Mahajan *et al.*, analyzed the MMC in India using CBCT presented with significant anatomical variations and stated that 3D imaging was a necessity for accurate identification [19]. Stomatitis *et al.*, also found morphological variations of MMC in a North Indian subpopulation, indicating that geographical and ethnic backgrounds significantly influence MMC characteristics [20]. In the results of our study, based on age distribution, gender and subtypes of teeth (specific tooth types,) we could not find significant differences in MMC presence, suggestive that factors such as patient age or gender were less effective for development of MMC. These results highlight the critical importance of widespread imaging and structured examination techniques for identifying all MMC at presentation to facilitate appropriately aggressive treatment.

CONCLUSIONS

The results of our study showed rate of MMC as 18%. We found statistically insignificant association of development of MMCs with age and gender of patients, side of tooth and previous history of dental treatment. These results also indicate that the occurrence of MMCs was primarily influenced by individual anatomical variability, not demographic or clinical factors. Consequently, advanced imaging was crucial for the accurate detection of MMCs to ensure effective endodontic treatment planning for all patients.

Authors Contribution

Conceptualization: AMC

Methodology: SN, MH

Formal analysis: SN, AS

Writing, review and editing: AR, MHA

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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Bone Marrow Morphology: A Key Diagnostic Tool in Various Hematological and Non Hematological Disorders

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ABSTRACT

Bone marrow morphology means microscopic examination of bone marrow cells and tissue samples obtained by aspirate and trephine biopsy. An invaluable tool for diagnosis of many hematological and non-hematological disorders, various types of cancer staging and metastases detection. Different kinds of anemia and leukemia can be accurately diagnosed and monitored. **Objective:** To check the spectrum of diseases which could be identified and diagnosed with the help of bone marrow morphology examination thus demonstrating its diagnostic utility and to check diagnostic concordance between aspirate and core biopsy. **Methods:** Cross sectional study with consecutive sampling technique conducted over period of one year. Samples of both Bone Marrow Aspiration (BMA) and trephine biopsy (BMB) were collected from all patients included in study after consent using standard protocols. Air dried smears were prepared from bone marrow aspiration samples while trephine biopsy tissues were processed by histopathological techniques. Routine staining such as Wright Giemsa stain, H and E stain and special cytochemistry were used to visualize the cellular architecture of bone marrow. **Results:** Out of 471 samples, males were predominant with the frequency of 63.9% and maximum patients (31.8%) were from the age group of 35-40 years. Most common clinical indication to conduct bone marrow examination was unexplained Cytopenia which accounted for 35.2% cases, followed by suspicion of Leukemia (28.5%). Malignant hematological disorders were more common as compared to benign disorders (64% vs 17.5%). Acute leukemia was the most commonly identified cancer with frequency of 27.6%. **Conclusions:** Bone marrow morphology till date remains low risk, economical, crucial diagnostic tool in especially in under resource country like Pakistan. It can guide physicians to plan proper and timely management of patients.

INTRODUCTION

Bone marrow morphology examination, including aspiration and trephine biopsy, remains a cornerstone of Hematopathology being a key tool in diagnosis of various hematological and non-hematological disorders despite the advancements in molecular and genetic diagnostics. Composition of the bone marrow depicts the presence of Hemopoietic stem cells with Erythroid, Myeloid, Megakaryocytic lineage cells, adipose cells and stromal cells which are supportive microenvironment in nature [1]. Bone marrow aspirate shows complete cytological details whereas trephine biopsy gives panoramic view of bone marrow architecture. Different sites are used for the sampling of bone marrow among which the most preferred site is posterior superior iliac spine. However, in infants, ideal site of bone marrow sampling is medial side of upper end of the tibia, slightly below the level of tubercle of tibia [2]. The standard approach to diagnosis of many different hematological and non-hematological disorders, is still based on bone marrow morphology assessment under light microscopy especially various malignant disorders like Acute and Chronic Leukemia, Lymphoma, bone marrow metastatic disease showing particular percentage of malignant hematopoietic cells or malignant secondaries of primary neoplasm arising from any other organ in body apart from bone marrow [3]. Though, the examination of bone marrow is a common procedure in the west and has been the primary diagnostic tool for hematological malignancies and other blood disorders. However, in

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Pakistan only major medical institutions such as those in Karachi, Lahore, and Rawalpindi, likely have been among the early adopters of this procedure. Bone marrow examination must be preceded by complete clinical assessment of the patient including clinical history, baseline hematological examination including complete blood count and peripheral smear examination followed by targeted radiological, microbiological and biochemical investigations if required [4]. Bone Marrow Aspirate (BMA) is a diagnostic procedure that involves extracting a small amount of liquid bone marrow for examination under light microscope after air dried smears are stained with routine Wright Giemsa stain. Information obtained from Bone Marrow Aspiration includes overall bone marrow cellularity including exact percentage of hematopoietic / abnormal cell counts, which can help in differentiating between proliferative and hypoplastic bone marrow disorders like Myelodyplasia and Aplastic anemia respectively [5]. It can also give significant information about morphological/ cytological detail about size, shape, cellular outline, cytoplasm and nuclei of different cells under investigation such as characteristic appearance of Lymphoblast, Myeloblast and other malignant Plasma cells, thus enabling Pathologists (Hematologists) to correctly diagnose different types of acute lymphoid leukemia, acute myeloid leukemia and plasma cell myeloma respectively [6]. Bone marrow aspirate smears can also be used for cytochemical staining such as Sudan Black B (SBB), Myeloperoxidase (MPO), Periodic Acid Schiff (PAS), Specific and Nonspecific Estrases (NSE) etc., which can help in classifying different types of Leukemia. Bone marrow aspirate can also be used for diagnosis of different infectious diseases by doing bone marrow aspirate cultures and sensitivity. Bone marrow morphology examination after staining aspirate smears with another special stain i.e., Perl's stain is still gold standard for diagnosis of Iron Deficiency anemia [7]. Bone Marrow Trephine Biopsy (BMB) is a diagnostic test where a small core tissue of bone marrow is removed for examination under microscope. It complements the information obtained from a bone marrow aspiration. Its examination under light microscopy gives detailed panoramic view of bone marrow cellularity and provides comprehensive overview of inflammatory cells percentage, presence of any extra medullary cells, dysplasia, and cellular atypia, patterns of infiltration by malignant lymphoma, metastatic disease, marrow packing with blasts and any degree of fibrosis. Presence of Histiocytosis, and Storage disorders are clearly diagnosed on trephine biopsy [8]. Granulomatous disease is another difficult diagnosis detected by trephine biopsy. Bone marrow trephine biopsy has another advantage that its can be used for another important diagnostic modality that is immunohistochemistry to study confirmation of diagnosis, extent of bone marrow infiltration and prognosis of many malignant neoplasms. Two pillars of bone marrow morphology exam such as Bone marrow aspirate and trephine biopsy are both complementary to each other however sometimes aspirated specimen is of very low volume and sometimes it is diluted with sinusoidal blood, in both these conditions bone marrow aspirate is devoid of cellular components and suboptimal for reporting [9]. Adequate core length trephine biopsy makes it ideal technique for providing information regarding marrow cellular and architectural changes occurring in marrow cavity due to various underlying malignant and nonmalignant processes.

Therefore, aim of present study was to check the spectrum of diseases which could be identified with the bone marrow examination at initial stages. Frequency and categorization of benign and neoplastic lesions were also checked to compare diagnostic concordance between BMA and BMB.

METHODS

The present study was conducted at the Pathology department (Hematology section) of King Edward Medical University/Mayo Hospital Lahore over the study period of one year from March 2023 to March 2024. Ethical approval was taken from the institute Ethical Review Board (Reference Number: 329/RC/KEMU). It was cross sectional study and samples were collected through consecutive sampling technique. Sample size was calculated by using win-pepi ver: 11.15 software with confidence level of 95%, acceptable difference = 0.05 [2]. A Total of 471 cases which fulfilled the inclusion criteria were selected in the study period. Inclusion criteria included cases from the both gender of age groups (1-60 years) in the study. All the patients that were referred for examination of bone marrow and also for staging of hematological malignancies were included in the current study. Exclusion criteria defined as diluted bone marrow aspirate and samples from the patients less than 1 year of age were excluded from the study. Demographic data like age and gender were recorded from all the included cases. Clinical indications were determined by taking into account, patients thorough clinical history and on the basis of complete blood count CBC and peripheral smear results. Both BMA and BMB were taken from each patient according to standard ICSH (International council for standardization in Hematology) protocol of bone marrow sample collection [5]. Written informed consent was taken from each patient before the procedure. Bone marrow aspirate was done from posterior iliac crest using aseptic techniques. Anterior superior iliac spine was used for the bone marrow sample collection from obese patients. Selected area from where the sample was taken was locally anesthetized first and then commercial

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bone marrow needle (with removable stylet) of appropriate size was used to take small amount (0.5ml) of bone marrow aspiration followed by collection of bone marrow trephine biopsy sample placed in Bouin's solution. Air dried smears were made from the bone marrow aspirate while for trephine biopsy, (>1cm) biopsy on gross examination was considered adequate. For the processing of bone marrow aspirate, a mono-layered smear was made from the concentrated marrow cells on the slide. After air drying, methanol was used to fix the smears. Slides were stained with Wright-Giemsa stain which contain methylene blue and eosin dissolved in methanol. After staining, slides were air dried and were observed under light microscope Olympus CX43 five head Microscope using 10x, 20x, 40x and 100x magnification by counting 400 cells to visualize the cytological detail and infiltration pattern of the bone marrow. For processing of bone marrow trephine biopsy, samples were initially decalcified. After this, samples were processed according to standard histopathological techniques including tissue processing and embedding in paraffin wax. Special stains such as Sudan Black B, Non-Specific Esterase (NSE), Acid Phosphatase, Periodic Acid Schiff (PAS), Reticulin stain was used according to the patient's clinical symptoms and probable disease identification. Photomicrographs were taken by digital camera attached to Olympus CX43 five head light microscope EP50 with 2592x1944 pixel resolution. Normal morphology of bone marrow was distinguished from pathological bone marrow by the presence of abnormal cells infiltrate in latter. Acute Leukemia was diagnosed and differentiated into Acute Lymphoblastic (ALL)and Acute Myeloblastic Leukemia (AML) according to WHO 2016 diagnostic criteria stating presence of 20% Bone marrow aspirate Blasts and classified according to FAB morphological classification by using special staining methods (SBB, MPO, PAS, AP, NSE) and subtyped by using immunohistochemistry on trephine biopsy. Similarly, remission assessment was done morphologically according to percentage of bone marrow blast (<5%). Chronic leukemia such as Chronic Myeloid Leukemia (CML) was diagnosed morphologically according to WHO 2022 criteria defined by Granulocytic Hyperplasia with variable number of blasts according to different stages of disease. Lymphomas were differentiated on the basis of morphologically different atypical lymphoid population and subtyped by immunohistochemistry. Multiple Myeloma was differentiated due to presence of >10% abnormal plasma cells in bone marrow morphology as part of WHO 2016 diagnostic criteria. MPN especially Myelofibrosis was one of the disorders that can only be diagnosed on bone marrow examination with Reticulin special stain. Non hematological metastatic disease was differentiated from hematological malignancies using specific morphology of malignant cells and use of immunohistochemistry [9]. Amongst Benign Hematological disorders, Dimorphic anemia was differentiated from Megaloblastic anemia by presence of two different erythroid maturation pattern with special stain (Perl's stain) used to diagnose iron deficiency anemia. Hypoplastic bone marrow disorders showed less than 20% cellularity in BMB exam. Malaria infection showed ring forms and gametocytes in bone marrow, Leishmania infection exhibited LD bodies in bone marrow while tuberculous granulomatous disease was differentiated on marrow morphology showing giant epitheloid cells and inflammatory cell infiltrate. While bone marrow aspirate culture isolated salmonella typhi. Storage disorders showed bone marrow infiltration by large histiocytic gaucher cells and foam cells. Data were collected and statistically analyzed by using SPSS software 27.0. Numerical data were expressed as mean. Frequencies and percentages were calculated for the univariate variables. Diagnostic concordance was the rate of agreement between BMA and BMB was expressed as percentage. Chi square test was used to evaluate any statistically significant difference between BMA and BMB.

RESULTS

A total of 471 samples of bone marrow aspiration and trephine biopsy for bone marrow morphology examination was processed during the study period. Out of which 63.9% (n=301) samples were collected from the male patients while 36.1% (n=170) samples were collected from the female patients. Age distribution showed that maximum samples were collected from the age group of 30-45years n=150, followed by age group of 45-60yrs and 15-30yrs (n=100) each table 1.

Table 1: Age Distribution of Patients

Age Group	Frequency (%)
Less than 15 Years	50 (10.6%)
15-30 Years	100 (21.2%)
30-45 Years	150 (31.8%)
45-60 Years	100 (21.2%)
More than 60 Years	71 (15.2%)
Total	471 (100%)

Most common clinical indication identified for which bone marrow examination was done, found to be Bi-Pancytopenia (35.2%, n=166) followed by suspected diagnosis and remission assessment of Leukemia including acute and chronic leukemia's (28.5%, n=134). Other common indications were summarized in table 2.

Table 2: Clinical Indications for which Bone Marrow Examination was done

Clinical Indications to Perform Bone Marrow	Frequency (%)
Evaluation of Cytopenias (Bi and Pancytopenia)	166 (35.2%)
Assessment of Anemia	53 (11.3%)
Diagnosis and Remission Assessment of Leukemia's	134 (28.5%)
Leucoerythroblastic Blood Picture	20 (4.2%)
Fever of Unknown Cause	64 (13.6%)
Thrombocytopenia	34 (7.2%)

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Most frequent complications associated with the sampling of bone marrow aspirate and bone marrow trephine biopsy were pain, anxiety, bleeding and dizziness. About 90% in individuals feel pain during the procedure in spite of the local anesthesia. While ratio of dizziness and bleeding was too low as compared to pain which was 1.09% and 1.82% respectively. Total 471 samples of bone marrow examination were processed for the identification of hematological and non-hematological diseases by using Giemsa and special stains. 72 samples showed normal bone marrow cellular architecture. Most common clinical condition observed was Leukemia (both acute and chronic leukemia/Lymphomas) which was 48.8% (n=130), followed by Remission of malignant tumors 11.8% (n=56). Detailed disease pattern observed in bone marrow examination was summarized in table 3.

Table 3: Disease Spectrum Observed in Bone Marrow Morphology Examination

Disease Pattern (Clinical Diagnosis)	Frequency (%)
Malignant Hematological Disorders	
Acute Leukemia	130 (27.6%)
Chronic Leukemia/Lymphoma	100 (21.2%)
Multiple Myeloma	11 (2.3%)
Myelofibrosis	5 (1.1%)
Remission of Malignant Tumors	56 (11.8%)
Non-Malignant Hematological Disorders	
Erythroid Hyperplasia	6 (1.3%)
Megaloblastic Anemia	21 (4.5%)
Dimorphic Anemia	6 (1.3%)
Hypoplastic Marrow	33 (7%)
ITP*	10 (2.1%)
Infective Pathology	6 (1.3%)
Non-Hematological Malignant Disorders	
Metastasis Staging	9 (1.9%)
Distribution of other Conditions	
Normal Study	72 (15.3%)
Storage Disorders	6 (1.3%)
Total	471 (100%)

*Idiopathic Thrombocytopenic Purpura

In this study, bone marrow morphology showed four peculiar fatal disease patterns requiring urgent diagnosis and adoption of early treatment plan. These four particular disorders can only be diagnosed and visualized through bone marrow exam. Photomicrograph A shows BMA stained with SBB special stain showing Acute leukemia classified as AML with maturation according to FAB classification. Rapid diagnosis with minimum cost was essential for patient as it was deadly disease and early management plan was extremely important especially in under resource country like Pakistan. Photomicrograph B shows a rare finding of presence of bone marrow Calcium Oxalate crystals in a patient who presented with cytopenias (anemia, platelet dysfunction) and bone pains. It's crucial to start early and individualized treatment. Photomicrograph C shows Myeloproliferative disorder (MPN-ET). This patient presented with portal vein thrombosis and thrombocytosis. Without bone marrow morphology, diagnosis of this disease was not possible without timely bone marrow exam showing characteristic large megakaryocytes with abundant cytoplasm and lobulated, stag horn nuclei. Photomicrograph D shows Bone marrow metastatic disease. In this disorder bone marrow trephine morphology was mandatory for staging of disease, without which treatment can't be started (Figure 1).

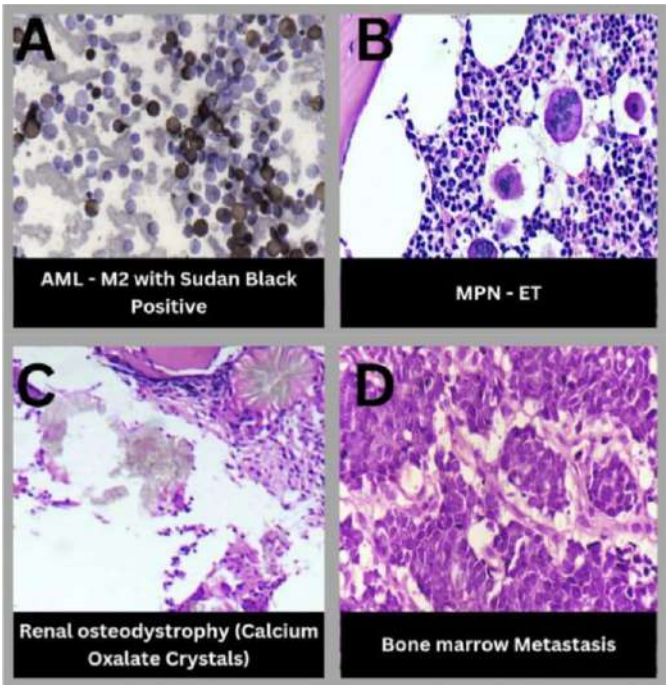

Figure 1: A: AMLM2 with SBB Positive B: MPN-ET (Essential Thrombocythemia) C: Calcium Oxalate Crystal (Renal Osteodystrophy) D: Bone Marrow Metastasis

Photomicrographs were taken by digital camera attached to Olympus CX43 five head light microscope EP50 with 2592x1944 pixel resolution. In present study, diagnostic concordance rate between BMA and BMB for diagnosis of various disorders was 88% while only 27 cases were missed on BMA alone and was diagnosed on BMB making diagnostic disagreement between both tools of bone marrow morphology almost negligible as depicted in table 4.

Table 4: Diagnostic Concordance between BMA and BMB

Disease Pattern (Clinical Diagnosis)	Frequency (%)
Malignant Hematological Disorders	
Acute Leukemia	130/130 (100%)
Chronic Leukemia/Lymphoma	93/100 (93%)
Multiple Myeloma	11/11 (100%)
Myelofibrosis	3/5 (60%)
Remission of Malignant Tumors	51/56 (91%)
Non-Malignant Hematological Disorders	
Erythroid Hyperplasia	6/6 (100%)
Megaloblastic Anemia	21/21 (100%)

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Dimorphic Anemia	6/6 (100%)
Hypoplastic Marrow	4/33 (%)
ITP*	10/10 (100%)
Infective Pathology	5/6 (83%)
Non-Hematological Malignant Disorders	
Metastasis Staging	5/9 (55%)
Distribution of other Conditions	
Normal Study	71/72 (98%)
Storage Disorders	2/6 (33%)
Total	418/471 (88%)

Comparison of the cases diagnosed by bone marrow aspirate and bone marrow trephine biopsy was statistically done by using Chi-square test. Diagnosed cases and missed diagnosis in both modalities were compared which showed statistically significant value of 0.012. This table showed there was a statistically significant difference between BMA and BMB diagnosis ($p < 0.05$). This means that the proportion of diagnoses being done or missed were statistically different between BMA and BMB, which shows the complementary nature of both modalities in bone marrow morphology interpretation (Table 5).

Table 5: Comparison of Cases Diagnosed in BMA and BMB

Cases	Diagnosis Done (Positive)	Diagnosis Missed (Negative)	Total	p-Value (Chi Square Test)
BMA	444	27	471	0.013
BMB	460	11	471	

Chi-Square Statistics: 6.1699, p-value: 0.0130

DISCUSSION

Bone marrow examination including both aspiration and trephine biopsy were considered complementary to each other and were very important and valuable tools for the identification of malignant as well as non-malignant hematological conditions [9]. Certain non-hematological conditions such as renal osteodystrophy - Calcium Oxalate crystals, Bone Marrow Metastasis can only be identified by bone marrow examination when performed after comprehensive morphological assessment of the selected patients [8]. Generally, it was amalgamation of different hints collected from the observations of different morphological parameters that eventually leads to exact diagnosis [10]. In the present study, total 471 bone marrow samples were examined from the patients of both genders and different age groups. Out of total samples, male gender outnumbered the female gender with the frequency of 63.9% and 36.1% respectively. Similar results were reported by Kumar V *et al.*, in which majority of the patients were males [11]. Another study also reported the predominance of males suffering from different hematological disorders as compared to females [12]. In this study, the age range of this study participants were from 1 years to more than 60 years. Similar to these results were reported by Pudasaini S *et al.*, Kibria SG *et al.*, and Mahfuz H *et al.*, which showed that maximum patients were from age group of 31-45 years [13-15]. Comparable to this results, two other studies also reported the similar findings [16, 17]. Various indications were observed in the current study for bone marrow examination, among which work up for the cytopenia and probability of different hematological malignancies were found to be the most common diagnosis from bone marrow morphology examination. In the present study, most common indication was cytopenia (35.2%, n=166), followed by identification of leukemia both acute and chronic leukemia (28.5%, n=134). In accordance to this results, Ahmed SQ *et al.*, also reported cytopenia as a common indication which was 38.3% [18]. Similar results were also reported by Pudasaini S *et al.*, in which cytopenia accounted for 22.8% of the total cases [13]. However, Gandapur AS *et al.*, (22.8) and Bashawri LA (11.9%) reported Cytopenia as the 3rd common indication for bone marrow examination in their studies [16, 19]. Major disease burden in this study comprise of malignant hematological and non-hematological disorders, for which bone marrow morphology examination was first and foremost requirement. In this study, out of 471 samples, only 15.3% (n=72) showed normal cellular architecture while 1.0% (n=6) were storage disorders including Gaucher disease and Nieman Pick disease. Bone marrow was infiltrated by characteristic abnormal histiocytic cells in storage disorders [20-22]. Paediatric patients included in this study constitue around 10%, mainly showed bone marrow infiltration by Acute Leukemia and storage disorders. These clinical conditions were debilitating and require early detection made possible by bone marrow Morphological exam. Moreover, bone marrow infiltration was part of diagnostic criteria in these disorders [23]. So here diagnostic usefulness of bone marrow morphology was clearly visible. Malignant hematological conditions accounted 64% (n=302) which were more predominant than non-malignant hematological conditions (17.5%, n=82). Comparable to this results, Mahfuz H *et al.*, from Bangladesh reported the predominance of hematological malignancies in his study (64.2%) than non-malignant conditions which were 22.4% [15]. In accordance to this results Chowdhury MRK also reported the high prevalence of malignant hematological diseases than non-malignant hematological conditions [1]. Majority of malignant cases were identified as acute leukemia (27.6%, n=130) in this study. Various other studies also reported the similar results [12, 20]. Multiple myeloma was identified in 2.3% (n=11) of cases of bone marrow examination. Comparable to these results, two different studies also reported 2.5% and 3.5% rate of multiple myeloma diagnosis through bone marrow examination [2, 14]. Among non-malignant hematological conditions, hypocellular marrow was observed in 7% (n=33) of cases. Another study also reported similar results with the percentage of 5.3% [13]. It's important to mention here that aplastic anemia and other hypocellular bone marrow syndromes can only be

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confirmed by bone marrow morphology on BMB [7]. In this study, megaloblastic anemia was identified in 4.5% (n=21) cases of bone marrow examination. Bashir *et al.*, Mahfuz H *et al.*, and Yadav S *et al.*, reported 8%, 2.63% and 6.5% frequency of megaloblastic anemia respectively [2, 15, 21]. Pudasaini S *et al.*, reported 12.3% frequency of megaloblastic anemia which was slightly higher than this study and could be attributed to the nutritional deficiencies of their native population [13]. Swift bone marrow morphological assessment and prompt treatment of megaloblastic anemia is mandatory as failure can lead to irreversible neurological damage in the form of sub-acute combined degeneration of spinal cord [24]. Less than 1.0% samples were found to be inadequate in this study, which were in accordance with the study by Ranabhat S *et al.*, who reported inadequacy of 0.87% samples in his study [9]. In this study, diagnostic agreement between BMA and BMB was around 89%, which was in accordance with Meenu Gilotra M *et al.*, who reported concordance rate as 87% [22].

CONCLUSIONS

Bone marrow morphology examination was a time-tested and valuable diagnostic tool in clinical practice, especially in resource-limited settings. It was relatively simple, cost-effective and has ability to provide a wealth of information regarding blood cells pathology, making it crucial in diagnosing and understanding etiopathogenesis of broad spectrum of blood disorders. In developing countries like Pakistan where access to advanced medical technologies such as flow cytometry, cytogenetic and molecular genetics were limited due to cost and lack of infrastructure, and not in reach of majority of population, bone marrow morphology serves as a reliable and accessible diagnostic as well as prognostic tool, aiding in prompt and accurate treatment for improved patient outcomes.

Authors Contribution

Conceptualization: MA
Methodology: RM, MA
Formal analysis: HS, SA
Writing, review and editing: MA, SA, RM, HS

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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Diagnostic Accuracy of Mammography and Ultrasonography Screening for Breast Cancer in Pregnant and Lactating Women

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ABSTRACT

Breast cancer was of significant health concern affecting women worldwide. **Objective:** To assess diagnostic accuracy of mammography and ultrasonography in differentiating malignant and benign breast lesions in pregnant and lactating women. **Methods:** A cross sectional retrospective study was conducted at Radiology department of Shahida Islam Medical Complex, Lodhran from May 2023 to April 2024. A sample size of 242 females was calculated. Electronic medical records were reviewed for radiological examination including screening ultrasound and mammography. All those pregnant and lactating females on which ultrasound and mammograms were performed were included. SPSS version 23.0 was used for data analysis. Diagnostic accuracy of both ultrasound and mammography were calculated in terms of malignant or benign and sensitivity and specificity. Mann-Whitney U test was applied between mammography, ultrasonography and BI-RADS categories. **Results:** Of 242 females, 110 underwent mammography and 132 underwent ultrasound. Negative mammography was observed in 71 females in which at biopsy, 24 were benign. Negative ultrasound with only benign lesion was seen in 68 females and 10 of which were confirmed at biopsy. Specificity of ultrasonography was 100 %, sensitivity 85.7 %, positive predictive value of 100 % while negative predictive value of 25 %. Specificity of mammography was 100 %, sensitivity 92.3 %, positive predictive value of 100 % while negative predictive value of 42.8 % ($p<0.001$). **Conclusions:** Although both ultrasound and mammography were found to be specific, use of mammography was considered better in terms of sensitivity and diagnostic accuracy.

INTRODUCTION

Worldwide, breast cancers have been regarded as the most common, having significant health concern affecting women worldwide, and presents unique challenges due to fetal radiation exposure concerns [1]. Radiological screening has a crucial role in early detecting breast cancer, but traditional modalities like mammography may pose risk to fetus as well as in breastfeeding infant. Hence, developing effective and safe screening strategies tailored to pregnant and lactating women is imperative [2]. Mammography is gold standard screening test for cancers of the breast in non-lactating or non-pregnant females. However, its use in pregnant and lactating women is limited because of potential risks linked to exposure of radiation to fetus [3]. Evidence-based guidelines were established by American College of Radiology (ACR) for various clinical disorders, however for screening of cancers of breast, limited published evidence persists in support of it for females that are either lactating or pregnant [4]. Nonetheless, screening for breast cancers through mammography is not contra-indicated amid pregnancy, especially for females that are prone to cancers of the breast [5]. If ultrasonography or biopsy of solid lesion reveals malignancy in pregnant or lactating females, digital breast tomosynthesis and mammography are recommended to be performed [6]. Thorough evaluation via mammography is advised in order to stage breast cancers in pregnant females loco regionally [7]. Another modality for evaluating lesions of the breast in pregnancy

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and lactation is ultrasonography, having the added benefit of no exposure to radiation and is a sensitive imaging technique [8]. Diffuse hypo-echogenicity along with increase in vascularity and fibro-glandular enlargement are observed in the breast in pregnancy. Conversely, diffuse hyper-echogenicity along with increased vascularity and prominent ductal systems are reported during lactation [9]. Ultrasound is an initial imaging test of choice in under 30-year-old pregnant and lactating females, given lack of radiation exposure. Females that are lactating and are 30 years and older are mostly imaged via both mammography and ultrasonography [10]. For reducing overall breast density, lactating females are advised to secrete milk immediately before imaging [11]. Magnetic Resonance Imaging (MRI) is not typically used for breast cancer screening in pregnant or lactating women due to the physiological increases in breast vascularity during pregnancy and lactation, which result in markedly increased background parenchymal enhancement. These changes may limit the sensitivity of MRI, and its use is generally reserved for delineating disease extent in lactating women with breast cancer [12, 13]. In conclusion, logical screening strategies for breast cancer in pregnant and lactating women involve the use of ultrasonography as the initial imaging modality, with mammography reserved for pregnant women with suspicious findings on ultrasonography or biopsy of a solid lesion revealing malignancy [14]. MRI is generally not used for breast cancer screening in pregnant or lactating women due to the physiological increases in breast vascularity during pregnancy and lactation. The evaluation of breast imaging studies during pregnancy and lactation is challenging and the ACR Appropriateness Criteria recommend that pregnant women with palpable masses or pathological nipple discharge should be initially evaluated by ultrasonography [15]. Mammography can be used as a supplement to ultrasonography for breast evaluations in pregnant women with palpable masses or pathological nipple discharge. Overall, the goal of breast cancer screening in pregnant and lactating women is to balance maternal and fetal well-being while ensuring timely and appropriate care [16]. In majority of pregnant and lactating females, screening for breast cancer is carried out using either ultrasonography or mammography, seldom are both strategies employed for proper and complete screening of females. Due to high economic burden and patient's inflow, both strategies are not always used for screening. Therefore, this study has been undertaken to compare and determine as to which of the two screening are better suited for breast cancer in pregnant and lactating women.

The objective of this study was to assess the diagnostic accuracy of mammography and ultrasonography in differentiating between malignant and benign breast lesions in pregnant and lactating women.

METHODS

A retrospective cross sectional study was carried out after ethical approval from the Ethical Review Committee of Shahida Islam Medical Complex, Lodhran IRB no. SIMC/H.R./7729/23. Since this was a retrospective study, therefore need for informed consent was waived. All the breast ultrasounds and screening mammograms that were performed for pregnant and lactating women during the study time period May 2023 to April 2024 at Radiology department of Shahida Islam Medical Complex, Lodhran, Pakistan were included in the study. Pregnant (any trimester) or lactating mothers (within first year postpartum) between ages 18 to 45 years and presenting with clinical signs or symptoms suggestive of breast cancer (e.g. palpable breast mass, nipple discharge or skin changes etc.) and willing to undergo mammography or ultrasonography as part of screening process were included in the study while females with a previous history of breast cancer or any other malignancy with last 5 years were excluded from the study. In addition, females having co-morbid conditions which might affect participation or interpretation of imaging results were also excluded. Sample size calculation was carried out using online software for sample size calculation (web) using sensitivity/specificity estimation (https://wnarifin.github.io/ssc/sssnsp.html) in accordance with a reference for formula [17]. Keeping 92.5 % sensitivity and 76.47 % specificity as reported in a local study and prevalence of breast cancer at 50 % as reported in another local research with 85 % confidence level, the sample size calculated was 245 [18, 19]. This study included a total of 242 patients. Patient's medical files were manually reviewed for complete history, clinical examination and radiological examination including screening ultrasound, mammography, diagnostic imaging and pathological results (if available), clinical outcome after follow up were recorded. Biopsy-proven lesions having pathological abnormality for over 3 months of radiologic or clinical follow up were included in the study while biopsy-proven lesions having pathological abnormality for less than 3 months of radiologic or clinical follow up were excluded and regarded as lost to follow up. Mammograms performed at the hospital used either digital technique (DMR and D2000, GE Healthcare) or standard film screen. Breast ultrasound was carried out by interpreting radiologist (GE Healthcare, GE Logiz 700 and ATL HDI 5000, Philips Healthcare). In case of focal problem such as focal thickening, lump or palpable mass, erythema etc. directed ultrasonography was done. In cases suspected of generalized breast involvement, entire breast underwent ultrasonography. For evaluation of symptomatic women, National Comprehensive Cancer Network's guidelines were taken into account. Generally,

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females below 30 years of age underwent ultrasonography only and only if clinical symptoms or imaging findings were inconclusive, then mammography was done. In females 30 years and above, both ultrasonography and mammography were performed. Nonetheless it was on the discretion of the consulting clinician to modify the protocol. Mammography Quality Standards Act (MQSA) was used by radiologist for interpretation of each examination. BI-RADS assessment was used for both ultrasonography and mammography examinations. If any specific BI-RADS assessment was not included, radiologist reviewed the reports and assigned ultrasound BI-RADS category based on the standard criteria viz. 1-3 as negative and 4-5 as positive [20]. For calculation of diagnostic accuracy overall and sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV), the following formulas were used.

$$\text{Diagnostic Accuracy: } \frac{TP + TN}{TP+TN+FP+FN}$$

True Position (TP)	False Positive (FP)	**PPV:** TP/ (TP+FP)
False Negative (TN)	True Negative (TN)	**NPV:** TN/ (TN+FN)
Sensitivity: TP/(TP+FN)	**Sensitivity:** TN/(FP+TN)	

Data were entered into Microsoft Excel and analyzed using SPSS version 23.0. Sensitivity and specificity of both ultrasound and mammography were calculated. Mann-Whitney U test was applied between mammography and ultrasonography and between BI-RADS categories. $P<0.05$ was considered as statistically significant.

RESULTS

Amongst the 242 female patients included in the study 27 were asymptomatic while 217 were symptomatic. The chief presenting complaint in 16 (6.72 %) females had a family history of breast cancer and attended OPD for checkup. Nine (3.73 %) were called back from screening and 02 (0.75 %) came for follow up with a previous lesion of BI-RADS 3. Palpable mass was present in 155 (64.01 %) females, 22 (9.01 %)) had erythema, 13 (5.37 %)) pain, 08 (3.3%) thickening, 05 (2.01 %) bloody nipple discharge, 02 (0.83 %) dimpling while breast firmness was reported in 04 (1.49 %), milk rejection and clear, yellow or milky discharge in 03 (1.24 %) each female (Table 1).

Table 1: Chief Presenting Complaint of Females with Breast Lesion (n=242)

Chief Presenting Complaint	Frequency (%)
Asymptomatic	
Family History of Breast Cancer	16 (6.72%)
Call Back from Screening	9 (3.73%)
Short Term follow up (Lesion Previously BI-RADS-3)	2 (0.75%)
Symptomatic	
Palpable Mass	155 (64.01%)
Erythema	22 (9.01%)
Pain	13 (5.37%)
Thickening	8 (3.3%)
Bloody Nipple Discharge	5 (2.01%)
Breast Firmness	4 (1.65%)
Milk Ejection	3 (1.24%)
Clear, yellow or milky discharge	3 (1.24%)
Dimpling	2 (0.83%)

A total of 110 females had undergone mammography and 132 had undergone ultrasound. Some females had undergone both. A negative mammography was observed in 71 (64.54%) females in. Benign calcifications were reported in 13 (11.81%) females while malignant in 03 (2.72%). Other benign / malignant findings were reported in Table 2. A negative ultrasound with only benign lesion was seen in 68 (51.51%) females. Solid mass (benign) was observed in 26 (19.69%) while malignant in 03 (2.27%) females. Other findings, their benign and malignant nature were reported in table 2.

Table 2: Baseline Characteristics of Lesions Evaluated using Ultrasonography and Mammography (n=242)

Techniques / Findings	Benign N (%)	Malignant N (%)
Mammography		
Negative	71 (64.54%)	0
Calcification	13 (11.81%)	3 (2.72%)
Mass	10 (9.09%)	0
Mass and Calcification	1 (0.91%)	1 (0.9%)
Architectural Distortion	0	1 (0.9%)
Focal Symmetry	9	0
Dense Lymph Nodes	0	1 (0.9%)
Others (Air-Fluid Level)	1 (0.91%)	0
Ultrasound		
Negative	68 (51.5%)	0
Solid Mass	26 (19.69%)	3 (2.27%)
Simple Cyst	10 (7.57%)	0
Complication Cyst	3 (2.27%)	0
Complex Cyst	5 (3.78%)	0
Dilated Ducts	6 (4.54%)	1 (0.75%)
Dilated Ducts with Solid Intra-Ductal Component	0	1 (0.75%)
Ill-Defined Attenuation	3 (2.27%)	1 (0.75%)
Subcutaneous Edema	2 (1.51%)	0
Sebaceous Cyst	2 (1.51%)	0
Inflammatory Lymph Mode	1 (0.75%)	0

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Figure 1 showed the graphical representation of both mammography and ultrasonography assessments in terms of their outcomes using BI-RADS. Outcome was regarded by clinical follow up or pathological analysis (biopsy confirmation). Specificity of ultrasonography was 100%, sensitivity 85.7%, positive predictive value of 100% while negative predictive value of 25%. Specificity of mammography was 100%, sensitivity 92.3%, positive predictive value of 100% while negative predictive value of 42.8%. A significant difference between both mammography and ultrasonography with the outcomes were observed ($p<0.001$).

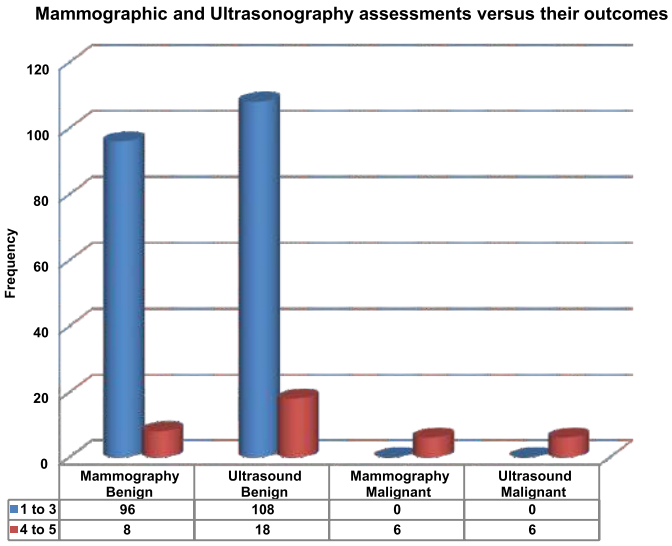

Figure 1: Graphical Representation of Mammographic and Ultrasonography Assessments versus Their Outcomes Using BI-RADS [$p<0.001$] (n=242)

This diagnostic test shows an accuracy of 92.7%. It correctly identified 96 cases as benign (true positives) with no false positives. However, it missed 8 malignant cases (false negatives), while correctly identifying 6 cases as malignant (true negatives). While the test was highly accurate, the presence of false negatives suggests some malignant cases were not detected (Table 3).

Table 3: Diagnostic Accuracy of Mammography (n=110)

Diagnostic Accuracy	Benign	Malignant
Positive Result	96 (True Positive)	0 (False Positive)
Negative Result	08 (False Negative)	06 (True Negative)
Diagnostic Accuracy	92.7 %	

This diagnostic test achieved an accuracy of 81.8%. It correctly identified 108 cases as benign (true positives) without any false positives. However, it failed to detect 18 malignant cases (false negatives) and correctly identified only 6 cases as malignant (true negatives). While the test effectively avoids misclassifying benign cases as malignant, the higher number of false negatives indicates a significant limitation in detecting all malignant cases (Table 4).

Table 4: Diagnostic Accuracy of Ultrasonography (n=132)

Diagnostic Accuracy	Benign	Malignant
Positive Result	108 (True Positive)	0 (False Positive)
Negative Result	18 (False Negative)	06 (True Negative)
Diagnostic Accuracy	81.8%	

DISCUSSION

The findings of this reported that both mammography and ultrasonography were safe, effective and accurate in terms of lesion identifying as well as keeping maternal and fetal/neonatal/infant health safe. Even though both screening techniques demonstrated 100% specificity and 100% PPV, sensitivity of mammography was higher than that of ultrasonography (92.3% vs 85.7%). Negative predictive value of mammography was also found to be higher than that of ultrasonography (42.8% vs 25%). Diagnostic accuracy of mammography was found to be higher than that of ultrasonography in our study (92.7% vs 81.8%). In a meta-analysis assessing the risk-benefit ratio of mammography in pregnant women with high-risk factors for breast cancer, it was observed that moderate sensitivity with low fetal radiation exposure risk was reported in pregnant women. The paper concluded that mammography many only be considered in high-risk cases after thorough risk assessment and shared-decision making [19]. Another retrospective comparative analysis of ultrasonography versus mammography in pregnant women reported that ultrasound demonstrated higher sensitivity (89 %) as compared with mammography (72 %) in detection of breast lesion without any fetal radiation exposure. The study concluded that ultrasound ought to be used as primary imaging modality for screening of breast lesions among pregnant women [20]. A study on the safety of contrast-enhanced MRI in lactating women observed that it was safely performed during lactation, even enhancing the diagnostic accuracy in breast cancer screening, however the study only included lactating women and not currently pregnant women [21]. Literature suggests that screening of pregnant and lactating females using ultrasonography or mammography has its advantages and disadvantages, for instance ultrasound was regarded as safe, accurate, versatile and easily accessible while on the down side, it has limited sensitivity, operator dependency and sometimes show inconclusive results [22, 23]. On the other hand, mammography can he highly sensitive, detect even micro calcifications, has well-established standardized protocols and complements ultrasound [24]. However, with mammography, risk of fetal radiation exposure was a major drawback coupled with the decreased sensitivity during pregnancy and lactation of the breast and was sometimes discomforting as it requires manual compressions [25]. In summary, both ultrasound and mammography have roles to play in breast cancer screening for pregnant and lactating women, but their use

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should be tailored to individual circumstances and risk factors. Ultrasound was generally preferred due to its safety and versatility, while mammography may be considered in specific cases where it can provide additional diagnostic information without undue risk to the fetus. Shared decision-making between patients and healthcare providers was essential to ensure that screening strategies prioritize both efficacy and safety [26-28]. Additionally, ongoing research and technological advancements may further improve the diagnostic accuracy and safety of breast cancer screening in this population. Although this study compared that two screening strategies among pregnant and lactating women, however this study was not free from limitations. The retrospective nature of the study and selection criteria of patients might have led to selection bias. In addition, limited sample size and the fact that this was a single centered study, cannot be authentically be generalized for the larger population. Further larger scale studies were required to generalize the findings reported in this study.

CONCLUSIONS

Although both ultrasound and mammography were found to be specific, use of mammography was considered better in terms of sensitivity and diagnostic accuracy. Further researches would be enlightening to the findings reported in this study.

Authors Contribution

Conceptualization: NM

Methodology: WA

Formal analysis: SB, MH

Writing, review and editing: NM, FU, SH, SB, ZUA, 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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Association of Oral Microbiome with Periodontal Disease Progression: A Longitudinal Study

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ABSTRACT

Periodontal disease, a prevalent oral health condition, is characterized by the inflammation and destruction of the supporting tissues around the teeth and poses significant challenges to global public health. **Objectives:** To examine the association between the oral microbiome and periodontal disease progression in a Pakistani population. **Methods:** A total of 350 patients aged ≥ 18 years, diagnosed with periodontal disease, were registered from August 2023 to February 2024. Participants were evaluated for periodontal health indicators, including probing depth and clinical attachment loss, and their oral microbiome profiles were analyzed using high-throughput sequencing of the 16S rRNA gene. Machine learning algorithms, including Random Forest and Support Vector Machines, were applied to predict disease progression based on microbial profiles. **Results:** Porphyromonas gingivalis and Tannerella forsythia were strongly associated with greater probing depths and clinical attachment loss ($\beta = 0.45$, $p < 0.01$), indicating their role in disease progression. Conversely, Streptococcus and Lactobacillus were linked to reduced disease severity ($\beta = -0.30$, $p < 0.05$). The oral microbiome exhibited high diversity, with Firmicutes (35%), Bacteroidetes (25%), Proteobacteria (20%), and Actinobacteria (15%) being the predominant species. The Random Forest model predicted disease progression with 85% accuracy (Area under the curve (AUC) = 0.87), emphasizing the predictive value of microbial profiles. **Conclusions:** It was concluded that the study confirms a strong link between specific oral microbiota and periodontal disease progression, emphasizing the importance of microbial analysis in predicting and managing periodontal health.

INTRODUCTION

Periodontal disease, characterized by inflammation and destruction of the supporting tissues around the teeth, is a significant public health concern worldwide. According to data from the Global Burden of Disease (GBD) Study in 2019, periodontitis is the seventh most prevalent disease worldwide, affecting 1.09 billion people (Institute for Health Metrics and Evaluation (IHME), 2020) [1]. Since 1990, the prevalence has increased significantly due to population growth and ageing [2]. The age-standardized prevalence of periodontitis was estimated at 11.2% in 2010 and rose to 13.1% in 2019 [2, 3]. These trends and variations in incidence and disease burden differ by sex, age, and geographical region [1-4]. Data specific to the French population are limited, but the GBD study 2019 estimated the age-standardized prevalence of severe periodontitis in France at 9.6% [2]. This is close to the 10.2% prevalence of periodontal pockets greater than 5 mm found in the 2002-2003 National Periodontal and Systemic Examination Survey, conducted on a stratified quota sample of 2,144 adults aged 35–64 years in France [5]. In Pakistan, the burden of periodontal disease is notably high, with recent studies indicating that around 40% of adults suffer from moderate to severe periodontitis [6]. This high prevalence underscores the urgent need for effective

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diagnostic and therapeutic strategies tailored to the Pakistani population. Despite the significant burden, there is limited research exploring the specific factors contributing to the progression of periodontal disease in this region [7]. Emerging evidence suggests that the oral microbiome, the complex microbial community inhabiting the oral cavity, plays a crucial role in the pathogenesis and progression of periodontal disease. The oral microbiota, part of the human microbiota, includes over 700 bacterial species, many of which are commensal and help maintain oral physiological balance [8]. Disturbances in this microbial balance, known as dysbiosis, can lead to periodontal diseases such as gingivitis and periodontitis. Furthermore, dysbiosis has been linked to systemic conditions, including the formation of oral cancer [9]. Previous studies have highlighted the association between the oral microbiome and periodontal disease progression. However, these studies often focused on specific bacterial species without considering the broader microbial community structure and its stability over time. For instance, research has shown that patients with periodontitis have a higher prevalence of pathogenic bacteria such as Porphyromonas gingivalis and Tannerella forsythia, yet these studies did not fully explore the dynamic interactions within the microbial community that contribute to disease progression [10]. Additionally, many studies did not account for confounding factors such as genetic predispositions, lifestyle factors, and systemic health conditions, which can significantly influence periodontal health [11].

This study aimed to address these gaps by conducting a longitudinal analysis of the association between the oral microbiome and periodontal disease progression in the Pakistani population. This research will contribute to the development of more effective diagnostic tools and therapeutic strategies tailored to the needs of individuals suffering from periodontal disease in Pakistan.

METHODS

This longitudinal cohort study was conducted at De'Montmorency College of Dentistry Lahore from August 2023 to February 2024, involving 350 patients suffering from periodontal disease. The study was approved by the Institutional Review Board, De'Montmorency College of Dentistry Lahore (3115/DCD). The sample size for this study was calculated based on the prevalence of periodontal disease and the expected effect size of the association between the oral microbiome and periodontal disease progression. Using a prevalence rate of periodontal disease in Pakistan of approximately 40%, a confidence level of 95%, and a margin of error of 5%, the sample size was determined using the formula for sample size calculation for proportions:

$$n = \frac{Z^2 \cdot p \cdot (1-p)}{e^2}$$

Where n is the required sample size, Z is the Z-value (1.96 for a 95% confidence level), p is the estimated prevalence of the condition (0.40), and e is the margin of error (0.05). This resulted in a sample size of approximately 369.6, rounded to 350 patients to account for potential dropouts and non-response rates. Participants aged 18 years or older, diagnosed with varying degrees of periodontal disease including gingivitis and periodontitis, and willing to provide informed consent were included [12]. Those excluded were individuals who had recent periodontal treatment (within the last 3 months), received antibiotics, used antimicrobial rinse therapy, or had poor oral hygiene, as these factors could significantly affect the oral microbiome and periodontal health. Survey questionnaires were developed to collect comprehensive demographic information, medical history, and oral health habits. These self-administered questionnaires were pretested in a small group to ensure clarity, relevance, and reliability. Pretesting involved feedback on the questions' understandability and completion time, leading to necessary revisions before the actual data collection. Probing depth (PD) was measured in millimetres using a periodontal probe, indicating the distance from the gingival margin to the bottom of the periodontal pocket, with deeper depths suggesting more severe disease. Clinical attachment loss (CAL) was also measured in millimetres, indicating the distance from the cementoenamel junction to the bottom of the pocket, reflecting the extent of periodontal tissue destruction. Bleeding on probing was recorded as an inflammation indicator. Samples were collected from subgingival and supragingival regions of different quadrants of the mouth to ensure a comprehensive assessment of the oral microbiome. Plaque samples were placed in sterile Eppendorf tubes containing a suitable transport medium, thioglycolate broth, while saliva samples were collected in sterile polypropylene containers. All samples were labelled, kept on ice, and transported to the laboratory within two hours to maintain microbial viability. To determine the relative abundance of different bacteria, microbial DNA was extracted from the samples and subjected to Polymerase Chain Reaction (PCR) amplification of the 16S rRNA gene. The PCR products were then sequenced using high-throughput sequencing technologies. The resulting sequences were processed

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and aligned against reference databases to identify bacterial taxa. The relative abundance of each bacterial species was calculated by dividing the number of sequences for each taxon by the total number of sequences in the sample and expressed as a percentage. To ensure high reliability and accuracy, data collection protocols included standardized training for researchers and clinical staff, periodic calibration sessions, double data entry, and regular monitoring and audits. Data were analyzed using SPSS version 27.0, and multivariate regression analysis and machine learning algorithms were implemented to determine the significance of relationships between microbial profiles and periodontal disease parameters. This comprehensive approach aimed to elucidate the factors influencing periodontal disease progression in the study population.

RESULTS

The study involved 350 patients with periodontal disease, with a mean age of 45.01 ± 8.23 years. The probing depth, an important measure of periodontal health, averaged 4.2 ± 1.0 mm, while clinical attachment loss averaged 3.5 ± 0.8 mm. Bleeding on probing was observed in 30 ± 10% of participants (Table 1).

Table 1: Demographic Data, Medical History and Oral Health Habits of the Patients

Parameter	Value
Demographic Information	
Mean Age (years)	45.01 ± 8.23
Gender	55 %Male, 45% Female
Medical History	
History of Diabetes	30%
Cardiovascular Conditions	20%
Smoking	15%
Probing Depth (mm)	4.2 ± 1.0
Clinical Attachment Loss (mm)	3.5 ± 0.8
Bleeding on Probing (%)	30 ± 10
Oral Health Habits	
Brushing Frequency (Twice Daily)	60%
Regular Mouthwash Use	30%
Regular Dental Check-ups	50% Irregular, 50% Regular

The relative abundance of bacterial species in the oral microbiome showed Firmicutes as the predominant phylum, constituting 35% of the microbiome, followed by Bacteroidetes (25%), Proteobacteria (20%), Actinobacteria (15%), and others (5%). The major bacterial phyla in subgingival plaque samples were highlighted (Table 2).

Table 2: Major Phyla in Subgingival Plaque Samples

Phylum	Value
Firmicutes	35
Bacteroidetes	25
Proteobacteria	20
Actinobacteria	15
Others	5

Analysis of specific bacterial taxa revealed that Porphyromonas gingivalis and Tannerella forsythia was associated with greater probing depths and clinical attachment loss. The mean probing depths for P. gingivalis and T. forsythia were 5.0 ± 1.2 mm and 4.8 ± 1.0 mm, respectively, with corresponding clinical attachment losses of 4.5 ± 1.0 mm and 4.3 ± 0.9 mm. In contrast, Streptococcus and Lactobacillus exhibited lower mean probing depths and clinical attachment loss, with probing depths of 3.8 ± 0.9 mm and 3.5 ± 0.8 mm, and clinical attachment losses of 3.2 ± 0.7 mm and 2.8 ± 0.6 mm, respectively (Table 3).

Table 3: Association between Microbial Taxa and Periodontal Disease

Microbial Taxa	Probing Depth (mm)	Clinical Attachment Loss (mm)
Porphyromonas Gingivalis	5.0 ± 1.2	4.5 ± 1.0
Tannerella Forsythia	4.8 ± 1.0	4.3 ± 0.9
Streptococcus	3.8 ± 0.9	3.2 ± 0.7
Lactobacillus	3.5 ± 0.8	2.8 ± 0.6

The microbial community exhibited a Shannon Diversity index of 3.2, indicating a high level of species diversity. The Simpson Diversity index was 0.9, suggesting high species evenness and dominance within the community. The evenness value was 0.8, reflecting a balanced distribution of species abundance (Table 4).

Table 4: Diversity Indices for Oral Microbiome

Diversity Index	Value
Shannon Diversity	3.2
Simpson Diversity	0.9
Evenness	0.8
Richness	150

The multivariate regression analysis identified that increased relative abundances of P. gingivalis and T. forsythia were significantly associated with greater probing depths ($\beta = 0.45$, $p < 0.01$) and clinical attachment loss ($\beta = 0.40$, $p < 0.01$). Conversely, higher levels of Streptococcus and Lactobacillus were associated with lower probing depths ($\beta = -0.30$, $p < 0.05$) and clinical attachment loss ($\beta = -0.25$, $p < 0.05$). The model explained approximately 55% of the variance in periodontal health indicators ($R^2 = 0.55$) (Table 5).

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Table 5: Multivariate Regression Analysis Results

Microbial Taxon	Probing Depth (mm) β	Clinical Attachment Loss (mm) β	p-value
Porphyromonas Gingivalis	0.45	0.40	<0.01
Tannerella Forsythia	0.45	0.40	<0.01
Streptococcus	-0.30	-0.25	<0.05
Lactobacillus	-0.30	-0.25	<0.05

Machine learning algorithms, including Random Forest and Support Vector Machine (SVM), were employed to predict periodontal disease progression based on microbial profiles. The Random Forest model achieved an accuracy of 85% and an area under the curve (AUC) of 0.87, indicating strong predictive performance. The SVM model also demonstrated robust performance with an accuracy of 82% and an AUC of 0.84. These models identified P. gingivalis, T. forsythia, and Streptococcus as key predictors of disease severity, highlighting their importance in disease progression (Table 6).

Table 5: Multivariate Regression Analysis Results

Model	Accuracy (%)	Area Under the Curve (AUC)	Key Predictors
Random Forest	85	0.87	Porphyromonas gingivalis, Tannerella forsythia, Streptococcus
Support Vector Machine (SVM)	82	0.84	Porphyromonas gingivalis, Tannerella forsythia, Streptococcus

DISCUSSION

Current study was designed to explore the association between the oral microbiome and periodontal disease progression. Through the analysis of microbial profiles in patients with varying degrees of periodontal disease, significant associations between specific bacterial taxa and periodontal health indicators were identified. The findings of our study highlight the complexity of the oral microbiome and its role in periodontal disease progression. The microbial diversity of the oral cavity was measured using Shannon and Simpson diversity indices. The Shannon Diversity index of 3.2 and the Simpson Diversity index of 0.9 show a high level of species diversity and consistency, respectively, within the oral microbiome. This diversity is a key constituent in maintaining oral health, as a balanced microbial community can help prevent the overgrowth of pathogenic bacteria that contribute to periodontal disease [13]. Current findings are consistent with previous research highlighting the significance of microbial diversity in periodontal health. Relvas *et al.*, (2021) state that a diverse microbial community is associated with healthier periodontal status, while reduced diversity is linked to disease progression [14]. Porphyromonas gingivalis and Tannerella forsythia were found to be significantly associated with greater probing depths and clinical attachment loss. These findings are justified by previous studies that have recognized these species as key pathogens in periodontitis. P. gingivalis and T. forsythia are known for their virulence that contribute to tissue destruction and immune evasion [15, 16]. The multivariate regression analysis in our study supports these links, showing a significant positive correlation between the relative abundance of these taxa and periodontal disease severity ($\beta = 0.45$, $p < 0.01$ for both taxa). These results are similar with the results of Ardila *et al.*, (2020), who reported that elevated levels of P. gingivalis and T. forsythia are predictive of disease progression [17]. Conversely, Streptococcus and Lactobacillus were associated with lower probing depths and clinical attachment loss, indicating a potential protective role in periodontal health. These genera are often considered beneficial members of the oral microbiome due to their involvement in maintaining ecological balance and inhibiting the growth of pathogenic species [18]. The inverse relationship between the abundance of Streptococcus and Lactobacillus and periodontal disease indicators ($\beta = -0.30$, $p < 0.05$) suggests their importance in supporting periodontal health. Similar results were described by scholars, who found that these genera are related to improved periodontal outcomes [19]. The use of machine learning algorithms, such as Random Forest and Support Vector Machine (SVM), provided valuable insights into the predictive potential of microbial profiles for periodontal disease progression. Both models demonstrated strong predictive performance, with accuracies of 85% and 82% and AUCs of 0.87 and 0.84, respectively. The identification of P. gingivalis, T. forsythia, and Streptococcus as key predictors of disease severity underscores their relevance in clinical assessments of periodontal disease [20]. These results are similar to the published literature, which highlighted the utility of machine learning in predicting periodontal outcomes based on microbiome data. Our findings have significant suggestions for the diagnosis and management of periodontal disease. The identification of specific bacterial taxa linked with disease severity highlights the potential for targeted therapeutic involvements aimed at modulating the oral microbiome.

CONCLUSIONS

It was concluded that there is an association between the oral microbiome and periodontal disease progression. The findings highlight the significance of microbial dysbiosis in periodontal pathogenesis and highlight specific microbial taxa implicated in disease severity. These results contribute to our understanding of the complex interplay between microbial communities and periodontal health, paving the way for the development of novel diagnostic and therapeutic approaches to combat periodontal disease.

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Conceptualization: RJ, MR, MFI, IE, SR, BZ
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Formal analysis: CR, DC DM
Writing-review and editing: ME

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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Evaluation of Platelet-Rich Plasma (PRP) Versus Topical Minoxidil (5%) in Combination with Oral Finasteride for the Treatment of Androgenic Alopecia

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ABSTRACT

Androgenic alopecia was an inherited condition leading to gradual thinning and loss of hair on the crown and frontal scalp. **Objective:** To compare efficacy of PRP and topical minoxidil (5%) when used in addition to oral finasteride for treating androgenic alopecia. **Methods:** This quasi experimental study was conducted at Dermatology Department of Akhtar Saeed Medical and Dental College Rawalpindi from March 2023 to August 2023. Total 80 patients of both genders (40 in each group) aged 18 to 65 years diagnosed with androgenic alopecia. Participants were divided into two treatment groups: Group A received monthly PRP injections oral finasteride and 1 mg daily, while Group B applied topical minoxidil (5%) twice daily oral finasteride 1 mg daily. Efficacy was labeled as a statistically significant increase in mean hair density of at least 20 hair/cm^2 from pre-treatment to post-treatment using a trichometer. All participants had baseline demographic factors and clinical data. Data were analyzed using IBM SPSS 27.0. **Results:** The comparison of mean hair density between Group A (PRP and Finasteride) and Group B (Minoxidil and Finasteride) showed that Group A had a significantly higher mean hair density compared to Group B (101.6 ± 11.2 hair/cm^2 versus 87.0 ± 9.0 hair/cm^2, $p < 0.001$), indicating that the treatment in Group A was more effective. **Conclusions:** This study found that platelet-rich plasma (PRP) as an addition to oral finasteride improves hair regrowth, density, and patient satisfaction more than PRP combined with topical minoxidil.

INTRODUCTION

Androgenic alopecia, often known as male pattern baldness or female pattern hair loss, affects men and women worldwide [1]. It is characterized by gradual, non-scarring hair loss in men's frontal and vertex regions and diffuse central scalp thinning in women [2]. Globally prevalence of androgenic alopecia is 50% in men and 30% in women [3]. The pathogenesis of androgenic alopecia is multifactorial, involving both genetic and hormonal factors. Genetic predisposition plays a key role, with inheritance patterns suggesting polygenic and multifactorial inheritance [4]. Hormonal factors, particularly androgens such as Dihydrotestosterone (DHT), are also implicated in the development of androgenic alopecia. DHT, a potent derivative of testosterone, binds to androgen receptors in susceptible hair follicles, leading to miniaturization of follicles, shortened anagen (growth) phase, and progressive hair thinning [5, 6]. Various risk factors have been associated with the development and progression of androgenic alopecia. Advancing age is a significant risk factor, with prevalence increasing with age

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in both men and women. Additionally, a positive family history of androgenic alopecia, particularly in first-degree relatives, increases the likelihood of developing the condition [7]. For male pattern baldness, the Norwood-Hamilton scale is used to grade hair loss amount and progression, while the Ludwig scale is employed to evaluate female pattern hair loss. Hair pull tests, trichoscopy, and scalp biopsies may be needed to confirm the diagnosis and rule out alternative hair loss reasons [8]. Treatment modalities include both pharmacological and non-pharmacological approaches. In its treatment landscape, combining therapies to enhance efficacy is an emerging approach. PRP therapy harnesses the regenerative properties of platelets to stimulate hair growth, minoxidil used topically dilates blood vessels, which in turn improves blood flow to the scalp's hair follicles. The most common therapy for androgenic alopecia is the 5-alpha-reductase inhibitor finasteride, taken orally. This medicine prevents testosterone from being converted to dihydrotestosterone, or DHT [9, 10]. Despite the availability of various treatment options, managing androgenic alopecia can be challenging, and outcomes may vary among individuals. While the condition is primarily cosmetic, its impact on psychological well-being should not be underestimated. This study addresses the need for evidence-based guidance on optimal treatment strategies for androgenic alopecia. Additionally, by evaluating these therapies in the context of Pakistan, where specific research on combination treatments for androgenic alopecia is limited, this study fills a crucial gap in the literature and provides valuable data for clinical practice in the region.

To evaluate the effectiveness of Platelet-Rich Plasma(PRP) compared to topical minoxidil (5%) when both are used in combination with oral finasteride for the treatment of androgenic alopecia.

METHODS

This quasi-experimental study was conducted at Dermatology Department of Akhtar Saeed Medical and Dental College Rawalpindi from March 2023 to August 2023. The study protocol received clearance from the Institutional Review Board (Ref No: ERC/120/AMDC). Written consent was taken from the patients. The sample size of 80 (40 in each group) was estimated using the WHO calculator (www.openepi.com), with 90% power of test and a two-sided alpha of 0.05. This estimation was based on a treatment efficacy of 77% in the PRP group and 40% in the topical Minoxidil group [17]. Male and female patients aged 18 to 65 years diagnosed with androgenic alopecia (Norwood-Hamilton scale grades II-V in men and Ludwig scale grades I-III in women) and receiving oral finasteride therapy for a minimum of 6 months were eligible for inclusion. Patients with a history of hypersensitivity or adverse reactions to PRP or topical minoxidil, pregnant or lactating women, individuals with concomitant medical conditions affecting hair growth, and those undergoing concurrent treatments for hair loss were excluded from the study. Participants were distributed into two treatment groups by lottery method: Group A received monthly PRP injections, while Group B applied topical minoxidil (5%) twice daily. Both groups were administered oral finasteride at a daily dose of 1 mg. Both treatments were administered in conjunction with oral finasteride therapy for duration of 6 months. Platelet Rich Plasma (PRP) was prepared using a standard protocol. Whole blood was collected from each participant into tubes containing an anticoagulant, followed by centrifugation at 1500 rpm for 10 minutes to separate the PRP. The resulting PRP was then activated using calcium chloride before injection. PRP injections were administered using a sterile technique, with 1 mL injected monthly into the scalp using a mesotherapy technique. Patients were given commercially available 5% topical minoxidil solution to apply 1 ml twice daily to the affected scalp areas. Patients were instructed to spread the solution evenly and allow it to dry completely before covering the scalp. Follow-up visits were scheduled on a monthly basis to administer PRP. Additionally, a comprehensive follow-up assessment was conducted six months after initiating treatment during which outcomes including changes in hair density and thickness were assessed using standardized phototrichograms. Efficacy was defined as the improvement in mean hair density, measured in hairs per square centimeter (hair/cm^2), from pre-treatment to post-treatment using a trichometer. Treatments were labeled as effective if there was an increase in mean hair density of at least 20 hair/cm^2. Patient satisfaction was evaluated using a self-assessment hair growth questionnaire, categorizing responses as worsening from baseline, not improving from baseline, or improving from baseline. The primary outcome measure was the change in hair density, assessed using standardized phototrichograms at baseline and at six months. Secondary outcome measures included changes in hair thickness and patient satisfaction with treatment. Treatment efficacy assessments were conducted by trained evaluators blinded to treatment assignment. IBM SPSS, version 27.0 was used to analysed the data. Chi-square test was applied to compare the categorical variables, which were given as percentages and frequencies. Means and Standard Deviations (SD) were used to compare continuous variables, and the Independent sample t-test was applied, p-value <0.05 was considered to be statistically significant.

RESULTS

The demographic details of patients in both groups were summarized in table 1. In both groups, males constituted the majority, comprising 70.0% in Group A and 77.5% in

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Group B, while females accounted for 30.0% and 22.5%, respectively. The mean age of patients in Group A was 29.30 ± 7.13 years and 31.25 ± 5.41 years in Group B, showing no significant difference (p = 0.172). Similarly, the duration of baldness showed comparable means between Group A (8.40 ± 3.17) and Group B (7.80 ± 3.11), with no statistically significant distinction (p = 0.396). 26 (65%) patients in Group A and 27 (67.5%) patients (65.7%) in Group B had family history of baldness. Among males, according to Norwood–Hamilton grades of baldness, Grade II (42.5% versus 40%) was most common, followed by Grade IV (35% versus 37.5%) alopecia with no significant difference. Similarly, among females, based on Ludwig scale, Grade I (72.5% versus 65%) followed by Grade II (27.5% versus 35%) with statistically insignificant difference, p=0.469. Group A had 17 smokers (42.5%) and Group B 15 (37.5%).

Table 1: Demographics of Patients of both Groups

Variables	Group A N (%) / Mean ± SD	Group B N (%) / Mean ± SD	p-Value
Gender			
Female	12 (30.0%)	9 (22.5%)	0.446 [a]
Male	28 (70.0%)	31 (77.5%)	
Age (Years)	29.30 ± 7.13	31.25 ± 5.4	0.172 [c]
Duration of Baldness (Months)	8.40 ± 3.17	17.80 ± 3.11	0.396 [c]
Family History of Baldness			
Yes	26 (65.0%)	27 (67.5%)	0.813 [a]
Norwood–Hamilton Grades of Baldness (Male)			
Grade II	17 (42.5%)	16 (40.0%)	1.000 [b]
Grade III	7 (17.5%)	6 (15.0%)	
Grade IV	14 (35.0%)	15 (37.5%)	
Grade V	2 (5.0%)	3 (7.5%)	
Ludwig Grades of Baldness (Female)			
Grade I	29 (72.5%)	26 (65%)	0.469 [a]
Grade II	11 (27.5%)	14 (35%)	
Smokers			
Yes	17 (42.5%)	15 (37.5%)	0.648 [a]
No	23 (57.5%)	25 (62.5%)	

a Chi-square test; b Fisher exact test; c Independent sample t test.

The pre-treatment means of hair shaft diameters for males and females were similar (p values = 0.135). While post-treatment means of hair shift diameters in both the groups increased which were statistically significant. For males these were (77.0 ± 2.5 µm versus 72.5 ± 3.2 µm) with p values < 0.001; while for females these were (73.0 ± 2.5 µm versus 69.5 ± 3.0) with p values < 0.001 given in table 2.

Table 1: Demographics of Patients of both Groups

Diameter of Hair Shaft (µm)	Group A Mean ± SD	Group B Mean ± SD	p-Value*
Male			
Pre-Treatment	69.0 ± 4.2	67.5 ± 3.8	0.135
Post-Treatment	77.0 ± 2.5	72.5 ± 3.2	< 0.001
Female			
Pre-Treatment	63.5 ± 3.8	62.0 ± 3.2	0.240
Post-Treatment	73.0 ± 2.5	69.5 ± 3.0	< 0.001

*Independent Sample t-Test

Table 3 showed that Group A had more hair post-treatment than Group B. Group A as well as Group B hair pull tests showed significant differences. Group A had a much higher rate of negative hair pull tests than Group B.

Table 3: Mean Hair Density (Hair/cm2)

Hair Density (Hair/cm^2)	Group A Mean ± SD	Group B Mean ± SD	p-Value [a]
Pre-Treatment	73.6 ± 8.2	76.9 ± 9.2	0.091
Post-Treatment	101.6 ± 11.28	7.0 ± 9.0	< 0.001

a Independent Sample t-Test

In table 4, Group A exhibited a significant increase in negative hair pull test results post-treatment (77.5%) compared to pre-treatment (37.5%), and also significantly higher compared to Group B (40.0%) post-treatment (p < 0.001). Group B showed a smaller increase in negative results from pre-treatment (35.0%) to post-treatment (40.0%) with a p-value of 0.035.

Table 4: Hair Pull Text (Negative Results)

Patient Satisfaction Score	Group A N (%)	Group B N (%)	p-Value [a]
Pre-Treatment	73.6 ± 8.2	76.9 ± 9.2	0.091
Post-Treatment	101.6 ± 11.28	7.0 ± 9.0	< 0.001

*Chi-Square Test

Pre- and post-treatment photographs in figure 1 illustrated enhanced hair shaft diameter and overall hair quality improvement with Platelet-Rich Plasma (PRP) therapy.

Figure 1: Pre and Post Treatment Photographic Assessment Showing Better Results with PRP

Table 5 showed a substantial difference in patient satisfaction scores between Groups A (6.9 ± 1.15) versus Group B (5.1 ± 1.62), p < 0.001.

Table 5: Comparison of Patient Satisfaction Regarding Growth of Hair between Group A and Group B

Patient Satisfaction Score	Group A Mean ± SD	Group B Mean ± SD	p-Value [a]
Pre-Treatment	6.9 ± 1.15	5.1 ± 1.62	< 0.001 [a]

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DISCUSSION

Among available treatments, topical minoxidil remains widely utilized, while PRP therapy, particularly when combined with Finasteride, was an emerging approach showing promising outcomes. Recent investigations have explored the efficacy of both agents, either individually or in combination therapy, with encouraging results [11, 12]. In current study, all participants fell within the age range of 18 to 60 years. The average age recorded was 29.30 ± 7.13 years in Group A and 31.25 ± 5.41 years in Group B. Shah KB *et al.*, also reported mean age similar to current study which was 31.12 versus 30.04 years [12]. In another study carried out by Verma K *et al.*, the mean age was 25.7 ± 3.8 years and 25.07 ± 4.5 years in Group A and Group B respectively which contrast with current study [13]. There was a slightly higher proportion of male with 70% in group A and 77.5% in group B patients compared to female 30% and 22.5% in both groups in current study. Afzal G *et al.*, showed slightly lower proportion of males (65.7%) in Group A, while proportion of males in Group B (77%) was comparable with current study [14]. In current study, the hair pull test was negative in 77.5% patients of Group A and 40% patients of Group B. Similarly, Afzal G *et al.*, found 77% negative hair pull tests in Group A versus 40% in Group B [14]. The average hair loss time in this study was 8.40 ± 3.17 months in Group A versus 7.80 ± 3.11 months in Group B. This observation aligns with Afzal G *et al.*, who found shorter hair loss duration in both groups (7 ± 5 versus 6.9 ± 5.8 months) [14]. The average hair loss time in Hajheydari Z *et al.*, was 23.10 months, unlike this study [15]. Among males, according to Norwood–Hamilton grades of baldness, Grade II (42.5% versus 40%) and Grade IV (35% versus 37.5%) alopecia was more common, followed by Grade III (17.5% versus 15%) and Grade V (5% versus 7.5%) in current study. Grade II alopecia affected 27.27% of patients, Grade I alopecia 22.12%, Grade III 21.78 %, Grade IV 10.8% and Grade V 6.6% of patients in the study by Krupa Shankar DK *et al* [16]. Among females, based on Ludwig scale, Grade I (72.5% versus 65%) followed by Grade II (27.5.5 versus 35%) in current study. The results were in line with what Afzal G *et al.*, found: in Group A, 75% of patients had Grade I alopecia and 25% had Grade II alopecia; in Group B, 62.5% had Grade I alopecia and 37.5% had Grade II alopecia [14]. For both males and females, Group A had a significantly larger hair shaft diameter post-treatment compared to Group B (males: 77.0 ± 2.5 µm versus 72.5 ± 3.2 µm, $p < 0.001$; females: 73.0 ± 2.5 µm versus 69.5 ± 3.0 µm, $p < 0.001$). Study conducted by Ruthvik S *et al.*, showed high proportion of increase in hair shaft diameter in Group A (15.3%) as well as Group B (10%) compared to current study [17]. Elena EP *et al.*, demonstrated that mean diameter of hair increased by 11.6% (39.8 to 44.4 µm) and by 1.8% (39.3 to 40 µm) in Group A and Group B respectively, which contrast with current study. In current study, the mean hair density increased by 38% (73.6 to 101.6 /cm^2) in Group A and by 13.1% (76.9 to 87 /cm2) in Group B [18]. Wu S *et al.*, showed less increase in hair density in Group A (26.5%) and Group B (8.9%) compared to current study [19]. The average satisfaction score for patients in Group A was 6.9 ± 1.15, whereas for patients in Group B it was 5.1 ± 1.62, according to study. In a study conducted by Verma K et al., the average satisfaction score was 6.56 ± 1.09 in Group A and 4.85 ± 1.46 in Group B. y. In contrast to this findings, Shah R *et al.*, found a significantly larger proportion of subjects in Group A who tested negative for hair pull (91.7% versus 69.4%) [13, 20]. Current study faced limitations due to its unblinded design, limited sample size, absence of a placebo control, and a brief follow-up duration. Moreover, factors like hair washing and brushing frequency could potentially impact the outcomes of the hair pull test. Consequently, future research endeavors should prioritize larger sample sizes, extended follow-up periods, and inclusion of control groups to address these limitations effectively.

CONCLUSIONS

Current study found that Platelet-Rich Plasma (PRP) as an addition to oral finasteride improves hair regrowth, density, and patient satisfaction more than topical minoxidil.

Authors Contribution

Conceptualization: SS
Methodology: ME, SS, SA, AA
Formal analysis: AH, MR
Writing, review and editing: SA, AA, ME

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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Comparison of Postoperative Analgesic Effectiveness of Bupivacaine and Bupivacaine Plus Dexmedetomidine Wound Infiltration in Abdominal Surgeries under General Anesthesia

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ABSTRACT

Abdominal surgeries were major surgical procedures that were performed at any teaching hospital. Pain control was a major concern during intra-operative as well as post-operative periods in these patients. **Objective:** To compare post-operative analgesic effectiveness of bupivacaine and bupivacaine plus dexmedetomidine wound infiltration in abdominal surgeries under General Anesthesia. **Methods:** This randomized controlled trial was conducted at the Department of Anesthesia, Sahiwal Teaching Hospital Sahiwal from 1st April, 2024 till 31st May 2024. Sixty-four patients underwent a pre-operative assessment on the day before surgery. Both Groups received wound infiltration with studied drugs at the end of surgery. After surgery, patients were assessed for pain using a Visual Analog Scale (VAS) and data was collected and analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. **Results:** The mean post-operative analgesia duration of the patients on bupivacaine was 11.78 ± 1.64 but the mean post-operative analgesia duration of the patient on bupivacaine plus dexmedetomidine was 19.19 ± 2.49. (2-tailed significance 0.001). The mean opioid consumption in mg of the patients in bupivacaine was 20.69 ± 4.31 but the mean opioid consumption in mg of the patient in bupivacaine plus dexmedetomidine was 10.88 ± 4.53. (2-tailed significance 0.001). In bupivacaine, patients with bradycardia were 0% and patients without bradycardia were 100% but in bupivacaine plus dexmedetomidine, patients with bradycardia were 15.6% and patients without bradycardia were 84.4%. **Conclusions:** There was a difference in the analgesic effectiveness of dexmedetomidine when added to bupivacaine in wound infiltration in abdominal surgeries.

INTRODUCTION

Abdominal surgeries, those are some complicated procedures that happen everywhere, especially in teaching hospitals. But Pain is a big deal during and after these surgeries [1]. Pain can make a huge difference in how patients bounce back. Good pain management can speed up recovery, shorten hospital stays, and take some of the pressure off healthcare facilities [1]. It can mess with a person's quality of life and even up the chances of complications or, heaven forbid, death. And that's not a risk we want to take. There are the usual suspects like intravenous drugs like opioids and NSAIDs (ever heard of Ketorolac or Ketamine?). But we've also got some more advanced techniques. There's nebulization, multimodal analgesia, patient-controlled analgesia (which is pretty neat—you can think of it like having a remote control for your pain relief), epidurals, caudals, and peripheral nerve blocks [2]. One simple yet effective method is wound infiltration [2]. It's like a targeted attack on pain right where

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it hurts, using local anesthetics. There's a chance of things like toxicity or allergic reactions, especially with certain types of anesthetics. But sometimes you've got to risk it to get that sweet relief [3]. And speaking of relief, there's been some interesting research in this area. For example, adding ketamine to bupivacaine seems to delay when patients first start feeling pain after something as major as an abdominal hysterectomy. And mixing up ropivacaine and dexmedetomidine seems to work wonders for folks getting lumbar discectomies [4]. Plus, using dexmedetomidine in various ways during surgery or in the wound seems to mean less need for morphine afterward, which is great because opioids come with a laundry list of side effects. Some studies have even gone meta, combining data from lots of other studies, and found that using stuff like dexmedetomidine in wound infiltration during abdominal surgery can mean less reliance on opioids overall [5]. Mixing up anesthetics with others can not only keep pain at bay but also make patients feel a whole lot more relaxed during and after surgery. Using a mix of bupivacaine and dexmedetomidine seems to be a game-changer when it comes to keeping pain in check after surgery. Patients in these studies needed less pain relief overall compared to those who just got bupivacaine alone [6, 7].

So this study was intended to check if there is better pain relief from bupivacaine and dexamethasone then dexamethasone alone.

METHODS

This Randomized controlled trial was conducted at the Department of Anesthesia, Sahiwal Medical College/Sahiwal Teaching Hospital, Sahiwal after approval of the study. Sample size will be calculated using an open epi WHO calculator comparing two means, using Confidence interval = 95 %, and power of study 80%. [3].

$$\text{Sample size} = \frac{2SD^2 (Z_{\alpha/2} + Z_{\beta})^2}{d^2}$$

SD (Standard Deviation) = 0.69 from previous study [3], Za/2 = Z0.05/2 = Z0.025 = 1.96 (From Z table) at type 1 error of 5%, Zb = Z0.20 = 0.842 (From Z table) at 80% power, d = effect size = difference between mean values = 0.479, n= 32 (in each group). A total of 64 patients were selected and divided into two groups, each group consisting of 32 patients. Non-probability consecutive sampling technique was used. Inclusion criteria was age limit: 18-60 years, gender of patient i.e., male or female, Patients listed for abdominal surgeries, American Society of Anesthesiologists (ASA) status of I or II. While the Exclusion Criteria was patients with a history of drug allergy, patients who have undergone any analgesia in the past 24 hr, patients with liver disease, kidney disease, cardiac disease, sickle cell anemia, severe preeclampsia, or CNS disorder on history, clinical and laboratory assessment American Society of Anesthesiologists (ASA) status III or IV, patients with morbid obesity, raynaud's disease, patients on adrenoceptor agonists, antagonists, or narcotics before the operation. The duration and type of abdominal surgery, patient comorbidities were also excluded. The hospital's ethical committee gave their approval via Letter No: 103/IRB/SLMC/SWL once they had obtained informed written consent from each patient, making sure they met the necessary inclusion criteria and provided their demographic information. Patients were then divided randomly into two groups. Prior to their surgeries, all patients underwent a pre-operative assessment. Two hours before surgery, they were given a pre-medication of oral midazolam at a dosage of 0.05 mg/kg. Using a computer-generated random number table, patients were assigned to either Group I or Group II. Group I received 20 mL of 0.25% bupivacaine for wound infiltration at the conclusion of surgery, while Group II received the same amount of bupivacaine along with 1 µg/kg of Dexmedetomidine. The individual responsible for preparing the study drugs was not involved in collecting the data. Anesthesia induction was carried out using intravenous propofol (2–2.5 mg/kg) and nalbuphine (0.1mg/kg). Tracheal intubation was facilitated by administering succinylcholine intravenously at a dosage of 1.5 mg/kg. Throughout the surgery, anesthesia was maintained with isoflurane (0.6 mac), 60% nitrous oxide, 40% oxygen, and atracurium (0.5mg/kg bolus followed by a maintenance dose of 0.15mg/kg every 30 minutes). Intraoperative monitoring included electrocardiogram leads II and V5, non-invasive blood pressure readings taken at 5-minute intervals, oxygen saturation levels, end-tidal carbon dioxide measurements, and nasopharyngeal temperature. Patients were ventilated using intermittent positive pressure ventilation to ensure normocapnia. Heart Rate (HR) and Mean Arterial Pressure (MAP) were kept within 20% of their pre-operative values. If hypotension (MAP <20% of baseline or <65 mmHg) occurred, patients were treated with a saline infusion and, if necessary, phenylephrine injections intravenously. Bradycardia (HR <40 beats/min) was addressed with an intravenous bolus of atropine (40 µg/kg) during both the intraoperative and postoperative periods. Prior to completing the surgery, all patients received intravenous paracetamol (15 mg/kg) and ondansetron (0.1 mg/kg). Residual neuromuscular blockage was reversed with intravenous neostigmine (0.05mg/kg) and glycopyrrolate at the end of the surgery. Tracheal extubation was performed based on standard extubation criteria. Postoperative pain management consisted of intravenous paracetamol (15 mg/kg) every 8 hours and ondansetron (0.1 mg/kg) every 8 hours for nausea and vomiting. Patients were then transferred to the Post-Anesthesia Care Unit (PACU), where they were assessed by anesthesia residents and trained nursing staff who were unaware of the drugs administered during the study. Pain levels were evaluated using the Visual Analog Scale (VAS)

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every 30 minutes for the first 4 hours and then every 2 hours for the next 24 hours. The time from the local wound infiltration to the first request for analgesia was recorded. Ketorolac (30 mg) was administered as rescue analgesia if the VAS score was 4 or higher. Postoperative hemodynamics were monitored every 15 minutes for the first 2 hours and then hourly for the next 24 hours. Breakthrough pain was managed with intravenous nalbuphine (0.1mg/kg) as needed. The total opioid consumption over 24 hours was noted for both groups in terms of milligrams. The occurrence of postoperative complications related to the studied drugs, such as bradycardia and hypotension, was recorded for 24 hours postoperatively. Data were collected using a structured questionnaire. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 26.0. Quantitative variable like (height, weight, and age) was presented by using mean ± SD. A comparison of quantitative variables (height, weight, and age) between groups was done using an independent sample t-test. Chi-square test was used to compare qualitative variables with a p-value ≤ 0.05 as significant.

RESULTS

The mean age of the patients in bupivacaine was 43.13 ± 12.39 but the mean age of the patient in bupivacaine plus dexmedetomidine was 41.69 ± 10.08. The mean weight of the patients in bupivacaine was 74.31 ± 6.42 but the mean weight of the patient in bupivacaine plus dexmedetomidine was 72.41 ± 5.95. The mean BMI of the patients in bupivacaine was 25.12 ± 2.12 but the mean BMI of the patient in bupivacaine plus dexmedetomidine was 24.86 ± 1.94. The mean post-operative analgesia duration of the patients in bupivacaine was 11.78 ± 1.64 but the mean post-operative analgesia duration of the patient in bupivacaine plus dexmedetomidine was 19.19 ± 2.49. The mean opioid consumption in mg of the patients in bupivacaine was 20.69 ± 4.31 but the mean opioid consumption in mg of the patient in bupivacaine plus dexmedetomidine was 10.88 ± 4.53. In bupivacaine, males were 59.4% and females were 40.6% but in bupivacaine plus dexmedetomidine, males were 62.5% and females were 37.5%. In bupivacaine, patients with bradycardia were 0% and patients without bradycardia were 100% but in bupivacaine plus dexmedetomidine, patients with bradycardia were 15.6% and patients without bradycardia were 84.4%. In bupivacaine, patients with hypotension were 6.3% and patients without hypotension were 93.7% but in bupivacaine plus dexmedetomidine, patients with hypotension were 25% and patients without hypotension were 75%. In bupivacaine, patients with nausea were 9.4% and patients without nausea were 90.6% but in bupivacaine plus dexmedetomidine, patients with nausea were 6.3% and patients without nausea were 93.7%. In bupivacaine, patients with vomiting were 6.3% and patients without vomiting were 93, 7% but in bupivacaine plus dexmedetomidine, patients with vomiting were 3.1% and patients without vomiting were 96.9%. The table shows that adding Dexmedetomidine to Bupivacaine in abdominal surgeries significantly extends post-operative analgesia duration and reduces opioid consumption, with similar patient demographics between the two groups (Table 1).

Table 1: Patient Demographics and Postoperative Outcomes Comparison

Variables	Bupivacaine Alone (Mean ± SD)	Bupivacaine Plus Dexmedetomidine (Mean ± SD)
Age	43.13 ± 12.39	41.69 ± 10.08
Weight	74.31 ± 6.42	72.41 ± 5.95
BMI	25.12 ± 2.12	24.86 ± 1.94
Post-Operative Analgesia Duration in Hour	11.78 ± 1.64	19.19 ± 2.49
Opioid Consumption in mg	20.69 ± 4.31	10.88 ± 4.53

The table indicated that Group 2 (Bupivacaine + Dexmedetomidine) experienced significantly longer post-operative analgesia and reduced opioid consumption compared to Group 1 (Bupivacaine alone) (Table 2).

Table 2: Postoperative Analgesia and Opioid Use

Variables	Groups of Patients	(Mean ± SD)
Duration of Post-Operative Analgesia	Group 1 Bupicain	11.78 ± 1.64
	Group 2 Bupicain+ Dexmedetomidine	19.18 ± 2.49
Opioid Consumption / 24 hr	Group 1 Bupicain	20.69 ± 4.31
	Group 2 Bupicain+ Dexmedetomidine	10.88 ± 4.53

The table showed a significant increase in the incidence of bradycardia in Group 2 (Bupivacaine + Dexmedetomidine) compared to Group 1 (Bupivacaine alone), with a p-value of 0.026 (Table 3).

Table 3: Bradycardia Group Comparison

Variables			Groups of Patients		p-Value
			Group 1 Bupicain	Group 2 Bupicain + Dexmedetomidine	
Bradycardia	Yes	Count	0	5	0.026*
	No	Count	32	27	

*Calculated by Independent Sample t test

DISCUSSION

This study dove into the realm of postoperative pain, exploring how dexmedetomidine, when added to bupivacaine in wound infiltration after abdominal surgeries, might impact recovery. This α2-adrenoceptor agonist was known to work its magic in peripheral nerve blocks, though the exact mechanisms were still a bit of a mystery [8]. Taking potential central analgesia, vasoconstriction, and anti-inflammatory effects here. Those patients who received the dexmedetomidine and bupivacaine combo seemed to have some extended

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postoperative relief. Taking an average of 19.18 hours of analgesia, compared to just 11.78 hours with bupivacaine alone. That's a pretty substantial difference, statistically speaking ($p < 0.05$). And it gets even better. Not only did the dexmedetomidine group experience longer pain relief, but they also needed less opioid pain medication 20.69 mg compared to 10.88 mg for those who only got bupivacaine ($p < 0.05$). More patients in the dexmedetomidine group experienced bradycardia and hypotension. While that might sound alarming, it's not entirely unexpected given the nature of the medication. Thankfully, there was no significant difference in nausea and vomiting between the two groups ($p > 0.05$), so at least there's that. These findings align nicely with a meta-analysis it was stumbled upon [9]. It turns out that mixing dexmedetomidine with local anesthetic in wound infiltration during abdominal surgery doesn't just reduce the need for postoperative pain relief—it also prolongs the duration of analgesia. Another randomized double-blind study with 60 patients showed a significant difference in morphine consumption between those who received ropivacaine and those who got bupivacaine ($p = 0.03$) [10]. The ropivacaine group needed significantly less morphine 185 mg compared to 220 mg. But it's not just about the medications use it's also about how it was administered them. Intravenous dexmedetomidine, whether as a bolus or infusion, has been shown to prolong sensory and motor blockade in randomized clinical trials [11]. Speaking of recovery, a randomized clinical trial on laparoscopic cholecystectomy patients revealed some interesting results [12]. Those who received bupivacaine during surgery experienced less pain at their shoulder and port sites, plus they had fewer bouts of vomiting in the first six hours post-op. Not to mention, they needed less opioid pain medication overall. Looks like bupivacaine might be a real MVP when it comes to postoperative pain relief [13, 14]. And let's not forget about the trocar sites. In other studies, on laparoscopic cholecystectomy patients, bupivacaine infiltration at these sites proved to be an effective method for relieving postoperative pain [15-17]. Whether it was combined with gallbladder fossa infiltration or not, bupivacaine got the job done [18]. Now, of course, this study wasn't without its limitations. Hence it was acknowledged that the need for a larger sample size to fully understand the side effect profile of dexmedetomidine. Plus, it was not for sure whether the cardiovascular effects associated with dexmedetomidine were dose-dependent or not [19, 20]. But Rome wasn't built in a day, and groundbreaking medical research isn't either. Contributing to the ever-growing body of knowledge aimed at making patients' lives better.

CONCLUSIONS

It was concluded that dexmedetomidine when added to bupivacaine in wound infiltration in abdominal surgeries significantly increases the post-op duration of analgesia and has an opioid-sparing effect.

Authors Contribution

Conceptualization: NS
Methodology: HT
Formal analysis: MSA
Writing, review and editing: MS, MUM, NS, SR

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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Association of Preterm Delivery with Urinary Tract Infection and Preventive Role of Ceftriaxone

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ABSTRACT

Urinary tract infections (UTIs) are the leading cause of maternal morbidity and poor birth outcomes. Pregnancy changes increase UTI risk. A larger bladder, less tone, and a shift in vaginal flora are changes. Eradicating pathogens in the urogenital tract can lower the risk of infection-related preterm labor by stopping the progression of asymptomatic bacteriuria into a more serious infection. **Objective:** To determine the association of preterm labor with urinary tract infection and the preventive role of ceftriaxone. **Methods:** A case-control study was conducted at the Department of Obstetrics and Gynecology, Khyber Teaching Hospital, Peshawar, from 14 December 2021 to 10 June 2022. 130 pregnant women who met the selection criteria were recruited from the hospital's post-delivery wards. The participants were then separated into a case group and a control group. Protocols for treating UTIs in female were followed. Ceftriaxone was administered to the group of participants who were UTI-positive. **Results:** The mean age of female in the case group was 28.88 ± 7.18 and in the controls group was 28.97 ± 6.85 years. The mean gestational age at delivery in cases was 34.28 ± 1.34 weeks and in controls 39.4 ± 1.11 weeks. There was a significant association between preterm labor and urinary tract infection (p= <0.05). Administration of ceftriaxone reduced the risk of preterm labor (p=0.001). **Conclusions:** It was concluded that there is a significant correlation between UTIs and premature labor and ceftriaxone plays an important role in reducing preterm delivery of UTI patients.

INTRODUCTION

Preterm labor is the onset of labor after 28 weeks and before 37 weeks of gestation as observed by regular uterine contractions leading to progressive cervical changes [1]. Some identified factors include anatomic abnormalities of the uterus and cervix, premature rupture of the membranes, placenta previa or abruption, trauma, excessive uterine enlargement, as in multiple gestation and hydramnios, and infection [2]. UTI is one of the many etiological factors of preterm labor. In pregnant women, UTIs are classified either as asymptomatic bacteriuria, or symptomatic infections such as acute cystitis and acute pyelonephritis [3, 4]. UTI during pregnancy has a significant impact on pregnancy outcomes, mainly premature labor and low birth weight [5, 6]. The unwanted sufferings of pregnant mothers and their offspring could easily be prevented by early screening and prompt treatment of UTI in pregnancy [7]. Multiple studies reported that those women who had UTIs during their

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pregnancy were approximately 2 times more likely to have preterm labor [8, 9]. It has been reported in studies that the frequency of UTI was significantly higher in female with preterm labor [5, 6, 10]. Another study showed that the frequency of UTI was 10.4% in female with preterm labor and 5.2% in female delivered at term [11]. One more study showed that the frequency of UTI was 5% in female with preterm labor while 2.5% in female delivered at term [12]. The existing literature reveals a discrepancy regarding the association between urinary tract infections (UTIs) and preterm labor, with limited research addressing this relationship. Furthermore, no local studies have been identified that could clarify whether UTIs are a risk factor for preterm labor and delivery. To provide local evidence on this association, which could inform future recommendations for more effective screening methods for UTIs in pregnant women. Early detection and treatment could prevent preterm labor, safeguarding the health of both mothers and their fetuses in our local context. By generating local evidence, this study seeks to enhance clinical practice. This study aimed to assess the association between preterm labor and UTIs and to evaluate the preventive role of ceftriaxone.

METHODS

A case-control study was conducted in the Department of Obstetrics and Gynecology at Khyber Teaching Hospital, Peshawar, from December 14, 2021, to June 10, 2022. After getting approval from the Hospital Ethical Committee with Reference No. CPSP/REU/OBG-2020-020-10263. 130 pregnant female who fulfilled selection criteria from post-delivery wards were recruited. A total sample size of 130 female was calculated, with 65 female in each group. The sample size was determined to achieve a study power of 80% and a significance level of 5%. The percentage of urinary tract infection (UTI) was noted as 13.46% in the cases and 1.92% in the controls. The sampling technique employed was non-probability, consecutive sampling. The inclusion criteria involved female aged 18-40 years, parity <5, delivered within the last 24 hours, and exclusion criteria involved female with multiple fetuses, congenital malformation, fetal demise, antepartum hemorrhage, gestational or chronic hypertension, diabetes, uterine fibroids, anemia, abortion in a previous pregnancy, history of preterm delivery in previous pregnancy and those with incomplete antenatal record. Cases were those female who underwent preterm delivery, which was defined as active labor (>3 contractions in 10 minutes with Bishop score >4 and cervical dilation <4cm), before completion of 37 weeks of gestation as per the last menstrual period date. Controls were those who delivered at term (>37 weeks of gestation as per last menstrual period) After taking informed consent their demographic profile like; name, age, gestational age, parity, BMI, gestational age at delivery, and mode of delivery and treatment with ceftriaxone will be noted. Then they were divided into two groups i.e. cases and controls. Then female were asked and the medical record was assessed for the presence or absence of UTI during pregnancy, which was labeled if there was the presence of a history of persistent UTI during pregnancy i.e. presence of fever (temperature >99oF), and pathogen detected in a urine sample on urine culture i.e. growth of more than 105 colony-forming units per milliliter of the bacterium as per antenatal record and history. Female with UTI were managed as per standard protocol. All this information was recorded on proforma. SPSS version 22.0 was used to enter and analyze the collected data. Mean ± Standard Deviation was computed for age, gestational age, and BMI. Frequency and percentage were computed for parity, mode of delivery, and UTI. The odds ratio was calculated to measure the association of preterm labor with UTI. OR >1 was taken as significant. Data were stratified for age, gestational age, parity, BMI, and mode of delivery. Post-stratification, the odds ratio was calculated to measure the association of preterm labor with UTI for each stratum. OR >1 was taken as significant.

RESULTS

The basic demographic characteristics of the female enrolled in the study, with 65 cases and 65 controls showed that the average age of participants in both groups was quite similar, with cases having a mean age of 28.88 ± 7.18 years and controls having a mean age of 28.97 ± 6.85 years. Gestational age at the time of study enrollment showed a notable difference, with cases having a mean gestational age of 34.28 ± 1.34 weeks compared to 39.40 ± 1.11 weeks in controls, indicating that the cases were generally earlier in their pregnancies than the controls. Regarding body mass index (BMI), the cases had a slightly lower average BMI (24.27 ± 3.20 kg/m^2) compared to the controls (24.92 ± 3.14 kg/m^2). This difference, although small, could be relevant in understanding the health and nutritional status of the study participants. When examining the mode of delivery, a higher percentage of cesarean sections was observed among cases (60%) compared to controls (49.2%). Conversely, vaginal delivery was more common in the control group (50.8%) than in the cases (40%). Parity distribution revealed that among cases, the highest percentage (33.85%) was of nulliparous women (parity 0), followed by (23.08%) of women with parity 2. In contrast, in the control group, parity 2 was the most common (29.23%), followed by parity 1 (26.15%). This distribution suggests that the cases included more first-time mothers compared to the controls (Table 1).

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Table 1: Basic Demographics of Female Enrolled in the Study (n = 130)

Variables		Cases (n= 65)	Controls (n=65)
Age (Years)		28.88 ± 7.18	28.97 ± 6.85
Gestational Age (Weeks)		34.28 ± 1.34	39.40 ± 1.11
BMI (kg/m^2)		24.27 ± 3.20	24.92 ± 3.14
Mode of Delivery	Vaginal Delivery	26 (40%)	33 (50.8%)
	Cesarean Section	39 (60%)	32 (49.2%)
Parity	0	22 (33.85%)	15 (23.08%)
	1	13 (20%)	17 (26.15%)
	2	15 (23.08%)	19 (29.23%)
	3	8 (12.31%)	9 (13.85%)
	4	7 (10.76%)	5 (7.69%)

The prevalence of urinary tract infections (UTIs) and related factors between the study groups was compared and showed a significant difference was observed in the occurrence of UTIs, with 30.8% of the cases having a UTI compared to only 6.2% of the controls. This result, with a p-value of 0.000 and an odds ratio (O.R) of 6.77 (95% CI: 2.167-21.203), indicates a strong association between UTIs and being in the case group. All 65 cases received treatment with ceftriaxone, while none of the controls required this treatment, highlighting the clinical management of UTIs in the study group (p-value = 0.001, O.R: 5.98, 95% CI: 3.278-22.404). When stratifying by age groups, 42.9% of the cases aged 18-30 years had a UTI compared to none in the control group, with a highly significant association (p-value = 0.00, O.R: 0.571, 95% CI: 0.429-0.761). In the 31-40 years' age group, the prevalence of UTIs was similar between cases (16.7%) and controls (14.8%), with no significant association (p-value = 1.00, O.R: 1.15, 95% CI: 0.275-4.813). Parity-wise analysis showed that among nulliparous women (parity 0), 36.4% of the cases had a UTI, while none of the controls did (p-value = 0.008, O.R: 0.636, 95% CI: 0.64-0.873). For women with one previous delivery (parity 1), 53.8% of the cases had a UTI compared to only 5.9% of the controls, showing a significant difference (p-value = 0.003, O.R: 18.66, 95% CI: 1.879-185.399). No significant associations were found in women with higher parity (parity 2-4). In terms of delivery mode, 23.1% of cases with vaginal delivery had a UTI compared to 9.1% of controls, but this difference was not statistically significant (p-value = 0.13, O.R: 3.000, 95% CI: 0.671-13.404). However, among those who underwent cesarean sections, 35.9% of cases had a UTI compared to just 3.1% of controls, which was statistically significant (p-value = 0.001, O.R: 17.36, 95% CI: 2.134-141.206). Finally, BMI analysis showed that 32.4% of cases with a BMI ≤ 25 had a UTI, compared to 12.1% of controls, with a borderline significant difference (p-value = 0.043, O.R: 3.48, 95% CI: 0.995-12.166). In women with a BMI > 25, 28.6% of cases had a UTI compared to none in the control group, indicating a significant association (p-value = 0.001, O.R: 0.714, 95% CI: 0.565-0.903)(Table 2).

Table 2: Comparison of UTI between Study Groups (n=130)

Variables		UTI	Study Groups		p-value	O.R (95% CI)
			Cases n (%)	Controls n (%)		
UTI		Yes	20 (30.8%)	4 (6.2%)	0.000	6.77 (2.167-21.203)
		No	45 (69.2%)	61 (93.8%)		
Treatment with Ceftriaxone		Yes	65 (100%)	0 (0%)	0.001	5.98 (3.278-22.404)
		No	0 (0%)	0 (0%)		
Age Groups	18-30	Yes	15 (42.9%)	0 (0%)	0.00	0.571 (0.429-0.761)
		No	20 (57.1%)	38 (100%)		
	31-40	Yes	5 (16.7%)	4 (14.8%)	1.00	1.15 (0.0275-4.813)
		No	25 (83.3%)	23 (85.2%)		
Parity	0	Yes	8 (36.4%)	0 (0%)	0.008	0.636 (0.64-0.873)
		No	14 (63.6%)	15 (100%)		
	1	Yes	7 (53.8%)	1 (5.9%)	0.003	18.66 (1.879-185.399)
		No	6 (46.2%)	16 (94.1%)		
	2	Yes	3 (20%)	2 (10.5%)	0.634	2.125 (0.307-14.725)
		No	12 (80%)	17 (89.5%)		
	3	Yes	1 (12.5%)	1 (11.1%)	1.000	1.143 (0.060-21.870)
		No	7 (87.5%)	8 (88.9%)		
	4	Yes	1 (14.3%)	0 (0%)	1.00	0.857 (0.633-1.160)
		No	6 (85.7%)	5 (100%)		
Delivery	Vaginal delivery	Yes	6 (23.1%)	3 (9.1%)	0.13	3.000 (0.671-13.404)
		No	20 (76.9%)	30 (90.9%)		
	C-sections	Yes	14 (35.9%)	1 (3.1%)	0.001	17.36 (2.134-141.206)
		No	25 (64.1%)	31 (96.9%)		

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BMI	≤25	Yes	12 (32.4%)	4 (12.1%)	0.043	3.48 (0.995-12.166)
		No	25 (67.6%)	29 (87.9%)		
	>25	Yes	8 (28.6%)	0 (0%)	0.001	0.714 (0.565-0.903)
		No	20 (71.4%)	32 (100%)		

DISCUSSION

In pregnant women, UTIs are the most prevalent kind of infection that may cause maternal morbidity and poor delivery outcomes. A higher risk of UTI is associated with the physiological changes that occur during pregnancy. These changes include an increased bladder volume, reduced bladder tone, and a shift in the vaginal flora. The first sign of an infection is often asymptomatic bacteriuria, which may develop into a lower tract infection (acute cystitis) in thirty percent of patients and can cause an upper tract infection (acute pyelonephritis) in as many as fifty percent of patients. Despite the obvious connection between UTIs and maternal and newborn morbidity, very little is known regarding the frequency of UTIs during pregnancy and their correlation with premature labour among women who are pregnant. The finding of this study contributes to the existing body of knowledge of UTI amongst pregnant women specifically about the findings of this research study and when compared to previous and recent studies. We noted a high prevalence of UTIs among pregnant women; a finding that is consistent with the studies done across the globe and leverages the fact that such infections pose a significant public health burden. According to the present study, the prevalence of UTIs in pregnant women was consistent with findings from other regions. A systematic review conducted by Mlugu EM *et al.*, on pregnant women in Latin America reported a UTI prevalence ranging from 1.78% to 56%, depending on the country and specific population studied [13]. This broad range highlights the variability in UTI prevalence due to geographical, socio-economic, and healthcare-related factors. Similarly, a study from Tanzania reported a UTI prevalence of 34.3% by dipstick urine analysis and 41% by culture, with no significant difference in prevalence between pregnant and non-pregnant women [14]. Out of all the isolated bacteria the highest percentage was observed with *E.coli* which was in line with the new global trends in leading uropathogenic bacteria causing UTIs. Studies by Jalil MB *et al.*, and Alzahrani MA *et al.*, showed that *E. coli* is the most predominant UTI pathogen cohabitant with other Gram-negative bacteria like *K. pneumonia*, and *P. Aeroginosa* [15, 16]. However, a concerning trend in antimicrobial resistance (AMR) was observed, with a significant proportion of uropathogens exhibiting multi-drug resistance (MDR). Mohamed, A. H *et al.*, conducted their study in Somalia and found out most of the isolated bacteria were found to have resistance levels to at least one agent belonging at least to three different antimicrobial categories hence making it difficult for the bacteria to be treated [17]. The findings of a study by KS HK, *et al.*, also coincided with the present investigation in which the majority of uropathogens exhibited MDR [18]. Several recent papers have examined the relationship between UTIs and pregnancy outcomes. Bacterial UTIs during pregnancy increase the risk of poor outcomes in pregnancy such as preterm delivery, low birth weight, and preeclampsia. As per the evidence of the research Werter DE *et al.*, stated that UTI particularly in pregnancy increases the risk of preterm delivery [5]. In another study done by Gebremedhin KB *et al.*, in Ethiopia, there is implies clear correlation between UTI, and preterm labor [19]. A study by Bee Bee Hajira HS *et al.*, also showed similar results [20]. Due to the increased concern of AMR, much importance is given to preventive strategies and the rational use of antibiotics. In the recent past, researchers have investigated the efficacy of cranberry supplements as well as probiotics as the other potential preventive measures for repeated UTIs among pregnant women. Further, the value of regular cross-sectional screening and the correct utilization of Antibiotics cannot be overemphasized because several scientific works recommend the versatility of treatments according to the local AMR profile to enhance effectiveness without increasing resistance.

CONCLUSIONS

The study concluded the interrelation between UTIs and pregnancy complications including preterm labor. The results also show that women with preterm labor were three times more likely to develop a UTI than women who did not have preterm labor, suggesting the need for pregnant women to be regularly screened for these conditions and to receive appropriate treatment should they develop. Given the use of Ceftriaxone in the singular fashion for the management of these conditions in this population, it's critical to devise diverse antibiotic algorithms to tackle increasing antimicrobial resistance. The study also identifies those particular patient characteristics that predispose patients to have an increased risk of developing UTIs; it finds that increasing age and previous history of pregnancy, or parity, are two important determinants and calls for prevention interventions to be targeted in the light of these findings.

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Authors Contribution

Conceptualization: SS, ST
Methodology: SS, SF, SW, LSN, BSH, ST
Formal analysis: LSN
Writing-review and editing: SS

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

Conflicts of Interest

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Original Article

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Efficacy Comparison of Low Level Laser Treatment with Muscle Energy Procedure Among Diabetic Patients Suffering from Frozen Shoulder

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ABSTRACT

Frozen shoulder incidence in diabetic patient is twice as high as normal controls. There are various conventional as well as electrotherapies for its treatment within which low-level laser therapy versus muscle energy technique are well debated for efficacy in diabetic patients frozen shoulder. **Objective:** Comparative analysis of effectiveness of low-level laser therapy and muscle energy technique among diabetic patients with frozen shoulder. The study design was comparative study. The Place and Duration of Study was Department of Orthopaedic, Indus Medical College, Tando Muhammad Khan from 1st January 2023 to 30th June 2023. **Methods:** One hundred and twenty patients who were having diabetes mellitus (type 1 and type 2) and suffering from frozen shoulders were enrolled. The conventional therapeutic exercise included exercises like pendulum, arm overhead, finger wall ladder, twisting arm outwards, overhead pulley, cross-body reach exercises, hand behind-back exercise and outward rotation exercise. Muscle energy technique was administered in cases where restriction in shoulder flexion, as well as abduction, external rotation was observed. **Results:** There were 59% females and 41% males with majority being within the age group of 45-65 years. It was observed that there was a significant variance between pain scores at pretreatment and post treatment stages with highest value decrease observed in muscle energy technique group II. The ROM was least improved in control group only treated through conventional protocol. **Conclusions:** The Muscle energy technique is slightly more effective than low-level laser therapy technique in terms of pain, inflammation reduction and angular movements.

INTRODUCTION

Diabetes Mellitus is a global challenge with an advanced number of cases in twenty first century. It is related with genetic and lifestyle predisposition causing a critical public health concerns [1, 2]. According to an estimate around 537 million worldwide are suffering from diabetes mellitus wherein the number is expected to intensify up to 643million globally by year 2030 and 783 million by 2045 [2]. Low-income countries are at a higher risk than other parts of the world. In this context around 4.2 million people were found to have type 2 diabetic in the Sub-Sahara Africa region. The pr4e4velance of undiagnosed cases of diabetes mellitus type 2 in African countries is considered up to 67% which is almost twofold than other developed countries having a prevalence of 37% respectively. This increased number of diabetes cases builds the risk of mortality and complicative morbidities among this region at the higher than other part of the world [3]. Diabetic patients having uncontrolled glycemia are at higher risk of complications and additional morbidities including neuropathy, retinopathy, cardiovascular disease, and

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paralysis leading to increased health cost and care [4, 5]. Microvascular and macrovascular complications are highly significant in diabetes. Beside this, musculoskeletal concerns have also been highlighted in the Diabetes mellitus patients [5, 6]. Recent studies have identified the fact the incidence of musculoskeletal issues in diabetes patients is 1.7 to 2.1 times higher than in non-diabetic patients [7, 8]. However, due to non-life-threatening conditions the issue is many times overlooked. The complications associated with musculoskeletal disease result in organ complication as well as complications related with internal organs and chronic low-grade inflammation [9-12]. Frozen shoulders are a major concern with painful and disabling fibro proliferative disorders [13, 14]. It features gradual onset of pain and limitation of movement only up to a glenohumeral range. This can resist routine activities without bringing any radiological evidence while diagnosis [15, 16]. The average frequency of frozen shoulders in diabetic patients is about 13.4% higher than non-diabetic patients [17]. The life impact of frozen shoulders is not only related to physiological effects but also related with psychological variances with a high tendency of anxiety and depression as well as sleep deprivation among patient [18]. There are various methods introduced for treating frozen shoulders and easing the patient's life either suffering from diabetes mellitus or not. Conventional therapeutic exercises as well as electro therapy methods including Low-Level Laser Therapy (LLLT) has emerged with promising sensory system for the frozen shoulder treatment of frozen. The LLLT has bio stimulating, analgesic and anti-inflammatory effects [19]. One hand physiotherapist however prefers using another technique recognized as Muscle Energy Technique (MET) which applies gentle manipulations on lengthen-shortened spasmatic muscles resulting in reduction of edema and pain [20]. The present study was designed to compare the LLLT and MET for the treatment of frozen shoulders in diabetic patients. The results of the study have presented assuring data for opting the most efficient method of frozen shoulder treatment.

METHODS

The present study was designed as a comparative analysis which was conducted at Department of Orthopaedic, Indus Medical College, Tando Muhammad Khan from 1st January 2023 to 30th June 2023. A total number of 120 patients who were having diabetes mellitus (type 1 and type 2) and suffering from frozen shoulders were enrolled in this study. Patients with declined active-glenohumeral ROM at least of ≥20 degree for last 3 months in least 3 movements, as flexion less than 144°, abduction less than 120° and external rotation as less than 72°.Thoses patients which were suffering from bilateral/unilateral shoulder-symptoms were also included in the study. A written informed consent was taken from each enrolled patient while the study was priorly approved by ethical committee through institutional review board (IRB No. Ltr/IMCH2022/0000196). Both gender patients within the age group of 18-65 years and having clinical symptoms of diabetes as well as frozen shoulder was included in this study. Those patients who were already diagnosed with neuropathy, stroke, Parkinson's disease, brachial plexus injury, injury to cervical-spine with/without radiculopathy as well as those having injury/surgery of their shoulder, malignancy, tumor, shoulder arthritis were excluded from the research. The samples size was generated from available sample size calculation with open EPI using prevalence of frozen shoulder in diabetic patients as 13.4% and using 95% CI, 80% power of test and 5% margin of error [13]. The patients were divided into three groups. Each group had 40 patients in it. Group I was treated for frozen shoulder through LLLT and Conventional Therapeutic Exercise (CET) while Group II were treated with MET and CET. Group III were controls to mitigate the risk of placebo and only received CET. Each treatment plan was conducted as double-blind strategy where each group patient was given a specific treatment for 8 months (LLLT or MET) while group III was given only CET treatment. The CET included exercises like pendulum, arm overhead, finger wall ladder, twisting arm outwards, overhead pulley, cross-body reach exercises, hand behind-back exercise and outward rotation exercise. LLLT was performed through 3B laser therapy unit having 810m wavelength, output power as 60 Mw and the spot size as 0.5 cm2. Painful shoulder regions were irradiated through5.4 j/cm2 power density 50% duty cycle of 50%. The laser was performed for 30 seconds per region. To reduce the skin and probe reflection the region under treatment was cleaned by methylated spirit. MET was administered in cases where restriction in shoulder flexion, as well as abduction, external rotation was observed. The details of treatment have been previously described in literature [21]. The outcomes of the research were measured in terms of primary and secondary outcomes. The primary outcomes were measured in terms of Shoulder Pain and Disability Index (SPADI) and Visual Analog Score (VAS). The SPADI comprised of thirteen items which are further divided into 2 subscales (5: shoulder pain, 8: shoulder disability). Each element scoring is performed on zero (best score) to ten (worst score) rating scale. The higher the score, the greater the pain. The secondary outcome comprised of pain intensity, shoulder ROM, depression, IL-6 and anxiety. The shoulder pain intensity was valued through Numerical Pain Rating Scale (NPRS) having 11-point Likert scale, with zero as representing "no pain" while ten meant "worst imaginable pain". A 3cc blood was withdrawn from each or patient for measuring the IL 6 levels in the patients. The plasma was stored for the purpose in -80 degree freezer until analysis was performed. A well-structured

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questionnaire was used for compiling all the extracted data. The outcomes were compared and measured through SPSS version 26.0. T test and two-way ANOVA was used for interpreting of data. P value < 0.05 was considered as significant.

RESULTS

There were 59% females and 41% males in the present research with majority being within the age group of 45-65 years. This was followed by the age group 36-45 years. The mean age of the group I, II and III was 47.8 ± 2.5, 47.7 ± 2.7 and 49.5 ± 3.1 years respectively (Figure 1).

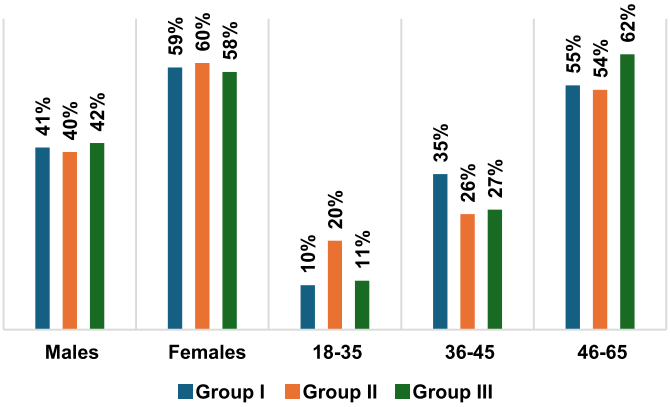

Figure 1: Comparison of Demographic Characteristic within Groups

The patients' pain was scored through VAS pain scoring and compared within the initial, 8 weeks' time and post treatment as an outcome among various groups. It was observed that there was a significant variance between pain scores at pretreatment and post treatment stages with highest value decrease observed in MET group II (Table 1).

Table 1: Comparison of VAS Score Pre and Post Treatment within Groups

VAS Score	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	P-Value
VAS Pre-Treatment	8.83 ± 1.63	9.11 ± 0.97	10.23 ± 1.5	<0.005
VAS Post Treatment	3.39 ± 0.89	2.59 ± 0.67	6.55 ± 0.99	<0.005

The Shoulder Pain and Disability Index (SPADI) was compared within groups and it was observed that there was a significant decrease in SPADI in LLLT (group I) followed by MET (Group II). However, there was a least decrease between pre and post treatment disability value in control group (Table 2).

Table 2: Comparison of Shoulder Pain and Disability Index (SPADI) within Groups

SPADI	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)	P-Value
Pre-Treatment	85.81 ± 10.56	84.65 ± 2.2	86.71 ± 10.11	<0.005
Post-Treatment	28.81 ± 10.25	28.32 ± 15.9	67.32 ± 10.05	<0.005

The numerical pain rating score presented the highest significant decrease in pain rating scale in group I followed by Group II and least decrease from pre to post treatment in Group III (Figure 2).

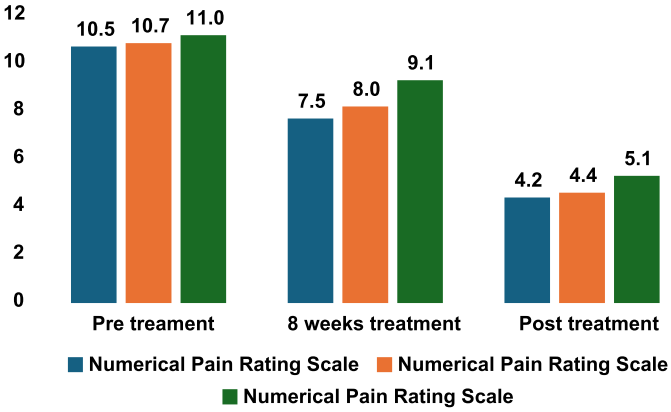

Figure 2: Comparison of Numerical Pain rating scale within groups

The blood plasma value of interleukin 6 showed the highest significant decrease in group II followed by group I with minimal variance among groups. The inflammatory marker presented the substantial decrease in inflammation in cases where LLLT or MET treatment was accompanied with conventional treatment methods (Table 3).

Table 3: Interleukin 6 Values Alteration from Pre to Post Treatment among Groups (n=120)

Variables	Interleukin- 6 Value in pg/mL		
	Group I (Mean ± SD)	Group II (Mean ± SD)	Group III (Mean ± SD)
Pretreatment	11.54 ± 1.12	11.55 ± 1.13	11.89 ± 1.9
8 Weeks Treatment	11.26 ± 0.77	11.25 ± 0.65	11.65 ± 0.95
Post Treatment	11.02 ± 0.67	11.01 ± 0.66	11.32 ± 0.81

P<0.05

The normal Range of Motion (ROM) of the shoulder is considered as an active movement within 180° flexion and abduction and 90° for external rotation according to the American Academy of Orthopedic Surgeons (AAOS). However in frozen shoulder the mean ROM was found as 3.43 ± 0.33º. Post treatment with LLLT and MET lead into a significant improvement as 115.8 ± 1.1º and 116.1 ± 0.7º in group I and group II respectively. The ROM was least improved in control group only treated through conventional protocol (Table 4).

Table 4: Comparison of Range of Motion (ROM) Pre and Post Treatment among Three Groups

Variables	Mean ± ROM Angle		
	Group I	Group II	Group III
Pretreatment	3.2 ± 0.4°	4.1 ± 0.3°	3.1 ± 0.4°
8 Weeks Treatment	61.5 ± 0.5°	61.2 ± 0.6°	60.4 ± 0.8°
Post Treatment	115.8 ± 1.1°	116.1 ± 0.7°	110.1 ± 0.2°

P<0.05

DISCUSSION

The comparative effectiveness of low-level laser therapy versus muscle energy technique in treating frozen

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shoulder, particularly among diabetic patients, is a pertinent topic in physiotherapy and rehabilitation. Adhesive capsulitis or frozen shoulder is a common condition characterized by pain and restricted shoulder movement. Diabetic patients are at an additional higher risk of developing frozen shoulder, making effective treatment strategies essential [21]. There were 59% females and 41% males in the present research with majority being within the age group of 45-65 years. This was followed by the age group 36-45 years. The mean age of the group I, II and III was 47.8 ± 2.5, 47.7 ± 2.7 and 49.5 ± 3.1 years respectively. In a previous study conducted by Venturin D *et al*, majority 57% were females and mean age of the presented cases was 46.9 years. These findings were in line with our studies.[13] Another study presented comparable results to our findings in which average age of the cases was 48.17 years.[19] The LLLT and MET can significantly reduce pain and improve function in patients with musculoskeletal conditions, including frozen shoulder [22, 23]. Present study was particularly designed for the comparison of LLLT and MET in context to frozen shoulder among diabetic patients. In the present study, both groups display significant changes in terms of pain reduction and angular movements. For better authentication of the results and efficacy analysis three various pain analyzing scores were applied in the present research. Previous study conducted by Hassan Hl *et al*, also supports the application of combination of pain scores for better comparatives results interpretation [8]. The patients' VAS pain scoring were compared within the initial, 8 weeks' time and post treatment as an outcome among various groups. It was observed among both study groups that there was a significant variance between pain scores at pretreatment and post treatment stages. Similarly, the Shoulder Pain and Disability Index (SPADI) was also significantly decrease in both study groups. In the present study result it was observed that both of the techniques are highly efficient with a slight higher efficacy of MET on LLLT. Although the MET superiority is not significantly recognizable. The present study results were in coordination with previously reported literature which has also reported similar findings and observed that pain scoring conducted through various pain scoring methods has efficient results in MET and LLLT group [8, 22, 24]. Alongside, the numerical pain rating score presented the highest significant decrease in pain rating scale in study participants and least decrease from pre to post treatment in control group. The inflammatory marker presented the substantial decrease in inflammation in cases where LLLT or MET treatment was accompanied with conventional treatment methods [20]. The normal range of motion was least improved in control group only treated through conventional protocol whereas it was significantly improved in other two groups of the study. Despite many physiotherapy interventions for frozen shoulder is available, there is still scarcity of data regarding superiority of one therapeutic intervention [25]. In current study the blood plasma value of interleukin 6 showed the highest significant decrease in group II followed by group I with minimal variance among groups. The inflammatory marker presented the substantial decrease in inflammation in cases where LLLT or MET treatment was accompanied with conventional treatment methods. Recent study conducted by Khalil R *et al* [20] presented same results in which, there was no difference between the groups when it came to the plasma levels of interleukin 6, however MET and CET had the greatest meaningful drop. In instances when LLLT or MET therapy was administered with traditional treatment approaches, the inflammatory marker demonstrated a significant reduction in inflammation. In frozen shoulder the mean ROM was found as 3.43 ± 0.33º. Post treatment with LLLT and MET lead into a significant improvement as 115.8 ± 1.1º and 116.1 ± 0.7º in group I and group II respectively. The ROM was least improved in control group only treated through conventional protocol. The results demonstrate that early range-of-motion exercises significantly enhance rehabilitation outcomes following surgical repair, including accelerated healing, reduced stiffness, and prevention of re-tears, in line with a previous research by Kjaer BH *et al.* [26]. Furthermore, neither tendon repair nor clinical results are improved by immobilization. Result of present study proved that both treatment showed substantial reduction in pain. The muscle energy technique is slightly more effective than low-level laser therapy as the former had slight improved reduction in pain observed than LLLT. Although the difference is not significant.

CONCLUSIONS

The low-level laser therapy as well as muscle energy technique among diabetic patients with frozen shoulder are highly effective techniques with both having a significant efficacy in treating the frozen shoulders of diabetic patients. The MET is slightly more effective than LLLT technique in terms of pain, inflammation reduction and angular movements as most of the pain test result presented slight more decrease in MET than LLLT. Although the difference is not significant.

Authors Contribution

Conceptualization: ASQ

Methodology: MZT, MAA, ZUA

Formal analysis: ASQ

Writing, review and editing: TH

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

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Clinical Outcome of Surgical Treatment of Giant Femoral Artery Pseudoaneurysms

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ABSTRACT

Femoral artery was used as an access site for cardiovascular procedures and by IV drug abusers, Femoral Artery Pseudoaneurysm (FAP) was a common complication associated with these procedures. **Objective:** To evaluate clinical outcome of surgical repair of femoral artery pseudoaneurysms. **Methods:** The prospective study was conducted in Doctors Hospital, Lahore from October 2022 to October 2023. The study included patients with giant femoral artery pseudoaneurysms who required surgical intervention. Data from a total of 50 patients were included in whom both peripheral vascular interventions and percutaneous cardiac catheterization was performed. Patients were followed up at 1-, 3-, 6- and 12 months postoperatively. SPSS version 23.0 was used for data analysis. **Results:** All patients underwent open surgical treatment. Of 50 patients, 25 (50%) had SFA pseudoaneurysm, 20 (40%) had CFA pseudoaneurysm and 5 (10%) had PFA pseudoaneurysm. The mean duration of clinical manifestations was 16.30 ± 7.74 days. Surgical repair was successful in all 50 (100%) patients and distal ischemia was fully resolved. There was no case of limb loss or post-operative mortality. One patient had an infection in the groin wound and had raised Total leucocyte count (TLC), which was resolved by early drainage and antibiotic treatment. Patients were followed up at 1, 3, 6, and 12 months and there were no signs of clinical or angiographic evidence of post-operative complications and changes in distal pulse. **Conclusion:** Surgical repair was first-line treatment for giant FAP. It was clinically feasible and has a high success rate and low complication rate.

INTRODUCTION

The femoral artery is used as an access site for cardiovascular procedures and by IV drug abusers, femoral artery pseudoaneurysm (FAP) is a common complication associated with these procedures [1]. There has been an increase in the incidence of pseudoaneurysm because increased complexity and number of invasive endovascular procedures [2]. The femoral artery is a commonly used access site for intra-arterial procedures. Access site complications such as vessel thrombosis, bleeding, arteriovenous fistula, emboli, and thrombosis are common clinical presentations. FAP is the most common complication with an incidence rate of 0.2-2% [3]. Incomplete closure of arterial puncture leads to FAP formation causing arterial blood to enter surrounding tissues creating a pulsating hematoma [3]. FAP presents as bruit or thrill and may cause pain and tenderness, local skin ischemia, neuropathy, and distal embolization [4]. It can also manifest as pulsatile mass, audible murmur and tremor [5]. Small pseudoaneurysms can be treated conservatively. Recently, femoral artery pseudoaneurysms have been managed through radiological instead of surgical intervention. Radiological

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intervention includes transcatheter embolization through thrombin, transcatheter fibrin adhesives, coils, and percutaneous injection of thrombin. While surgical intervention includes arterial repair and aneurysmectomy. Surgical intervention is done in case of large pseudoaneurysms or when radiological intervention has failed [6]. Audeh A et al., found that surgical repair resulted in complete resolution of giant femoral artery pseudoaneurysms and had no major complication [7].

There is a scarcity of local data on this topic, thus the aim of this study was to clinical outcome of surgical repair of femoral artery pseudoaneurysms.

METHODS

The prospective study was conducted in Doctors Hospital, Lahore from October 2022 to October 2023. The study included patients with giant femoral artery pseudoaneurysms who required surgical intervention. Pseudoaneurysms sized >2cm were considered giant FAP. FAP was diagnosed through clinical examination and Computed Tomography Angiography (CTA). Post-operatively, all patients were administered oral aspirin (75-150 mg/day) for 3 months. Patients were followed up at 1, 3, 6, and 12 months postoperatively. Patients with anastomotic site pseudoaneurysms were excluded. Data from a total of 50 patients were included and they underwent both peripheral vascular interventions and percutaneous cardiac catheterization. Informed consent of the participants was taken. The ethical review board of the hospital approved the study Ref: IRB/43/2022/01. To perform the procedure, the patient was placed in the supine position. The character of posterior tibial and dorsalis pedis pulses were recorded before, during, and after the procedure. The aneurysm was exposed through a vertical incision which was extended distally and proximally to view the Superficial Femoral Artery (SFA), Common Femoral Artery (CFA) and Profunda Femoral Artery (PFA). After exposing the pseudoaneurysm pouch, the hematoma was excavated and the distal part of PFA and SFA and proximal part of CFA were carefully dissected followed by placement of nylon tapes and 6/0 polypropylene suture. Twenty-five (50%) patients had small defects and underwent primary repair, 8 (16%) underwent vein patch repair. Eight patients (16%) received an interposition reversed saphenous vein graft, while nine patients (18%) underwent an interposition synthetic ePTFE graft. The primary outcome was success of surgical repair and resolution of ischemia. Secondary outcomes included postoperative mortality and complications and incidence of infection and limb loss. SPSS version 23.0 was used for data analysis. Descriptive analysis was performed to present variables by mean ± SD for categorical variables like BMI and age and by percentage for continuous variables.

RESULTS

The mean age of the participants was 49.07 ± 12.01 years. There were 16 (32%) females and 34 (68%) males. Thirty-three (66%) patients had groin pain and distal ischemia, 8 (16%) had infected pseudoaneurysm, 4 (8.1%) had leaking pseudoaneurysm and 5 (10%) had very large pseudoaneurysm (>5cm). All patients underwent open surgical treatment. Of 50 patients, 25 (50%) had SFA pseudoaneurysm, 20 (40%) had CFA pseudoaneurysm and 5 (10%) had PFA pseudoaneurysm. The mean duration of clinical manifestations was 16.30 ± 7.74 days. Surgical repair was successful in all 50 (100%) patients and distal ischemia was fully resolved. There was no case of limb loss or post-operative mortality. One patient had an infection in the groin wound and had a raised Total leucocyte count (TLC), which was resolved by early drainage and antibiotic treatment. TLC count was assessed by a hematologist. Patients were followed up at 1, 3, 6, and 12 months and there were no signs of clinical or angiographic evidence of post-operative complications and changes in distal pulse.

Table 1: Patient's Characteristics

Variables	Patients N (%) / (Mean ± SD)
Age (Years)	49.07 ± 12.01
Gender	
Male	34 (68%)
Female	16 (32%)
BMI	33.8 ± 6.4
Location of Pseudoaneurysm	
SFA	25 (50%)
CFA	20 (40%)
PFA	5 (10%)
Sign	
Pain	33 (66%)
Infection	8 (16%)
Rupture	4 (8.1%)
Enlargement (>5cm)	5 (10%)
Surgery	
Elective	3 (6%)
Emergency	47 (94%)
Intervention	
Primary Repair	25 (50%)
Vein Patch Repair	8 (16%)
Interposition Reversed Saphenous Vein Graft	8 (16%)
Interposition Synthetic ePTFE Graft	9 (18%)

DISCUSSION

In this study, we evaluated the outcome of the surgical repair of giant FAP. FAP was a complication associated with percutaneous-based interventions and IV drug abuse. Pseudoaneurysms occur due to incomplete closure of the arterial puncture site and result in hematoma formation and bleeding [8, 9]. A study found out that there has been an increase in incidence of FAP in recent years, its incidence

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after diagnostic procedures was 0.9%, and in therapeutic procedures was 9% [10]. Pseudoaneurysms were mostly found in the superficial femoral artery, and may also be present in the common femoral artery, deep femoral artery, and at the junction of superficial and deep femoral arteries. Stable pseudoaneurysms were benign and resolve spontaneously; however, 14% of pseudoaneurysms need open repair [11]. Minor Post-Catheterization Pseudoaneurysms (PCPA) may undergo thrombosis and were treated conservatively by the surgeons; however, this prolongs hospital stay, delays ambulation, and requires repeated sonographic evaluation. [12]. Development of more conservative techniques has diminished the role of surgery; however, surgical repair was required for managing large hematoma, infected pseudoaneurysms, FAP causing distal ischemia, neuropathy, soft tissue and skin ischemia and cases of failed percutaneous treatment [13]. Traditionally, surgery was the gold standard for treating femoral artery pseudoaneurysms, though it has a risk of complications in patients with cardiovascular disease. The results of our study reveal that various types of surgical procedures can effectively treat giant FAP. These results were in line with previous literature which suggests that open surgical repair has various benefits and fewer complications [14, 15]. Surgical repair was successful in all patients and there was only one case of post-operative infection which was resolved through drainage and antibiotic treatment. A study reported that groin incision was usually recommended in case of painful and enlarged pseudoaneurysms [16]. However, few studies reported that non-surgical closure of FAP using ultrasound-guided compression was successful in patients undergoing catheterization [17, 18]. Percutaneous thrombin injections were also used for treating FAP, currently thrombin injections with ultrasound-guided visualization were used [19, 20]. Duplex ultrasound-guided compression was another less invasive option but has limited efficacy. There was a general consensus that enlarged painful pseudoaneurysms should be repaired surgically. The limitation of this study was small sample sizes, larger studies were required for further analysis.

CONCLUSION

Surgical repair was the first-line treatment for giant FAP. It was clinically feasible and has a high success rate and low complication rate.

Authors Contribution

Conceptualization: AM
Methodology: AM, ANA, NF, SNJ
Formal analysis: SA
Writing, review and editing: AM, AU

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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Sex-Based Differences in Frontal Sinus Anatomy: A Cross-Sectional Study

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ABSTRACT

Within the frontal bone of the skull, directly above the eyebrows and behind the forehead, lies an air-filled chamber known as the frontal sinus. **Objective:** To investigate sex-based differences in frontal sinus anatomy, including measurements such as height, width, and area. **Methods:** This cross-sectional study was conducted at the Department of Anatomy, Women Medical and Dental College, Abbottabad from January 2023 to December 2023. A total of 300 participants were (N = 300). The participants were divided into two groups: 160 men and 140 women. The participants were physically examined using a radiological process. **Results:** The female and male mean age of 35.2 ± 18.5 years. The right and left side areas of the frontal sinus were significantly higher in males 77.7% and 82.8%, respectively; p = 0.0001) than in females. Males had a significantly greater height (73.3%) and 75.9 % (p = 0.0001) than females on both sides. It was shown that the right and left side widths in males 79.6% and 74.4% significantly higher, p = 0.0001 as compared to females. Males had more supra agger frontal cells and supraorbital ethmoid cells (78.1% and 81.2%, respectively; p < 0.0001). **Conclusions:** It was concluded that males have larger frontal sinuses in terms of height, width, area, and ethmoid air cell count than females. These results indicate that males have larger and more developed frontal sinuses than females.

INTRODUCTION

The frontal sinuses are air-filled chambers located within the frontal bone of the skull, positioned just above the eye sockets and behind the forehead. These paired sinuses are a part of the paranasal sinus system, which is a network of hollow spaces in the facial bones that connect with the nasal cavity. During childhood, the frontal sinuses grow and reach full maturity by early adulthood [1]. The frontal sinus is a sex discrimination indication; nonetheless, the frontal sinus sex discrimination rate was lower than that of the classic morphological approaches. We devised a novel approach that measures the frontal sinus area and index from lateral cephalogram radiographs to increase the sex discrimination percentage [2]. This narrow opening is called an ostiumthus permits mucus (liquid) to come out from its residence and go down toward the nose where It can be breathed out with following air. Some anterior ethmoid cavities vented into the medial turbinal, though others neared the nostril's perimeter. Healthy individuals may glimpse all-natural openings. The lamina completely plates the medial orbital wall, necessitating an incision through the anterior ethmoid bone to view. Fixed specimens expose the hard palate posterior to the nasal cavity. Ciliated cells in nasal and paranasal mucosa, including ethmoids and maxillae, coordinate mucus and debris propulsion toward Ostia draining into passages. Scattered ciliated cells line these cavities. For example, the frontal sinus secretes mucus via goblet rather than ciliated cells, keeping its region moistened and hospitable. While most sinus cavities exhibit concerted cilia, variances like frontal mucous membranes diversify constitution along

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the complex networked airways [3]. The sinus cavity is lined by a mucous membrane on the interior part of the sinuses. The hollow cavities filled with air lie in the skull region and generate mucus continuously. The mucus helps to keep the nasal passages inside moist and keeps the lining of the sinuses dampened. Meanwhile, it provides a physical barrier that is vitally necessary to ensure that any foreign object, bacteria or virus which might enter one's lungs thus making way for infection is blocked by mucus. The frontal sinus drains into the ethmoid cell group adjacent to it, or ethmoid cells but other parts of this area have pseudo-stratified ciliated cells. Cilia, hairlike structures finer than 10 microns, can act as brooms that pinch off and remove mucus or small solid objects from the sinuses. One of the leading candidates of how content within the sino-nasal cavity drains outward now is that ciliated cells with hair-like structures thinner than 10 microns sweep out mucus and dirt This is in contrast to the way Cilia overlap and collectively move: in the coordinated flows that lead to the motion of large biofilm aggregates across ostia toward natural or iatrogenic openings [4]. This is an example of normal anatomical drainage by an emissary conduit through which mucus comes and goes to the nasal cavity. In humans, the paranasal sinuses are connected by their ostia-the opening of one sinus into another. This enables mucus and air exchange between individual sinuses as well as with those of the nasal cavity itself [5]. In the head and neck region, one of the most challenging anatomical formations is the drainage system of our frontal sinuses. For many people, this opening is wider than the one that connects the frontal sinus to the surrounding structures, be it teeth or nostrils. Some individuals have them in between their navel and nasal cavity, among other anatomical stoppages, for instance. Any disturbance by inflammation causes any of the extra holes to assume a different position internally, thereby affecting the drainage sinuses' curves [6]. As a result, the sinuses will deviate from the expected functioning way causing functional chaos. The size of the nasofrontal duct in the frontal sinus can affect the path of drainage. It is a small channel that flows through the frontal recess and into the nasal cavity [7]. On one hand, when the nasofrontal duct is very large and wide open, this affects the path of drainage of the frontal sinus. The position of the nasofrontal duct at a far distance from the nasal floor because of the minimal attachment of the floor affects the amount and path of drainage. On the other hand, frontonasal duct patency is also influenced by the frontal sinus, which contributes to 34% of changes in front frequency. The frontal sinus may account for 37.5% of changes in duct patency, as draining occurs in the ethmoid infundibulum in approximately 81.8% of cases. On the drainage passage, Braun states that it has been noticed that the sinus opens in the middle nasal meatus [8]. The quality of functional results and understanding of the structure of this labyrinth improve with continuous research, but it is also one reason that success rates are much higher at present than in its initial report. The increased use though has significantly changed our perception of forehead sinus shape and adjacent sinus structures as seen on these high-resolution scans. The Fourier transform of three-plane images rendered by CT clearly shows important anatomic relationships. If the surgeon has an unusual level of expertise, may profit from utilizing that feature with optimum benefits to patients. Depending on how one interprets such data and what experience in this kind of operation has previously, combining these factors into some degree of predictability-procedure manipulation becomes more challenging than simply performing procedures later in an operating room environment. A surgeon can find the important structures of the frontal sinus and prepare a surgical approach that is structured according to the structure of complexity which it holds. Its specific anatological variations however have to be managed before performing the surgery [9, 10]. This study aimed to examine gender-based differences in frontal sinus anatomy, including measurements such as height, width, and area, as well as the presence of ethmoid air cells like the supra agger frontal cell and the supraorbital ethmoid cell.

METHODS

This cross-sectional study was conducted at the Department of Anatomy, Women Medical and Dental College, Abbottabad, from January 2023 to December 2023. The total number of participants in this study was (N=300). The participants were divided into two groups: male and female. The inclusion criteria included general population, both male and female sex and an age range of 18-52 years. No history of sinus disease, trauma, or surgeries affecting. Exclusion criteria were pregnancy, sinus surgery, and facial anomalies. The formula for calculating sample size often involves these factors. For a cross-sectional study comparing two independent groups (males vs. females), the sample size formula can be: n= 2.(z α/2+Zβ)2 σ2 / d2. Zα/2 is the critical value for the desired significance level (1.96 for α=0.05\alpha = 0.05α=0.05). Zβ is the critical value for the desired power (0.84 for 80% power). σ is the estimated standard deviation of frontal sinus measurements. d=0.05 is moderate effect size. Frontal sinus dimensions for both right and left sinuses (width, height & anteroposterior lengths) were measured from axial and coronal sections (4-mm slice thickness) using multi-detector computed tomography (MDCT) scanner. This study was approved by the Institutional Review Board (IRB) reference number (WMC /Estb/20042), Women Medical and Dental College, Abbottabad. Data were statistically analyzed using SPSS software 26.0. Independent T-test, when comparing the means of

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continuous variables Height, Width, and Depth between two separate groups, such as males and females, the independent t-test is utilized. Categorical Variables (Presence of Septa, Symmetry) were presented as frequencies and percentages. Odds ratios (OR) and confidence intervals (CI) are reported to describe the likelihood of these variations occurring in males versus females. The variables were considered to be significant, as indicated by a p-value of <0.05.

RESULTS

A total of 300 participants were included in the study, consisting of both males and females. Of these, 140 (46.6%) were female and 160 (53.3%) were male. The age range of the participants was between 18 and 52 years, with a mean age of 35.2 ± 18.5 years. Out of the 300 participants who underwent frontal sinus assessment (100%), this reduction in sample size was accounted for in table 1.

Table 1: Demographic Variables

Variables	Total Number of Participants = 300 Mean ± SD Or % Age
Age	
Mean ± SD	35.2 ± 18.5 years
Gender	
Female	(140) 46.6%
Male	(160) 53.3%
Frontal Sinus	
Present	300 (100%)

When analyzing the dimensions of the right and left frontal sinuses, there were generally notable dissimilarities between male and female participants. The measurements revealed a statistically significant difference in the area of the frontal sinuses between male and female participants. Specifically, the right and left side areas of the frontal sinus in male participants were found to be significantly higher 350 ± 49.5 and 352 ± 51.2 mm^2 respectively, compared to females, with a p-value of 0.0001. These findings imply a potential gender-based distinction in the development of sinuses, as shown in table 2.

Table 2: Evaluate The Area Variation in Frontal Sinus Anatomy in Both Gender

Area (mm^2)	Male	Female	p-value
Right Area	350 ± 49.5	310 ± 43.3	<0.0001
Left Area	35 2 ± 51.2	315 ± 42.5	<0.0001

Our findings show that there were often substantial disparities in the height of the right and left frontal sinuses between male and female gender groups. Specifically, the height on the right side was significantly reduced in female participants by 30.7 ± 4.2 mm, p = 0.0001 compared to males 35.5 ± .1 mm, while the height on the left side was also significantly reduced by 32.5 ± 2.5 mm, p = 0.0001 in females relative to males 37.6 ± 3.2 mm. On the other hand, males had significantly greater heights in both the left and right frontal sinuses, p = 0.0001 respectively, as compared to females in table 3.

Table 3: Evaluate The Height Variation in Frontal Sinus Anatomy in Both Gender

Height (mm)	Male (160)	Female (140)	p-value
Right Height	35.5 ± 5.1	30.7 ± 4.2	<0.0001
Left Height	37.6 ± 3.2	32.5 ± 2.5	<0.0001

In fact, in 40.3 ± 2.5 mm of male participants, the right side width was significantly higher than in female 36.5 ± 4.5 mm participants, with a p-value of 0.0001. Additionally, in 41.1 ± 3.5 mm of male participants, the left side width was also significantly greater than in female participants 32.3 ± 5.1 mm, with a p-value of 0.0001. Overall, our results indicate that males have a significantly greater width than females in both the right and left frontal sinuses, as shown in table 4.

Table 4: Evaluate The Width Variation in Frontal Sinus Anatomy in Both Gender

Width (mm)	Male	Female	p-value
Right Width	40.3 ± 2.5	36.5 ± 4.5	<0.0001
Left Width	41.1 ± 3.5	32.3 ± 5.1	<0.0001

Supra-Ager Frontal Cell prevalence is considerably higher in men (78.1%) than in women (64.2%). When a difference is statistically significant, the p-value is less than 0.0001. The prevalence of Supra Orbital Ethmoid Cells is significantly higher in males (81.2%) than in females (77.1%). A statistically significant difference is indicated by the p-value of less than 0.0001, and the odds ratio supports the significance of the difference by suggesting that males are more likely to have these cells. There were no statistically significant differences between the sexes in Agger Nasi Cells, Supra Ager Cells, Supra Bulla Cells, Supra Bulla Frontal Cells, or Frontal Septal Cells. Supra Agger Frontal Cell and Supra Orbital Ethmoid Cell show significant differences between genders, with males being more likely to have these cells. Significantly more common in males than in females, with a p-value <0.0001 and OR (0.31 (1.21-4.57) and (0.22 (1.10- 3.54) suggesting a notable difference. Data by sex were presented in table 5.

Table 5: Evaluate The Sex Variation in Frontal Sinus Anatomy in Both Gender

Anterior Cells	Male	*p-value*	Female = 140	*p-value*	Odd Ratio or 95% CI
Agger Nasi Cells	16 (10%)	1.5439	25 (17.8%)	1.6777	1.21 (0.32, 3.61)
Supra Ager Cell	19 (11.8%)	0.6590	30 (21.4%)	0.5232	2.11 (0.15, 3.41)
Supra Ager Frontal Cell	125 (78.1%)	<0.0001	90 (64.2%)	<0.0001	0.31 (1.21-4.57)
Posterior Cells					
Supra Bulla Cell	16 (10%)	3.7650	18 (12.8%)	1.8780	2.43 (0.13, 0.47)
Supra Bulla Frontal Cell	15 (9.3%)	0.5421	14 (10%)	1.9899	1.21 (2.2, 4.1)
Supra Orbital Ethmoid Cell	130 (81.2%)	<0.0001	108 (77.1%)	<0.0001	0.22 (1.10-3.54)
Middle Cell					
Frontal Septal Cells	40 (25%)	0.9879	20 (14.2%)	0.0098	3.81 (1.30-4.66)

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DISCUSSION

Frontal sinuses are unique to each individual. These sinuses vary significantly in size, shape, pneumatization, septation and position. This variation is influenced by genetics, age, and anatomy. Individual sinuses may grow and pneumatize differently owing to genetic variation [11]. Variations in the structure of the frontal bone and surrounding structures can have an impact on the sinus arrangement. The development of frontal sinuses takes time, and the level of pneumatization varies with age. Sinus volume and pneumatization levels can fluctuate throughout a person's life [12]. In the current study, we found that frontal sinus development and growth were linked to particular age-related stages of skull growth. The frontal sinuses often alter significantly during childhood, adolescence, and early adulthood, as part of the overall craniofacial development process. These modifications can be divided into many major stages: Frontal sinuses are typically missing or poorly formed at birth 18 years. As the skull grows and matures, the frontal sinuses expand and become more pneumatized. Growth is influenced by both puberty-related hormone changes and hereditary factors [13]. The timing and breadth of frontal sinus development vary between individuals and are affected by genetic, environmental, and craniofacial growth trends. Understanding age-related variations in frontal sinus development is critical for the accurate interpretation of imaging investigations and clinical assessments, especially in pediatric and adolescent populations. A maximum age restriction of 52 years ensured a proper anatomical morphology. The previous study was shown that age significantly involve in the frontal sinus development of male gender then female [14, 15]. For certain, sexual variances in grown persons' frontal sinus elevations would derive from an assortment of considerations. While it troubles all patients alike, idiosyncrasies in form or measurement may distinguish him or her. Ordinarily, males' craniums expand farther and traits more boldly, perhaps adding to more expansive frontal sinuses [16]. Hormonal fluctuations, especially throughout pubescence, can sculpt osseous maturation and face articulation. Testosterone in higher amounts among males than females could impact frontal sinus inflation and development. Too, innate tendencies may rework the elevation or profile of the frontal sinuses. Dissimilarities in the genetic codes governing craniofacial advancement might underlie the gender contrasts in frontal sinus height seen. Nonetheless, these results must be set in the context of this evaluation's demographic particulars along with any confounding elements that could sway frontal sinus shape. We agreed with the previous study [17]. The measurement for the width of both right and left side frontal sinuses were significantly greater in males than females, indicating a sex-based difference observed among genders regarding dimension [18]. The data indicate that the overall frontal sinuses are wider for males compared to females in this sample population. General morphological differences of males with broader faces and generally larger cranial dimensions compared to females account for wider frontal sinuses. Androgens, particularly testosterone which is more abundant in men than women may contribute to bone formation and remodeling leading to the increased size of frontal sinus cavities. The previous literature showed that the left and right width changes significantly in the male gender and the female [19, 20]. Males have significantly larger left and right frontal sinuses than females, and the size of the frontal sinuses is related to gender. For most of the time, males had a larger surface area of the left frontal sinus than females, on average. Males in general display larger cranial dimensions and more prominent facial characteristics than their female peers, which might be the basis of a larger area in the frontal sinus. Hormonal parameters such as testosterone affect bone growth and development. The proliferation and pneumatization of frontal sinuses might be influenced by androgens, which are more abundant in males—this would lead to a larger surface area. Locus-specific genetic variables related to gender differences could account for variation in the frontal sinus area between males and females. Gastronomic behaviour, level of physical activity, and exposure to environmental threats could all be influential factors in determining the focal between sexes of craniofacial. The previous study showed frontal sinus changes significantly in male gender than female [21, 22]. Our study proved that in colour, taste and properties of the supra agger frontal cell and supraorbital ethmoid cell of the frontal sinuses varied greatly in men from those found in their female counterparts. Bigger in males than females were those supraorbital ethmoid and supraagger frontal cells, respectively. The supra agger frontal cell and supraorbital ethmoid cell lie just adjacent to the frontal sinuses and one form of these are ethmoid air cells. Different shapes and sizes of frontal cells with variable degrees of pneumatization directly influence the morphology of neighboring sinuses The supra agger frontal cell and the infraorbital ethmoidal cells usually originated from both anterior air space in the region of frontonasales; the other two predisposing sites occupied by such kind of pattern, whereas all occur mainly at one side. This disrupts the passage of air and moisturize formed in social autism. The effect is dysfunction and free flow of fluids from frontal sinuses, which may adversely affect the sinus health state. We agreed with the previous study [23].

CONCLUSIONS

It was concluded that males have larger and more developed frontal sinuses than females, with males having larger frontal sinuses in terms of height, width, and area. As a cross-sectional study, it can only establish associations

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rather than causal relationships. Longitudinal studies would be needed to explore how anatomical differences might influence sinus health and disease progression over time.

Authors Contribution

Conceptualization: HI, MSK, NQH, OJ, AH, SS
Methodology: MSK
Formal analysis: CR, DC
Writing-review and editing: ME

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

Conflicts of Interest

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Seasonal Pattern in Firearm Injury-Related Cases at Casualty Department of a Teaching Hospital

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ABSTRACT

Firearm injuries pose a substantial public health concern worldwide, with their incidence and patterns varying across different regions and time periods. Understanding the temporal trends and seasonal patterns of firearm injury-related cases is essential for guiding preventive strategies and optimizing healthcare resource allocation. **Objective:** To determine the seasonal patterns and trends in firearm injury-related cases. **Methods:** A retrospective observational study was conducted at Casualty Department, Forensic Medicine Toxicology, Liaquat University Hospital, Hyderabad, Pakistan from 1st January 2021 to 31st December 2023. Four hundred and forty-three emergency cases associated with firearm injuries across the three years were enrolled. **Results:** The occurrences decreased from February to March and November to December, with peaks in August and January.Seasonal decomposition analysis further confirmed the presence of a noticeable seasonal trend, with spikes observed in January and August, indicating a potential surge in firearm injury incidences during festivals. Moreover, an increasing trend in firearm-related injuries was observed from March to August, suggesting increase in such incidents during warmer months. **Conclusions:** The firearm-related injuries exhibit seasonal patterns, spiking in summer(months from March to August), the cause of which needs to be elaborated in future researches.

INTRODUCTION

Emergency departments serve as critical hubs for the assessment, management, and treatment of patients presenting with acute medical conditions, traumatic injuries, and emergencies [1, 2]. The nature of cases that are encountered in emergency departments is diverse and it ranges from medical emergencies such as myocardial infarction and stroke to traumatic injuries resulting from motor vehicle accidents, falls, and interpersonal violence, including firearm-related incidents [3]. Emergency department of a teaching hospital also receives cases with legal and urgent nature that underline the importance of prompt and efficient medical intervention, as well as the documentation and preservation of forensic evidence in emergency department for potential legal proceedings [4, 5]. Firearm injuries include both intentional (e.g., assaults, homicides, suicides) and unintentional (e.g., accidental discharges, mishandling) incidents and these represent a significant proportion of trauma cases seen in EDs worldwide. Approximately 251,000 individuals worldwide lose their lives annually due to firearm-related incidents [6]. Beyond the fatalities, a larger number of individual's experience nonfatal injuries from such incidents,

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resultingin long-term physical, emotional, and socioeconomic consequences [7]. These injuries can result in disabilities, chronic pain, psychological trauma, and financial burdens that may continue throughout their lifetimes, underscoring the far-reaching impact of firearm violence on individuals and societies globally [8]. The severity and complexity of firearm injuries can vary extensively, depending on factors such as the type of firearm, caliber of the bullet, distance from which the weapon was fired, and anatomical location of the injury [6]. Survivors of firearm injuries often require urgent medical attention, which often includes surgical intervention, resuscitation and intensive care management [9]. The occurrence of diseases and injuries may exhibit seasonal patterns due to various environmental, biological, and sociodemographic factors. Seasonal variation in diseases and health-related outcomes has been documented in many reports. For instance, infectious diseases have long been recognized to follow seasonal patterns [10]. However, not only infectious diseases but chronic conditions might also be affected under seasonality. For example, seasonal variations in all types of cardiovascular disease have been observed in diverse populations and climates, with a primary focus on temperate regions [11]. The activity of rheumatoid arthritis, a systemic autoimmune disease attributed to persistent synovitis, was also reported to be influenced by seasonal changes [12, 13]. Similarly, a number of studies have explored the seasonality of crimes, including violent offenses such as assaults, robberies, and homicides [14, 15]. However, the potential seasonality of firearm injuries, which involve both intentional acts of violence and unintentional incidents, has acquired comparatively less attention, indicating the need of localized research to determine time-based patterns in firearm injuries.

Therefore, the present study aimed to determine the seasonality of firearm injuries by assessing the cases that were reported at casualty department of a teaching hospital at Hyderabad.

METHODS

The retrospective observational study was conducted in the Emergency Department of Liaquat University Hospital, Hyderabad, Pakistanfrom 1st January 2021 to 31st December 2023 with approval letter No. LUMHS/FM/37/21. A total of 443 emergency cases associated with firearm injuries were enrolled. All patients across all age groups who presented with emergency cases related to firearm injury were included in the present study. Inclusion criteria were limited to cases of emergency nature, specifically focusing on firearm injury-related incidents, while excluding non-gunshot or unrelated cases. Upon arrival, patients with firearm injuries were subject to undergo rapid assessment to prioritize care based on the severity of their condition. To identify and address life-threatening injuries promptly, immediate assessment of airway, breathing, and circulation was performed. The extent and severity of injuries, including gunshot wounds, associated fractures, and potential internal organ damage were assessed. Subsequently, intravenous fluid administration and blood transfusion were accomplished where indicated. Similarly, advanced cardiac life support protocols were followed for patients in cardiac arrest or with life-threatening conditions. All patients received wound debridement followed by fixation either during the same procedure or in subsequent surgeries. Antibiotics were administered to prevent infection development in wound. Following stabilization, the patients were referred to ICU, further surgeries, or hospitalization based on clinical needs. Data collection was performed using MS Excel sheets. The monthly frequency of firearm injury-related cases was recorded in MS Excel. The average and total occurrence of firearm injury-related cases were calculated in Excel using Excel datasheets. Then, the month-wise data that were collected in MS Excel was inserted into Statgraphics Centurion XIX software to determine the seasonal patterns and trends in firearm injury-related cases. Sampling intervals in Statgraphics Centurion XIX software were defined based on the months of the year, and the software's built-in models for time-series analysis and seasonal decomposition were utilized to determine patterns in the occurrence of firearm injury-related cases over the study period [16]. The findings were presented in terms of monthly frequency distributions and mean ± standard deviation (mean ± SD) for the three-year duration. Visual representation of the results was achieved through line graphs depicting the outcomes of seasonal decomposition.

RESULTS

Within this timeframe, the distribution of firearm injury-related cases exhibited variability, with 140 cases recorded in 2021, followed by 149 cases in 2022, and 155 cases in 2023. A detailed breakdown of the monthly and quarterly distribution and total cases for each month across the three-year period, along with corresponding mean values and standard deviations, is provided in table 1.

Table 1: Frequency of Firearm Injury Cases for Consecutive Years 2021, 2022 and 2023

Months	Years			N (%)	Mean ± SD
	2021	2022	2023		
January	17	24	22	63 (14.19)	21 ± 2.94
February	6	3	4	13 (2.93)	4 ± 1.2
March	9	4	7	20 (4.50)	7 ± 2.1
April	9	7	9	25 (5.63)	8 ± 0.94
May	10	11	12	33 (7.43)	11 ± 0.82
June	13	15	22	50 (11.26)	17 ± 3.86
July	16	17	21	54 (12.16)	18 ± 2.16

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August	21	27	26	74 (16.67)	25 ± 2.62
September	17	21	19	57 (12.84)	19 ± 1.63
October	11	11	8	30 (6.76)	10 ± 1.41
November	7	5	3	15 (3.38)	5 ± 1.63
December	4	4	2	10 (2.25)	3 ± 0.94

This table highlights certain trends, notably a decrease in the number of firearm injury cases observed from February to March and November to December, suggesting potential seasonal fluctuations in incidence rates. Conversely, August emerged as the month with the highest average number of firearm injuries, closely followed by January. To further elucidate the seasonal patterns in firearm injury-related cases, a seasonal index plot was generated (Figure 1).

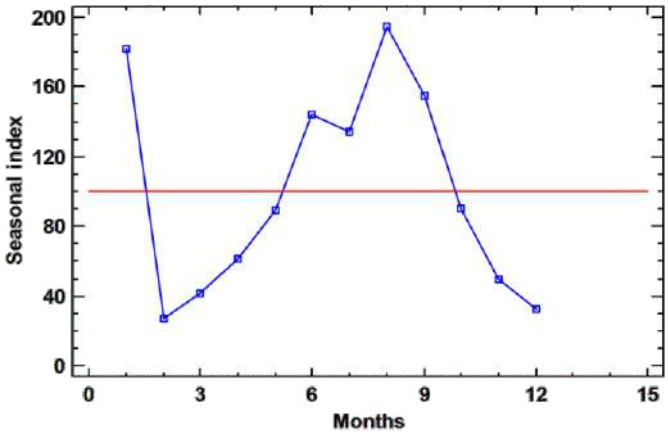

Figure 1: Seasonal Index Plot for Firearm Injury Cases

This graphical representation underscores the presence of a noticeable seasonal trend, with peaks observed in the months of January and August. Notably, there appears to be an upward trajectory in firearm injury cases from March to August, indicative of a seasonal surge in incidences during the warmer months. Conversely, a downward trend in reported firearm injuries is observed from September onwards, suggesting a potential seasonal decrease in incidence rates as cooler months approach. Moreover, Figure 2 provides additional insights into the distribution of firearm injury-related cases throughout the year at Liaquat University Hospital, Sindh, Pakistan. This graph highlights the variability in monthly frequency, with certain months exhibiting a notably higher number of cases compared to the average incidence across the year. Specifically, months such as January and August stand out as periods with elevated firearm injury-related case numbers, contributing to the decentered distribution observed around the average (Figure 2).

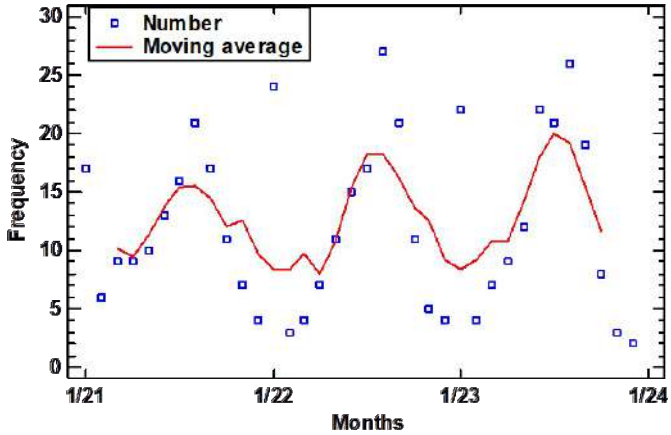

Figure 2: Smoothed Time Series Plot for Monthly Firearm Injury-Related Cases

DISCUSSION

Seasonal variation is important in healthcare, for example emergencies and medico-legal cases, because it can provide insights into the underlying factors that contribute to certain types of incidents or injuries. In the case of firearm injury-related cases, for example, seasonal variation can help to identify patterns in the timing and frequency of incidents, which can inform public health policies and interventions aimed at reducing firearm injury-related harms [15]. The present study observed that firearm injury-related cases show a potential link with seasonal variations, with higher incidences during certain months, particularly those characterized by warmer weather. Additionally, the highest incidences in January and August may be linked to the celebrations involving aerial gunshots for New Year and Independence Day celebrations, respectively. A previous study from Sindh, Pakistan reported that the primary occasions associated with aerial firing and subsequent stray bullet injuries were found to be wedding ceremonies, political rallies and New Year celebrations. Stray bullet injuries were also observed following aerial firing during cricket or hockey team victories, Pakistan Independence Day (14th August), cultural events in Sindh, and the Basant (Kite) festival in Punjab [16, 17]. When bullets from aerial firing descend and hit the ground, they can strike someone's head, spine, or other parts of the body. These injuries can range from superficial to very severe, potentially leading to fatal consequences [18]. Not only in developing countries like Pakistan, but the firearm injuries also appear to be a big challenge in developed countries with comparatively better implemented law and order. For instance, a viewpoint published in Journal of American Medical Association, a highly prestigious journal, termed the firearm-related injuries and mortality as a pandemic in United States [19]. Likewise, a study from United States found an alarming escalation in firearm injuries at five trauma centers during COVID-19, thus referring the firearm

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injuries as a parallel pandemic [20]. The present study also shows an upward trend in firearm-caused injuries with weather that exhibits monthly increase in temperature in the region. This observation has also been reported from other studies. Matthay ZA *et al.*, estimated the correlation between increased temperatures and elevated risk of firearm violence in the United States, both nationally and regionally [20]. The estimated risk of firearm incidents showed a nearly consistent increase as temperatures rose. Even moderately hot temperatures were linked to a higher risk of shootings. While the association was statistically significant, there was minimal variability between cities, suggesting that regional or climate-specific factors may influence the relationship between daily temperature and incident shootings. A research study in the United States utilized Arkansas Hospital Discharge Data spanning 10 years to identify factors predicting firearm assaults among young Black men aged 18 to 44. The analysis revealed that a significant proportion of hospital admissions due to firearm injuries occurred during the summer season [21]. Understanding the seasonal patterns of firearm injuries can inform preventive strategies, resource allocation, and emergency preparedness efforts aimed at reducing the burden of firearm-related violence and mitigating its impact on public health and safety. By analyzing the temporal distribution of firearm injury-related cases at a tertiary care teaching hospital's casualty department in Hyderabad, this study sought to contribute valuable insights into the epidemiology and dynamics of firearm violence in the region. The present study suggests a seasonal variation for firearm-related injuries being reported at emergency department of Liaquat University Hospital, Hyderabad. The incidence was higher in certain months, specifically those characterized by warmer temperatures. The observed decrease in firearm injury cases during the cooler months, from September onwards, suggests a potential seasonal decrease in incidence rates. This trend aligns with previous studies from the region, highlighting the impact of specific occasions and cultural practices, such as weddings, political rallies, and cultural festivals, on the occurrence of firearm-related injuries.

CONCLUSIONS

The firearm injuries follow a seasonal variation in the region, with higher incidences observed during certain months, particularly those characterized by warmer weather. The months of January and August emerged as periods with elevated firearm injury-related case numbers, which may be attributed to cultural and celebratory events involving aerial gunshots, such as New Year celebrations and Independence Day festivities. Firearm injuries represent a multifaceted public health issue with implications for emergency medicine, forensic science, and community well-being.

Authors Contribution

Conceptualization: MIP
Methodology: AR, NA
Formal analysis: HNA
Writing, review and editing: MIP, AS, UM, M, UW

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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Effect of Sodium Hypochlorite and Glutaraldehyde on Hardness of Calcium Sulphate Hemihydrate

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ABSTRACT

Calcium sulphate hemihydrate (CSH) is extensively used in dentistry for impressions, models, and casts due to its versatility. However, exposure to disinfectants like sodium hypochlorite and glutaraldehyde, commonly used in dental practices, can potentially alter CSH's mechanical properties. **Objective:** To measure the hardness of calcium sulphate hemihydrate cast after repeated immersion in sodium hypochlorite and glutaraldehyde solutions. **Methods:** This cross-sectional study was conducted at the Department of Prosthodontics, Institute of Dentistry LUMHS, Jamshoro and the Department of Mechanical Engineering, Institute of Mehran University of Engineering and Technology, Jamshoro. Test groups were divided into three groups i.e. Control group, Sodium hypochlorite (0.525%) and Glutaraldehyde (2%). Descriptive statistics were calculated. **Results:** Mean hardness in Group A was 8.94 ± 0.40, 8.40 ± 0.47 in Group B and 8.02 ± 0.59 in Group C. The mean hardness at the load of 10 kg in Group A, Group B and Group C was 7.01 ± 0.05, 7.31 ± 0.25, and 7.06 ± 0.04 respectively. Mean hardness at a secondary load of 60 kg in Group A, Group B and Group C was 6.95 ± 1.21, 7.48 ± 0.24 and 7.24 ± 0.05 respectively. The results showed a significant mean difference for mean hardness ($p = 0.000$), hardness at the load of 10 kg ($p = 0.000$) and hardness at the secondary load of 60 kg ($p = 0.036$). **Conclusions:** It was concluded that mean hardness was more in sodium hypochlorite group than control group and glutaraldehyde group.

INTRODUCTION

Numerous microorganisms found in saliva and blood are present in the oral environment. Some bacteria, fungi, and viruses, such as the HIV and Hepatitis-C viruses, may be fatal and incurable [1]. The bacteria may be spreading and becoming more common in the oral environment. Due to the poor state of infection control in our nation, both dental offices and dental laboratories must maintain and care for adequate infection control systems [2]. Evidence suggests that microorganisms can spread to the cast's surface from contaminated impressions, record bases, occlusion rims, and trial dentures [3]. Moslehifard E *et al.*, [4]. claim that between the time of manufacture and the distribution of a complete or removable partial denture, it may be essential to use disinfectants to clean the final cast at least seven times. The American Dental Association (ADA), the Centers for Disease Control (CDC), and other organizations have

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recommended a technique for disinfecting definitive casts that involves immersion in or spraying with a disinfectant [5]. Other methods, including adding chemicals to the gypsum while it is being mixed or using a die stone that contains a disinfectant, are said to have an impact on mechanical attributes like setting time and compressive strength along with dimensional accuracy [6]. It is crucial that the disinfectant not change the gypsum cast's physical characteristics, such as hardness [7]. When the wear process is believed to involve scratching, as in abrasive wear, hardness is used to indicate how resistant a material is to abrasion. Vickers, Knoop, Brinell, and Rockwell machines are frequently used techniques for evaluating hardness [8]. In their study of sodium hypochlorite's antimicrobial capabilities, Mansfield and White found that it reduces bacterial flow in experimental castings to zero in an hour [3]. It is widely utilized due to its accessibility and low cost [9, 10]. To ensure its effectiveness, the solution has to be produced fresh every day due to its weak stability [6-8]. According to a study, 2% glutaraldehyde is a highly effective disinfection with the fewest side effects on the cast's physical characteristics [10, 11]. Disinfection of the cast is essential to prevent cross-infection after every clinical visit but repeated disinfections might affect the physical properties of the dental cast, which in turn affects the retention, stability and dimensions of the final prosthesis [12]. This study aimed to compare the effects of two different disinfectants on the hardness of calcium sulphate hemihydrate (sodium hypochlorite and glutaraldehyde versus the control group). This study is beneficial for clinicians as well as technicians to maintain the physical strength and resistance to wear and abrasion of calcium sulphate hemihydrate for the fabrication of dental prostheses and the patients will have more stable prostheses.

METHODS

This study was conducted from April 2021 to November 2021 at the Department of Prosthodontics, Institute of Dentistry LUMHS, Jamshoro and the Department of Mechanical Engineering, Institute of MUET, Jamshoro (LUMHS/REC/-394). The sample size was calculated using an Epi tools analysis calculator. By taking the Mean 1 and variance 1 as 8.93 ± 0.73 (mean value of hardness of control group) [13] and Mean 2 and variance 2 as 8.35 ± 0.83 (mean value of hardness of sodium hypochlorite) [13] at a Confidence level of 95%, Power 80%, Ratio = 1:1, the sample size calculated was 74. It was divided into three groups. i.e. control group = 25, sodium hypochlorite = 25 and glutaraldehyde group = 25, so, the final sample size was 75. Inclusion criteria were specimen made from type-III dental stone, Specimen with immersion of test solution 1: Sodium hypochlorite and Specimen with immersion of test solution 2: Glutaraldehyde. Exclusion criteria were Specimens made of type I, and II dental plaster and Disinfectants such as Idophor, Formaldehyde, and Phenol. The data were collected from the Department of Prosthodontics, Institute of Dentistry, LUMHS, Jamshoro and the Department of Mechanical Engineering; Institute of MUET, Jamshoro. Gypsum specimens were prepared using Elite Model type III fabrications from Zhermack, Italy. By Adenosine Deaminase (ADA) Specification No. 25, hardness test samples with dimensions of 12 cm in height and 75 mm in diameter were manufactured and connected to a metal substrate. The silicone impression material was used to create the imprint materials. Dental stone was mixed with the recommended amount of powder and water in a rubber bowl, further blended by hand to achieve a smooth consistency, and then poured into the silicone mould using a mechanical vibrator (Vibromaster, BEGO, Bremen, Germany). A glass slab was then placed on top of the silicone mould to smooth out any uneven ends. The specimens (75 total, 25 per group) were permitted to set for an hour at room temperature. The cylindrical specimens were removed from the moulds after a setting period. Three groups of type III dental stones that had been prepared both before and after being disinfected with 0.525% sodium hypochlorite and 2% glutaraldehyde were used in the test group. In each group, there were 25 specimens. For their impact on the hardness of the cylindrical test specimen, three different solutions were used to prepare the disinfectant solution. Group acting as a control (using Slurry, a calcium sulphate supernatant solution in distilled water). Sodium hypochlorite (0.525%) is the first test solution. Glutaraldehyde (2%) is the second test solution. Immersion took place at room temperature for 30 minutes. The cylindrical specimens were taken out of their respective baths after immersion and left to dry for 24 hours at room temperature. Seven cycles of immersion & drying at room temperature were carried out, with the immersion bath solutions being changed after each cycle. The average number of immersions in a disinfecting solution required for the manufacture of fully and partially detachable prostheses was determined to be seven cycles. The Rockwell hardness testing device was created to gauge a substance's hardness. It has a two-stage application stainless-steel ball indenter. Stage one requires a weight loss of ten kilograms and stage two a weight loss of sixty kilograms. After being repeatedly submerged in disinfectants, the gypsum specimens of type III dental stone were placed on the Rockwell platform with the head of the instrument reduced until the indenter met the specimen's surface. At that point, a minor load was applied. The dial gauge had a reading of zero. A hardness reading was obtained after the secondary load had been applied for a minute. Thus, three sets of specimens received an aggregate of 75 readings. The SPSS version 21 program was used to enter and evaluate the data. The mean

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hardness and standard deviation (SD) of the data collected after contrasting the measurements of the specimens to the control group were calculated using descriptive statistics. For the three study groups (control group, glutaraldehyde, and sodium hypochlorite), frequency and percentage were compared. The mean hardness of the three groups was compared using a one-way ANOVA test. P values under 0.05 were regarded as significant.

RESULTS

This research aims to compare the hardness of calcium sulphate hemihydrate casts immersed repeatedly in glutaraldehyde and sodium hypochlorite solutions. The initial level of hardness in the control group was 8.64 + 0.63, the hardness of the Sodium hypochlorite (0.525%) group was 8.24 + 0.96 and the hardness of the Glutaraldehyde (2%) group was 7.96 + 0.93. The control group's findings were statistically insignificant (p = > 0.05), despite the high level of difficulty (Table 1).

Table 1: Hardness Level 1 Comparison in All Groups n=40

Study Groups	Hardness at Level 1		Mean Difference	p-value
A vs B	8.64 ± 0.63	8.24 ± 0.96	0.400	0.234
A vs C	8.64 ± 0.63	7.96 ± 0.93	0.680	0.018
B vs C	8.24 ± 0.96	7.96 ± 0.93	0.280	0.486

Group A = Control group (with Slurry, a supernatant solution of Calcium Sulphate in distilled water)
Group B = Test solution I: NaCl (0.525%)
Group C = Test solution II: Glutaraldehyde (2%)

The average hardness level at 10 kg in the control group was 7.02 + 0.51, the hardness of the Sodium hypochlorite (0.525%) group was 7.32 + 0.25 and the hardness of the Glutaraldehyde (2%) group was 7.06 + 0.48. The hardness level was high in the Sodium hypochlorite (0.525%) group, while the results were statistically insignificant (p = >0.05) (Table 2).

Table 2: Hardness Level 10 kg Comparison in All Groups n=40

Study Groups	Hardness at 10 kg		Mean Difference	p-value
A vs B	7.02 ± 0.51	7.32 ± 0.25	-0.298	0.234
A vs C	7.02 ± 0.51	7.06 ± 0.48	0.680	0.042
B vs C	7.32 ± 0.251	7.06 ± 0.48	0.280	0.257

Group A = Control group (with Slurry, a supernatant solution of Calcium Sulphate in distilled water)
Group B = Test solution I: Sodium hypochlorite (0.525%)
Group C = Test solution II: Glutaraldehyde (2%)

The average hardness level at 60 kg in the control group was 6.95 ± 1.212, the hardness of the Sodium hypochlorite (0.525%) group was 7.48 ± 0.249 and the hardness of the Glutaraldehyde (2%) group was 7.25 ± 0.053. The sodium hypochlorite (0.525%) group had a high hardness level, but the results were not statistically significant (p > 0.05) (Table 3).

Table 3: Hardness Level at 60 Comparisons in All Groups n=40

Study Groups	Hardness at 60 kg		Mean Difference	p-value
A vs B	6.95 ± 1.212	7.48 ± 0.24	0. 640	0.534
A vs C	6.95 ± 1.212	97.25 ± 0.05	0.880	0.296
B vs C	7.48 ± 0.249	37.25 ± 0.053	0.240	0.238

Group A = Control group (with Slurry, a supernatant solution of Calcium Sulphate in distilled water)
Group B = Test solution I: Sodium hypochlorite (0.525%)
Group C = Test solution II: Glutaraldehyde (2%)

DISCUSSION

There are varieties of microorganisms, fungi, and viruses that can be found in the atmosphere of a dentist practice and many of them have been connected to debilitating and life-threatening diseases [14-16]. The practice of general dentistry requires constant and direct physical interaction between the dental clinic and the dental laboratory [17]. It is possible to prevent a significant amount of the cross contamination that occurs when infectious materials are moved from the dental clinic to the dental laboratory [18]. As a result, every effort must be taken to prevent the possible spread of illness in the dental office and to stop these germs from mixing with one another. In this study, the average hardness level was high 7.32 + 0.25 in the Sodium hypochlorite (0.525%) group compared to the Glutaraldehyde (2%) group 7.06 + 0.48 and control group 7.02 + 0.51, while results were statistically insignificant. In a comparison of this study, Sanad ME *et al.*, [19] reported that the mean Hardness of group a Slurry (Group A) sample was 21.5, 0.525% sodium hypochlorite (Group B) was 15 and that of 1% Peroxygenic acid (Group C) was 21.4. Both the groups such as Slurry (Group A) and 1% Peroxygenic acid (Group C) showed same hardness. Sodium hypochlorite (Group B) showed lesser values as compared to Slurry (Group A) and Peroxygenic acid (Group C). Gypsum samples submerged in disinfectant solutions showed a decrease in hardness, which may have been caused by a chemical reaction between the disinfectant and stone. Gypsum may have reacted with this intense residual disinfectant to create decreased hardness. The mechanical strength differences between gypsum cleaned in all sorts of solutions are not of statistical significance, they added, based on the reasoning presented. On the other hand, 0.525% hypochlorite & Virkon [1% Peroxygenic acid] were examined by Moslehifard E *et al.*, [4] for their impact on the hardness of dental gypsum casts. They discovered that the reduction in hardness, which is least in the dental stones cleaned with Virkon [1% Peroxygenic acid], is caused by the development of micropores. Gypsum's compressive strength increases and the setting time lowers when 5.25% sodium hypochlorite solution is added, according to Craig RG [20] but all other physical characteristics stay the same. Because the studies mention utilizing several chemical disinfectants for spray & immersion disinfection for each

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impression and cast, immersion disinfection was employed. The full sets of parallel lines on the cast were studied using a stereo zoom microscope at a low magnification of 10, in low-angle lighting. Hardness can be measured using a micro-indenter with the Rockwell hardness scale. In one investigation, mean dimensional changes in gypsum specimens disinfected using sodium hypochlorite & glutaraldehyde were greater than those in slurry [21-24]. Gypsum products submerged in sodium hypochlorite and glutaraldehyde did not exhibit any discernible differences in dimensional change; instead, the solution's interaction with the toothstone caused the change [25-28]. In this study average hardness level at 60 kg in the control group was 6.95 ± 1.212, the hardness of the Sodium hypochlorite (0.525%) group was 7.48 ± 0.249 and the hardness of the Glutaraldehyde (2%) group was 7.25 ± 0.053. The hardness level was high in the Sodium hypochlorite (0.525%) group, while the results were statistically insignificant (p = >0.05). In a comparison of these results, Kumar RN *et al.*, [13] found that sodium hypochlorite had a worse impact on the tested properties than glutaraldehyde and chlorhexidine solutions. The hardness was measured using the Rockwell hardness test (R scale) with smaller loads of 10 kg and 60 kg. The hardness of the surface of type IV dental stone could be improved by coating its surface using cyanoacrylate resin, according to a study by Derrien G [29] that looked at the impact of cyanoacrylate on that stone's surface hardness. The current study had several limitations as a consequence, the results of the present investigation would have been impacted. In addition, these findings cannot be extended with perfect certainty to other brands of similar materials because there is a chance that even minute differences in chemical composition could result in dramatically different reactions. Skills on the part of the doctor are also necessary for the correct further manipulation of specimens.

CONCLUSIONS

It was concluded that as per the study conclusion it has been revealed the mean hardness at load of 10 kg and 60 kg was slightly more in the sodium hypochlorite group than in the control group and glutaraldehyde group. This study gives insight for clinicians as well as technicians to maintain the physical strength and resistance to wear and abrasion of calcium sulphate hemihydrate for the fabrication of dental prostheses and the patients will have more stable prostheses.

Authors Contribution

Conceptualization: IAF
Methodology: MA
Formal analysis: ABM
Writing-review and editing: MA, ABM, MA, UBS, GAB
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Knowledge, Attitude and Practice (KAP) Study on Dengue Fever among Medical Students in Dera Ismail Khan, Pakistan

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ABSTRACT

Dengue is a public health problem and a leading mosquito-borne viral disease. In Pakistan, the dengue virus has been the source of several epidemics. **Objective:** To find frequency, distribution, and association of KAP regarding dengue fever among students with gender and type of Students. **Methods:** This descriptive cross-sectional study using stratified random sampling was conducted in the Gomal Medical College (GMC). Sample size 235, an equal proportion of students from each class were randomly selected. Data were analyzed by using SPSS version 23.0. For inferential statistics, 95% CI was used. The chi-square test was used with $p < 0.05$ considered significant. **Results:** Among 235 students, 111 (47.3%), and 214 (91.1%) had good knowledge and attitude respectively. Preventive practices were as follows: 127 (54%) had good practices, 65% used mosquito repellents, and 58% used mosquito nets. There was no association of KAP with gender. Among 87 pre-clinical students, 29 (33%), 77 (89%), and 44 (51%) had good Knowledge, Attitude, And Practice (KAP) respectively. Among 148 clinical students, 82 (55%), 137 (93%), and 83 (56%) had good KAP respectively. There was an association between knowledge and Type of students at p = .002. **Conclusions:** It was concluded that 47%, 91%, and 54% of students had good KAP respectively. KAP wasn't associated with gender. The type of students was associated with knowledge while attitude and practice were not significant.

INTRODUCTION

The most common viral illness in humans spread by mosquitoes is dengue, a significant public health concern [1]. It is caused by one of the four serotypes of the dengue virus. The disease is prevalent in the tropical and subtropical regions of the world [2]. In Pakistan, the dengue virus has been the source of several epidemics. In 1982, there was the first report of dengue fever in Pakistan, affecting 12 out of 174 individuals [3]. About half of the world's population is in danger from dengue, a vector-borne viral infectious disease that is sensitive to climate change and poses a serious threat to public health in over 120 nations [4]. The first recorded incidence of dengue fever in Khyber Pakhtunkhwa was in Swat in August 2013, but the illness originally appeared in Karachi in 1994, Khyber Pakhtunkhwa topped the list of states with dengue infections in 2013, with 3177 cases reported [3]. Among these, several variables contribute to the spread of dengue fever. The rate of virus spread has risen due to changes in the environment and people moving about quickly [5]. Dengue may cause a wide range of clinical symptoms, from flu-like symptoms to serious illnesses including dengue shock syndrome and dengue haemorrhagic fever. Without appropriate care, the mortality rate from severe dengue might reach over 20% [6]. The World Health Organization (WHO) released and executed a "Global Strategy for Dengue Prevention and Control" aimed at reducing dengue fever deaths and morbidities by 2020 and determining the actual disease burden [7]. The best preventative measures for controlling dengue fever are vector control and avoiding mosquito bites, as there is currently no vaccine or

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prophylactic medication available [8]. In Pakistan, there is currently no regular vaccination available. Therefore, the cornerstone of disease prevention is the avoidance of mosquito breeding and personal protection from mosquito bites [9]. Dengue has serious detrimental effects on society and the economy, and it may significantly restrict economic growth [10]. With years of implementation experience, both developed and developing nations have faced several challenges in achieving their goals, which include encouraging their citizens to adopt healthier lifestyles [11]. The occurrence of dengue fever has significantly decreased in China thanks to strategies such as increased environmental sanitation, personal protection, national reporting system vector mosquito control, and public awareness. New technologies are also being developed for vector control [12]. For vector control programs, pesticides fall into four major classes: Organochlorines, carbamates, pyrethroids, and organophosphates [13].

The study aimed to find out what knowledge, attitudes, and behaviours undergraduate medical students had regarding dengue.

METHODS

A descriptive cross-sectional study was conducted in the Department of Community Medicine, Gomal Medical College, Dera Ismail Khan, Pakistan from Oct -2023 to Jan-2024. The project commenced after approval from the ethical review committee of the institute with Institutional Review Board (IRB) reference number 82/GJMS/JC. The confidentiality of the participants was assured. The target population was students in Gomal Medical College from 1st professional year to the final professional year. A stratified random sampling technique was used, a probability sampling technique. On the Raosoft sample size calculator, for the population of 600 with a confidence level of 95 percent, margin error of 5 percent and response rate of 50 percent the sample size was 235. Among 235 sample sizes, 5 strata were made using the proportionate strata method to give each professional year an equal chance of representation in data i.e., the strata were 41 students from 1st professional year, 46 students from 2nd year, 46 students from 3rd year, 54 students from 4th year, and 48 from the final professional year. Then for each stratum selection was done with random sampling in respective professional years. A self-made pre-coded questionnaire was constructed using literature on dengue KAP studies [2, 14]. The questionnaire consists of two sections: (1) Demographic information: Gender with two attributes (a) male, (b) female, Type of students with two attributes (a) preclinical i.e., 1st and 2nd professional years, (b) clinical i.e., 3rd, 4th, and final professional years. (2) Research variables; (a) Knowledge regarding Dengue fever, (b) Attitude towards Dengue fever and (c) Preventive Practices of Dengue. For questions of Knowledge, Attitude and Practice assessment, responses to questions were coded such that correct answers were scored 1 and incorrect answers were scored 0. The total scores for Knowledge, Attitude and Practice were 12, 5 and 5 respectively. For Knowledge, Attitude and Practice three categories were made (a) poor (< 33%), (b) fair (< 67%) and (c) good (> 67%). During the data collection time professional year students were having annual exams preparation and students were not available in college, so the questionnaire was distributed using Google Forms and its link was made available to students who were included in this study through social media app (WhatsApp). As it was easy and convenient to follow each participant response. The study was explained to the students upon receiving the questionnaire, the consent was obtained from all participants and help was provided to anyone having trouble in filling. The obtained data were analyzed using descriptive statistics (frequency, percentage) and for inferential statistics, we calculated the confidence interval for proportion at 95% using SPSS version 23.0. The chi-square test was used to determine any statistically significant association among variables. p-value = < 0.05 was considered statistically significant. All research and sociodemographic variables were described as frequency and percentages. Assessment was done by using a scoring system. For questions of Knowledge, Attitude and Practice assessment, responses to questions were coded such that correct answers were scored 1 and incorrect answers were scored 0. The total scores for Knowledge, Attitude and Practice were 12, 5 and 5 respectively. For Knowledge, Attitude and Practice three categories were made poor = having a score < 33%, fair = < 67%, good < 100.

RESULTS

This research study had 235 students in total. About 179 (76%) of the 235 students were male, and 56 (24%) were female. Pre-clinical year students made up 87 (37%) and clinical year students made up 148 (63%) of the student pool. The students' demographic features are shown in table 1.

Table 1: Demographic Characteristics of Participants

Variables	Attributes	Frequency (%)	Total
Gender	Male	179 (76%)	235
	Female	56 (24%)	
Type of Students	Preclinical years	87 (37%)	235
	Clinical years	148 (63%)	

According to data, out of 235 students, 5 (2.1%) had little information about dengue fever, 119 (50.6%) had fair knowledge, and 111 (47.3%) had good knowledge. Few students were able to correctly identify the peak dengue biting time, definitive treatment, and confirmation test. Most students have heard about dengue fever, including its

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causative agent, mode of transmission, breeding site, common symptoms, and pain management. Students' attitudes regarding dengue disease were mostly positive. Data on attitudes concerning dengue disease revealed that 1 person (0.4%) had a poor attitude, twenty participants (8.5%) had a fair attitude, and 214 participants (91.1%) had a good attitude. Students' preventive measures against dengue fever were as follows: 127 (54%) had good level practices, 75 (31.9%) had fair level practices, and 33 (14%) had poor level practices. The frequency distribution is shown in table 2.

Table 2: KAP Frequency Distribution of Students Regarding Dengue Fever with 95% Confidence Interval

Categories	Frequency (%)	95 % CI	
		Lower	Upper
Knowledge			
Poor	5 (2.1)	0.4	4.3
Fair	119 (50.6)	45.1	56.2
Good	111 (47.3)	41.7	52.8
Total	235 (100)	100	100
Attitude			
Poor	1 (0.4)	0.0	1.3
Fair	20 (8.5)	5.1	12.4
Good	214 (91.1)	87.1	94.9
Total	235 (100)	100	100
Practice			
Poor	33 (14)	9.8	19.1
Fair	75 (31.9)	26.3	37.9
Good	127 (54)	48.5	60.4
Total	235 (100)	100	100

Correct Responses to Knowledge Questions of Students Regarding Dengue Fever are shown in table 3.

Table 3: Correct Responses to Knowledge Questions of Students Regarding Dengue Fever (N=235)

Knowledge Questions	N (%)
Heard about dengue?	226 (96.2)
Causative agent of dengue fever?	180 (76.6)
Dengue mode of transmission?	217 (92.3)
Dengue mosquito breeding site?	176 (74.9)
How does dengue mosquito look like?	152 (64.7)
Peak biting time of dengue mosquito?	69 (29.4)
Common symptoms of dengue?	185 (78.7)
Incubation period of dengue?	213 (90.6)
Is there any definitive treatment for dengue fever?	112 (47.7)
Drug commonly used for pain management in dengue fever?	149 (63.4)
Vaccine of dengue	148 (63)
Confirmation test for dengue?	88 (37.4)

The knowledge distribution among the 148 male participants was as follows: 4 (2.2%) had poor level knowledge, 87 (48.6%) had fair level knowledge, and 88 (49.2%) had good level knowledge. Out of the 56 female participants, 1 (1.8%) had poor understanding about dengue disease, 32 (57.2%) had fair knowledge, and 23 (41%), had good knowledge. The stat on male attitude is as follows: 1 (0.6%) had a poor attitude, 16 (9%) had a fair level, and 62 (90.4%) had a good level. while 52 (93%) of the female participants had a good level attitude and 4 (7%), had a fair level attitude. Male participants' preventive practices showed that 28 had a poor level (15.6%), 62 had a fair level (34.6%), and 89 had a good level (49.8%). Of the female students, 38 (68%) had good preventative practices, 13 (23%) had fair practices, and 5 (9%), had poor preventive practices. Using the chi-square test, it was shown that there was no significant correlation between students' gender and their knowledge, attitudes, or preventative practices. As the p-values greater than 0.05, the values of association with Gender are shown in table 4.

Table 4: KAP Association of Dengue Fever with Gender

Gender	Knowledge			Total	Pearson Chi-square		
	Poor	Fair	Good		Value	df	p-value
Male	4	87	88	179	1.245	2	0.536
Female	1	32	23	56			
Total	5	119	111	235			
Attitude							
Male	1	16	162	179	0.500	2	0.779
Female	0	4	52	56			
Total	1	20	214	235			
Practice							
Male	28	62	89	179	5.709	2	0.058
Female	5	13	38	56			
Total	33	75	127	235			

Data showed Among 87 preclinical years participants the knowledge distribution was as follows, 1 (1%) with poor level knowledge, 57 66%) with fair level knowledge and 29 (33%) with good level knowledge of dengue fever. While among 148 clinical years' students 4 (3%) with poor level knowledge, 62 (42%) with fair level knowledge and 82 (55%) with good level knowledge on dengue fever. On applying chi-square test there was significant association between knowledge on dengue fever with Type of students with p = 0.002. Attitude among 87 preclinical year students 10 (11%) with fair level attitude while 77 (89%) with good level attitude. Among 148 clinical year students 1 (0.7%) with poor level attitude, 10 (6.3%) with fair level attitude and 137 (93%) with good level attitude. Among 87 preclinical year students, 14 (16%) with poor level practices, 29 (33%) with fair level practices and 44 (51%) with good level preventive practices. While in clinical years out of 148, 19 (13%) with poor level practices, 46 (31%) with fair level practices and 83 (56%) with good level practices. On applying the chi-square test there was no significant association between the Attitude and preventive practices of students with Type of students with p-values greater than 0.05. the values of association with type of Students are given in table 5.

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Table 5: KAP Association of Dengue Fever with Type of Students

Gender	Knowledge			Total	Pearson Chi-square		
	Poor	Fair	Good		Value	df	p-value
Pre-clinical	1	57	29	87	1.312	2	0.002
Clinical	4	62	82	148			
Total	5	119	111	235			
Attitude							
Pre-clinical	0	10	77	87	2.132	2	0.344
Clinical	1	10	137	148			
Total	1	20	214	235			
Practice							
Pre-clinical	14	29	44	87	0.808	2	0.668
Clinical	19	46	83	148			
Total	33	75	127	235			

DISCUSSION

This research study was carried out in a medical college in Dera Ismail Khan, Pakistan, to find out the knowledge, attitudes, and behaviours of undergraduate medical students regarding dengue, as the dengue is most common viral illness in humans spread by mosquitoes, a significant public health concern. The majority of participants were males (76%) in this research study which is somewhat different from KAP-based research on dengue fever among local people of Karachi, Pakistan by Ali *et al.*, 2023 [15]. However, it aligns with the KAP study of Zohra *et al.*, 2024 in the Malakand region, Pakistan in which male participants were predominant [16]. Although Dengue fever is prevalent in Pakistan, we discovered in our study that only 47 % of students have a good level of knowledge about dengue which is likely due to a lack of awareness programs, seminars should be arranged to address the issue which is slightly less than the previous study by Saghir *et al.*, 2022 [17]. The majority of students have heard about dengue fever, its causative agent, its mode of transmission of dengue, its breeding site, common symptoms of dengue fever, and pain management in dengue fever, and few students were able to correctly identify the peak biting time of dengue, about confirmation test and any definitive treatment for dengue [18]. The majority of the students obtained a high attitude percentage about 91% had a good attitude in our study as the participants knew the importance of dengue as a public health-related issue and should be controlled which was somewhat like KAP based study of Phuyal *et al.*, 2022 [19]. The practice frequency distribution was also not that much high than the previous KAP studies on dengue only 54% of students have good practice toward the prevention of dengue fever as proper awareness and appropriate preventive methods are prime in controlling dengue limited resources and personal habits can be the reason for low preventive practices which was somewhat like the previous study of Qureshi *et al.*, [20]. The preventive practices of students' responses show that about 65% of students use mosquito repellents, 75% of students keep windows and doors closed to avoid mosquito biting, about 58% of students use mosquito nets and 76% use full sleeves clothes to avoid dengue biting [21]. Our study results showed that the students have a relatively better attitude than their knowledge and practices which is according to a study of Rahman *et al.*, 2022 [22]. As limited resources and personal habits and lack of community involvement in dengue control may change the outcome of preventive practices, excellent practices did not always follow from excellent information [23]. A comparison of the participants' gender did not yield any apparent variation in their level of knowledge of dengue. Both males and females have the same understanding of dengue fever, like Alvarado-Castro VM *et al.*, 2024., [24]. Most students in our study had a positive outlook in their attitude toward Dengue fever with no significant correlation with gender both males and females had good levels of attitude towards dengue fever as dengue is a public health-related issue and should be controlled like in Saghir *et al.*, 2022 [17]. Male and female research participants did not differ in their approaches to dengue prevention. Similar results were shown in the previous study by Banik *et al.*, 2020, which found that gender had little impact on dengue prevention behaviours this can be due to social behaviours and personal habits [25]. Although there was an association of knowledge with type of students with (p-value = .002) with clinical years having good knowledge on dengue this can be due to their wards rotation to hospitals where they get enough exposure regarding public related health issues. There was no association between the attitude and practice of students with the type of students in our study. Both preclinical and clinical years students have almost the same attitude and practice in our KAP study on dengue fever among students.

CONCLUSIONS

It was concluded that dengue fever among medical students 47% had a good level of knowledge of dengue, 91% with a good level of attitude towards dengue and 54% with a good level of preventive practices. There was no association of Knowledge, attitude and practice with gender. By checking the association of knowledge with the Type of students, the clinical years' students had good knowledge while attitude and practice were not statistically significant.

Authors Contribution

Conceptualization: NA, MO
Methodology: NA, AI, FUR, MJ
Formal analysis: NA, FUR, MK, MJ
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Original Article

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Correlation between the Predictive Accuracy of Computed Tomography Severity Index and Clinical Metrics in Acute Pancreatitis at a Tertiary Care Hospital Lahore

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ABSTRACT

Acute pancreatitis was a common clinical emergency and presents with a vast spectrum of severity and clinical outcomes. The Computed Tomography Severity Index (CTSI) was widely used to evaluate extent of pancreatic inflammation and necrosis. **Objective:** To compare the CTSI with the clinical severity of acute Pancreatitis in local settings. **Methods:** It was a retrospective cohort study done on 136 cases diagnosed with acute pancreatitis between 2017 to 2023 at Lahore General Hospital, Lahore, Pakistan. Patients received contrast-based Computed Tomography (CT) within 30 days of onset. CTSI scores were independently assessed by two experienced radiologists. Clinical severity was categorized as mild, moderate and severe pancreatitis. Statistical analysis was done with SPSS 26.0 which involved descriptive, correlational statistics, sensitivity and specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), predictive Accuracy along with ROC curve analysis and Cohen's kappa statistic. **Results:** The patients were 74.3% males and had a median age of 51 years. CTSI demonstrated 79.37% sensitivity, 83.56% specificity, 80.65% PPV and 82.43% NPV in determining clinical severity as mild, moderate and severe with a predictive accuracy of 81.62%. Cohen's kappa of 0.72 reflected substantial agreements between the CTSI and clinical severity assessment. Under the ROC Curve (AUC) the area was 0.87, showing an excellent diagnostic performance. **Conclusions:** CTSI provides a moderate to fair agreement with clinical severity assessments in acute pancreatitis. It effectively differentiates between mild, moderate and severe cases, supporting its assessment and management.

INTRODUCTION

Acute pancreatitis is an acute development of pancreatic inflammation, with clinical symptoms ranging from mild to severe discomfort, and fatal complications including systemic inflammatory response syndrome and multi-organ failure [1-5]. Timely and correct assessment is crucial for guiding therapeutic decisions. Various clinical scoring systems, including the modified Atlanta classification and the Sequential Organ Failure Assessment (SOFA) score, are utilized in stratifying cases into mild, moderately severe, and acute severe pancreatitis categories based on factors like organ failure and local complications [6]. There are several radiological tests and scoring systems that can be used to access the severity of the disease to guide management and outcome. Among the most commonly used tests are computed tomography, magnetic resonance imaging, and ultrasound, and scoring

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systems include Ranson, Acute Physiology and Chronic Health Evaluation II and Bedside Index for Severity in acute pancreatitis scores. Computed tomography is considered the gold standard due to its high sensitivity and specificity, while magnetic resonance imaging and ultrasound can provide additional information. Scoring systems utilize clinical and laboratory parameters to classify patients into mild, moderate, or severe disease [7]. Computed Tomography (CT) imaging, particularly CTSI is essential for diagnosis and managing acute pancreatitis [8]. It gives insight about possible complications and outcome of acute pancreatitis [9]. Studies show the importance of CTSI corresponding clinical severity scores for better patient management [10]. In a recent study CTSI and Modified CTSI (MCTSI) were compared with clinical severity scores and it was concluded that higher the score the poor the prognosis and vice versa [9]. In another study, concluded that CTSI is a wonderful tool for predicting disease severity and prognosis of acute pancreatitis [11]. Similarly, in another retrospective study, Cucuteanu B et al., found that the CTSI and modified CTSI scores highly correlated positively with the severity of pancreatitis showing a 97.0% sensitivity and 95.0% specificity with Under the Curve (AUC) area of 0.969 [12]. Despite CTSI vast usage, its correlation with 1clinical severity scores like the modified Atlanta classification and SOFA score has not been comprehensively assessed across different clinical settings, particularly in tertiary care centres in various geographic regions [13].

This study aimed to address this issue by comparing CTSI with clinical severity assessments in a tertiary care facility, analysing 136 patients with acute pancreatitis who underwent contrast-enhanced CT within 30 days of clinical onset [14]. CT scan and clinical assessment improve the treatment plan of acute pancreatitis [15]. Our study objective was to compare the CTSI with the clinical severity of acute Pancreatitis in local settings.

METHODS

This retrospective study was carried out at Lahore General Hospital - Lahore from 1st July 2017 to 30th June 2023 to investigate the correlation between CTSI and acute pancreatitis clinical severity [16] under the principles outlined in the Declaration of Helsinki [17] after getting ethical approval vide letter No AMC/PGMI/LGH/article/Research No/047/2024. 136 patients who had acute pancreatitis and had contrast enhanced CT abdomen within one month of symptoms were included in this study from the hospital medical file records by using prevalence of Acute Pancreatitis as 10.90% at 5% margin of error and 95% confidence level using following formula:

$$n = \frac{Z^2 - \frac{a}{2} p\,(1 - p)}{d^2}$$

Hospital departmental permission was taken for all patients' record inclusion before enrolment [18]. Patients with incomplete clinical or CT record were excluded from the study. Patient demographic details, signs and symptoms, etiology and clinical outcome were recorded on a predesigned proforma. Two experienced radiologists then independently analysed the available CT images of the patients and calculated CTSI. The CTSI had 10 point in total score by assigning 0 to 4 points to pancreatic inflammation and 0 to 6 points for necrosis. The severity of pancreatitis was graded as mild (0-3 points), moderate (4-6 points) and severe (7-10 points) [19]. Where there was a discrepancy in the scoring between the two radiologists, a uniform consensus review was conducted to reach single conclusion to ensure accuracy and reliability of the radiological analysis. The clinical severity of pancreatitis for each patient was calculated as mild, moderate and severe disease. Mild was labelled on the basis of pancreatitis in the absence of organ failure and local or systemic complications. Moderate as pancreatitis with the presence of transient organ failure or local or systemic complications and severe on the basis of pancreatitis with persistent organ failure. Then 2x2 contingency table was made and all true positive and negative and false positive and negative cases of acute pancreatitis were entered. Sensitivity, specificity PPV, NPV and predictive accuracy were calculated to see the diagnostic performance of CTSI in identifying mild, moderate, severe cases of acute pancreatitis. The data were analysed by using SPSS 26.0. The demographic and clinical characteristics of the patients were summarized as descriptive statistics. Cohen's kappa statistic was used to quantify level of agreement between clinical severity and CTSI. ROC curve was analysed to determine the predictive value of CTSI in determining clinical severity, and AUC area was calculated to determine the accuracy of CTSI.

RESULTS

Out of 136, 101 (74.3%) were males and 35(25.7%) were females. The median age of the patients was 51.0 years. Biliary cause (69.1%) was the most common etiology identified. It was followed by metabolic cause (14%), pancreatic neoplasm (6.6%), mutation in cationic trypsinogen gene, serine protease 1 (PRSS1) (5.9%), drugs (2.2%), alcohol (1.5%) and pancreatic divisum (0.7%). There were 119 (87.5%) patients with non-necrotic pancreatits, 15 (11%) with necrotic pancreatitis and 2 (1.5%) as nonspecific presentation. There were 44 (32.4%) patients with fluid in peri-pancreatic area.110 were of acute pancreatitis (80.9%) and 2 (1.5%) were acute on chronic cases. CTSI calculated showed 48 (35.2%) were normal, 64 (47.0%) mild, 16 (11.8%) moderate and 8 (5.9%) severe pancreatitis cases as shown in table 1.

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Table 1: Demographics of Categorical Variables

Metrics	Category	Frequency (%)	p-Value
Gender	Male	101 (74.3%)	0.118
	Female	35 (25.7%)	
	Total	136 (100%)	
Etiology	Alcohol	2 (1.5%)	0.135
	Biliary	94 (69.1%)	
	Divisum	1 (0.7%)	
	Drugs	3 (2.2%)	
	Genetic	8 (5.9%)	
	Metabolic	19 (14%)	
	Pancreatic Neoplasm	9 (6.6%)	
	Total	136 (100%)	
Necrotic or Non-Necrotic	Non-Necrotic	119 (87.5%)	0.042
	Necrotic	15 (11%)	
	Unspecified	2 (1.5%)	
	Total	136 (100%)	
Fluid	Absent	92 (67.6%)	0.076
	Present	44 (32.4%)	
	Total	136 (100%)	
Acute or Chronic or Acute on Chronic	Chronic	24 (17.6%)	0.009
	Acute	110 (80.9%)	
	Acute on Chronic	2 (1.5%)	
	Total	136 (100%)	
CTSI	Normal	48 (35.2%)	0.014
	Mild	64 (47%)	
	Moderate	16 (11.8%)	
	Severe	8 (5.9%)	
	Total	136 (100%)	

The ROC curve analysis showed an AUC of 0.87, concluding good predictive value of CTSI for clinical severity. The sensitivity and specificity of the CTSI were 79.37% and 83.56%, respectively; the PPV and NPV were 80.65% and 82.43% respectively with a predictive accuracy of 81.62% suggesting moderate diagnostic performance. Cohen's kappa of 0.72 reflected substantial agreements between the CTSI and clinical severity assessment (Table 2).

Table 2: Predictive Accuracy of Computed Tomography Severity Index in Acute Pancreatitis

Clinical Findings	CTSI Findings N (%)		
	Positive	Negative	Total
Positive	50	12	62
Negative	13	61	74
Total	63	73	136
Sensitivity	79.37%		
Specificity	83.56%		
Positive Predictive Value	80.65%		
Negative Predictive Value	82.43%		
Predictive Accuracy	81.62%		
Under The Curve Area (AUC)	0.87%		
Cohen's Kappa	0.72%		

The ROC curve showed good sensitivity (Y axis) versus specificity (X-axis) for different thresholds with Under the Curve (AUC) area of 0.87, depicting good predictive value of CTSI. The blue line showed CTSI performance, while grey dotted line was reference line with under the curve area (AUC =0.87). The curve indicates that CTSI can reliably tell acute pancreatitis severity level (Figure 1).

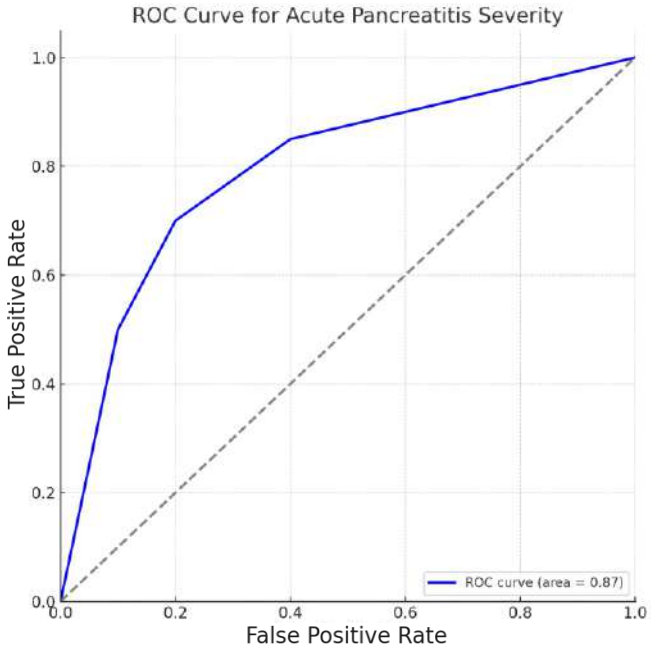

Figure 1: Receiver Operating Characteristic (ROC) Curve with AUC

DISCUSSION

In this study CTSI showed a moderate to fair agreement of clinical severity and prognosis of acute pancreatitis. The calculated sensitivity and specificity further endorsed its good performance. This has been in consistent with the study conducted by Tahir H *et al* [20]. Mathai MJ and colleagues in their study on 150 acute pancreatitis patients concluded high level of accuracy of the CTSI in predicting complications and clinical outcomes [21]. Parmar G *et al.*, in their prospective 80 patients study concluded that CTSI and modified CTSI were better predictors of severity, clinical outcome and mortality compared with Ranson's criteria, with modified CTSI being more accurate and better predictor than CTSI [22]. Olpin JD *et al.*, in their study concluded significant correlation between necrotic and non-necrotic acute pancreatitis for disease severity and prognosis as we saw in our study [23]. Balthazar JA *et al.*, in their study concluded that pancreatic necrosis affects the clinical outcome of acute pancreatitis as we found in our study [24]. Jiang X *et al.*, found similar results as our chi-square test results that further endorsed the importance of CTSI [25]. Cho IR and colleagues in their study on 103 patients of acute pancreatitis found out that CTSI (0.851, p<0.001) was useful predictor in 42(40.8%) patients of early mild acute pancreatitis only however our study didn't find variations in CTSI score across various severity groups [26]. This discrepancy is also noted by Kim K and colleagues in their study that CTSI was only capable to

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identify mild acute pancreatitis [27]. Yang Q *et al* in their study Based on the multivariate logistic regression analysis showed that CTSI ≥4 (OR,12.942;95% CI,7.267–23.049, p < 0.001) were identified as independent risk factors for severe acute pancreatitis [28]. Zhang *et al.*, in their study on 683 recurrent acute pancreatitis(RAP) and 1,829 acute pancreatitis(AP) patients found out that the most common etiologies were hypertriglyceridemia and cholelithiasis, respectively. The RAP group had lower extrapancreatic inflammation on CT scores and Acute Physiology and Chronic Health Evaluation II scores than the AP group in the early stage (both P<0.001). The RAP group had higher CTSI scores than the AP group in the late stage (P=0.022). [29]. Yamamoto *et al* in their study on 1097 patients found that the AUC of the CTSI for mortality was 0.65 (95 % confidence interval [CI:] [0.59–0.70]; p < 0.001) making CTSI better predictor [30]. Gupta P and colleagues also found CTSI importance for acute pancreatitis severity and prognosis as ours. They emphasized that it should be used along with clinical severity scores for a better management [31].

CONCLUSIONS

It was concluded that CTSI accurately correlates with clinical severity in acute pancreatitis. It effectively differentiates between mild, moderate and severe cases, supporting its assessment and management. Hence suggested CTSI should be included in the standard assessment protocols for early recognition of high-risk patients. However large sample size studies were required to refine the CTSI in its implementation in various clinical settings.

Authors Contribution

Conceptualization: FS, JM, SS, AZT, AAM, MD, AAM, MD, SR, IUH, GUNT

Methodology: FS, JM, SS, AZT, AAM, MD, AAM, MD, SR, IUH, GUNT

Formal analysis: FS, JM, SS, AZT, AAM, MD, AAM, MD, SR, IUH, GUNT

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

Conflicts of Interest

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Original Article

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Diagnostic Significance and Association of Reticulin Fibrosis in Benign Hematologic Disorders

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ABSTRACT

Reticulin fibrosis is a feature of benign illnesses. Reticulin staining is used to identify benign hematological abnormalities in bone marrow, with trichrome staining being the most appropriate procedure for histological examinations. **Objective:** To assess the association of reticulin fibrosis to benign hematological disorders. **Methods:** Patients with benign hematologic illnesses such as iron deficiency anemia, megaloblastic anemia, aplastic anemia, and immune thrombocytopenic purpura at department of hematology, Sheikh Zayed Medical Complex, Lahore were included. The sample size was 96 cases, with 24 cases for each disorder. Bone marrow samples were taken from the anterior iliac spine of patients diagnosed with benign hematologic diseases. The reticulin fibers were graded using the Thiele grading scale. **Results:** The gender distribution was significant, with ITP and IDA being higher in females, whereas MA was more prevalent in men. The age distribution was almost the same, with ITP the lowest mean age was 40.5 years, while the highest mean age was 46.7 years in cases with aplastic anemia. Reticulin stain results showed significant differences among the four groups, with all cases in MA, IDA, and AA having grade-0 results. **Conclusions:** The reticulin stain can distinguish between ITP and other hematological illnesses, as well as grade reticulosis in bone marrow biopsies, making it a helpful tool for detecting benign hematological disorders.

INTRODUCTION

The hematopoietic system consists of organs and tissues where hematopoietic cells grow, mature, and remove. The extracellular matrix primarily is made of calcium phosphate and mineral salts, and cells make up the bone marrow. Bony cells consist of osteoblasts, osteoclasts, and osteocytes [1]. Both organic and inorganic elements, such as calcium and phosphorus, magnesium, and carbonate, make up the bone marrow matrix. Calcium and phosphorus occupy bony space in the form of hydroxyapatite crystals, along with collagen fibers. Collagen, reticular, and amorphous ground material constitute the organic part of the bone marrow matrix [2]. Whereas reticular cells provide a framework to support hematopoietic cells, sinusoidal endothelial cells serve as specific barriers for extravascular and vascular areas [3]. Reticulin fibrosis is a feature of several benign illnesses, such as megaloblastic, iron deficiency, and folate deficiency anemias, which are classified as acquired disorders. Disorders such as hemoglobinopathies, thalassemia, sickle cell anemia, autoimmune hemolytic anemia, and bleeding disorders can manifest as reticulosis [4]. Throughout the world, Iron Deficiency Anemia (IDA) is a prevalent kind of nutritional anemia. Diagnosis of IDA involves many physiological and biochemical features of red cells, including blood ferritin levels, MCV, serum iron level, transferrin saturation, and hypochromic features [5-7]. Retic cells, the youngest form of erythrocytes, are used

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to project iron status. Hemoglobin content in reticulocytes is crucial for diagnosing IDA. Immature cells typically have two dots of reticulin fibers, while a greater number of reticulin dots are seen in more immature forms [8]. According to a new study, reticulocyte hemoglobin equivalent is crucial for IDA diagnosis and may serve as a useful biomarker for diagnosing iron deficiency and IDA [9]. Megaloblastic Anemia (MA) is a condition characterized by the absence of essential micronutrients like vitamin B12 and folate, which affect the maturation process of erythrocytes in the bone marrow. This results in the formation of large RBCs with an asynchrony between cytoplasm and nucleus, which during the processes of maturation and proliferation interacts with DNA synthesis [10]. All myeloid cell lines cause the bone marrow to develop into hypercellular, with erythroid components taking precedence. These erythroid blasts show oval-shaped, massive features with a lacy nucleus and immaturity, which are regarded as suspicious to folate and/or vitamin B12 insufficiency [11]. Ovoid red blood cells with an MCV greater than 115 are indicative of a nutritional shortage, which is thought to be caused by low folic acid and vitamin B12 levels in MA [12, 13]. Usually, megaloblastic bone marrow is related to anemia because of inefficient erythropoiesis [14]. Aplastic anemia is a rare bleeding disorder where the lymphatic system lacks cell lines, leading to uncontrolled bleeding and infections. The autoimmune disorder attacking bone marrow stem cells is the main cause, but other factors like chemotherapy, radiation treatments, exposure to toxins, viral infections, pregnancy, and certain drugs can also affect cell line production [15]. Diagnosis involves physical examination, baseline investigation, radiograms, and bone marrow analysis. The interpretation of a bone marrow biopsy is dependent upon cellularity, myeloid series proportions, megakaryocytic and erythrocyte cell lines, bone constituents, and reticulin [16]. Immune thrombocytopenia, is an autoimmune bleeding disorder, caused by antibodies against platelet antigens, leading to the destruction of platelets [17]. The main reason for ITP is the binding of glycoproteins to IgG antibodies. ITP can happen for no apparent reason or as a result of comorbid illnesses like autoimmune diseases, whereas autoimmune disorders can develop as a result of genetic predisposition and environmental triggers. Numerous microorganisms, such as bacteria, viruses, and parasites, are linked to autoimmune diseases [18]. Although the pathophysiology of ITP is not well understood, it is thought to be a dysregulation of the immune response, with T-cells controlling plasma cells during antibody-mediated destruction, which is triggered by B-cell autoreactive clones [19]. They produce IgG auto-antibodies, which attach to platelet glycoproteins on their surface and transport them to the reticuloendothelial system for lysis. Another independent multidirectional mode causing ITP is impaired platelet formation [20, 21]. Regarding the staining process, the hematoxylin and eosin (H and E) staining process is a standard procedure used in all histopathology labs worldwide. On the other hand, reticulin fibers, which branch out from fine textiles, can be difficult to see in H and E preparations. The most appropriate procedure for histological examinations of bone marrow is pre-sensitization with potassium permanganate (PH of 9.0), which allows for the accurate visualization of these fibers [22]. Moreover, regarding the cellularity of bone marrow, the state depends on underlying conditions and is determined by bone marrow biopsy and aspirate, which are utilized for the definitive detection of pancytopenia and other hematological problems [22, 23]. Reticulin stain analysis must be done in accordance with recognised guidelines in order to meet the goal of our study. With respect to reticulin fibrosis, this is detected by trichrome staining [24].

Thus the goal of the current study was to use reticulin stains to identify different benign hematological abnormalities in bone marrow, as they vary by geography and ethnicity. This study must be a significant contribution to the body of literature as it will also offer enough details about the applicability of this method in Pakistan.

METHODS

The cross-sectional study included patients of IDA, MA, iron transfusion polymorphism (ITP), and AA from Sheikh Zayed Medical Complex Lahore from 20 July 2022 to 20 December 2022. The research was approved by the Institutional Review and Research Advisory Board (IRB ID: SZMC/IRB/Internal/87-B/2022) of Sheikh Zayed Postgraduate Institute. The patients' consent was obtained before to the study. Adopting a conservative approach, we estimated a sample size of 96 patients (24 instances for each disease category) using a 95% confidence level and a 10% margin of error. We also included in the predicted incidence of fibrosis Grade-1 (22%). A convenient sampling strategy was employed. There were a total of 144 patients in the research, with 24 instances each representing four distinct hematological disorders: Iron Deficiency Anemia (IDA), Megaloblastic Anemia (MA), Aplastic Anemia (AA), and iron transfusion polymorphism (ITP). The inclusion criteria included male and female adults, who were patients with iron deficiency anemia, megaloblastic anemia, oraplasticanemia. Patients with malignant hematologic disorders and individuals undergoing chemotherapy for any malignant disease were excluded. Using a laboratory sample collection approach, the study gathered data on 96 patients with benign hematologic illnesses (IDA, MA, ITP, and AA). Using a trephine Jamshidi needle, bone marrow samples were taken from the anterior iliac spine of individuals who had been diagnosed with benign hematologic diseases. The

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biopsies were processed in the histology department after being fixed in 10% neutral-buffered formalin. Every slide was stained with reticulin, and then deparafinization, oxidation, bleaching, ferric chloride treatment, and drying were carried out. Using low, medium, and high power, the dyed slides were examined under a microscope. Numerous reticulin fiber-related observations were noted, including their quantity, density, thickness, and ratio to normal haemopoietic tissues. The reticulin fibers were graded using the Thiele grading scale, with grades ranging from 0 to 3 (there is an enormous network of reticulin fibers that are densely and diffusely increased, and there is also localized and severe osteosclerosis). The study assessed the prognostic value of reticulin fibrosis grades in benign hematological disorders. The data were analyzed by using SPSS version 25.0. Quantitative variables were provided as mean and standard deviation, whilst qualitative variables showed up as frequency and percentage.Chi-square tests were used to assess the association of hematological disorders among four group to reticulin grades, where p-value below 0.05 was considered significant.

RESULTS

There were 43 (44.8%) males and 53 (55.2%) females among all cases(figure 1).

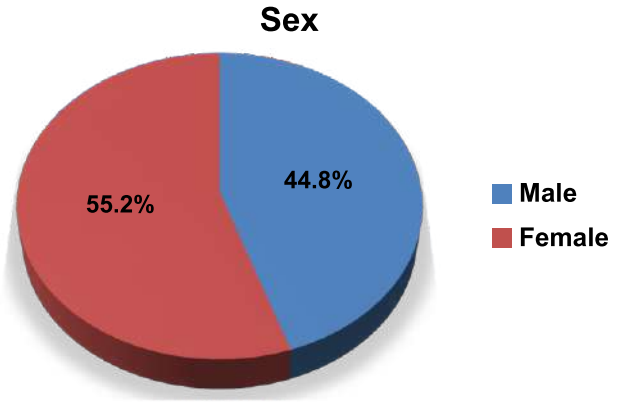

Figure 1: Gender Distribution of all Cases

Among the four categories, there was a statistically significant difference in the distribution of genders (p = 0.008). Males were more likely to have the MA, but females had much greater rates of IDA and ITP. Aplastic anemia patients were evenly distributed by gender(Table 1).

Table 1: Gender distribution of cases for four different hematological disorders(n=96)

Disorder	Gender		Chi-Square	p-Value
	Male Frequency (%)	Female Frequency (%)		
Iron Deficiency Anemia	8 (33.3%)	16 (66.7%)	11.92	0.008
Megaloblastic Anemia	17 (70.8%)	7 (29.2%)		
Aplastic Anemia	12 (50%)	12 (50%)		
ITP	6 (25%)	18 (25%)		

All four categories had similar case age distributions. Everyone in the groups is around the same age. Despite the fact that Aplastic anemia had a higher average age of 46.7 years and ITP the lowest at 40.5 years, the difference was not statistically significant (p = 0.707)(Table 2).

Table 2: Age Distribution of Cases with Four Different Disorders

Disorder	Age Mean ± SD
Iron Deficiency Anemia	42.3 ± 16.5
Megaloblastic Anemia	43.6 ± 19.3
Aplastic Anemia	46.7 ± 19.8
ITP	40.5 ± 19.3

The results of the reticulin stain were collected for four groups, and it was noted that there were substantial differences in the findings among the four groups (p-value <0.001). A total of 12 cases (50.0% of the total) in ITP had a grade of 0, 11 cases (45.8% of the total) had a grade of 1, and 1 case (4.2%) had a grade of 2. All cases in IDA, MA, and AA had a grade of 0 (Table 3).

Table 3: Diagnostic Finding on Reticulin Stain for Benign Hematological Disorders

Disorder	Bone Marrow Biopsy Finding on Reticulin Stain				
	Grade-0 N (%)	Grade-1 N (%)	Grade-2 N (%)	Likelihood Ratio	p-Value
Iron Deficiency Anemia	24 (100%)	0 (0%)	0 (0%)	39.07	<0.001
Megaloblastic Anemia	24 (100%)	0 (0%)	0 (0%)		
Aplastic Anemia	24 (100%)	0 (0%)	0 (0%)		
ITP	12 (50%)	11 (45.8%)	1 (4.2%)		

DISCUSSION

Megaloblastic anemia was more common in males and iron deficiency anemia and immune thrombocytopenia in women, according to our study's results, which showed a statistically significant difference in gender distribution across the four groups (p-value = 0.008). The present study's most important discovery included an examination of four hematological illnesses and the predictive usefulness of reticulin fibrosis grades. With a p-value less than 0.001, the findings of the reticulin stain were substantially different across the four groups. Twelve patients (or 50%) had grade-0 reticulin stain in ITP, eleven cases (or 45.8%) had grade-1, and one case (or 4.2% of the total) had grade-2. Not a single instance in IDA, MA, or AA had a grade. In contrast, 61.8% of patients with more than 5% sideroblasts were determined to have IDA in a different research that employed reticulin stain in a bone marrow inquiry. Nevertheless, class 0, 1, 2, and 3 were detected in 14.54%, 63.63%, 14.54%, and 7.27% of the patients, respectively [26]. Eighteen percent of the patients in this research had high-grade alterations, whereas the remaining patients had low-grade changes. This study also showed a correlation between anemia and higher lactate dehydrogenase levels and high-grade alterations with ITP. More intriguingly, the IPSS distinct risk categories and the correlation between the RCO score and mortality were found to be significant (p=0.013). The Ing-rank test demonstrated that the probability of survival could be

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distinguished between high and low-grade patients. The current research's findings are equivalent to those of this study with regard to ITP, but not with regard to MA, AA, or IDA. The same criteria and measures employed in this investigation were also utilized by Ern *et al.*, to distinguish between bone marrow fibrosis and non-fibrosis in thrombocytopenia patients, and no statistically significant difference was found in any of the parameters [24-26]. When interpreting the results, it is important to keep in mind that our study had several limitations. Firstly, the sample size was small, so our findings may not be applicable to a larger population. Secondly, we couldn't establish causal relationships between the variables because our study was cross-sectional. Lastly, we didn't control for potential confounding factors like lifestyle and genetics that could influence the development of hematologic disorders.

CONCLUSIONS

Reticulin stain is useful for diagnosing ITP since it can distinguish ITP from other hematological illnesses and detect reticulosis grades in bone marrow biopsies, according to the study's findings. Prospects of the current study include the correlation between the reticulin score and mortality, the classification of risk groups based on IPSS, and the chance of survival concerning the reticulin score.

Authors Contribution

Conceptualization: YS
Methodology: RC, UW, YS, AH
Formal analysis: QAA
Writing, review and editing: AH, UW, RC, SH

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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Investigating the Association between Maternal Iron Supplementation and Neonatal Jaundice

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ABSTRACT

Neonatal hyperbilirubinemia, being the most common cause of admission in the neonatal period, remains a global burden, especially in low- and middle-income nations. Addressing the mother's risk factors for neonatal jaundice was crucial for delivering better neonatal healthcare. One possible risk factor for neonatal hyperbilirubinemia is maternal iron supplementation. **Objective:** To analyze the effect of maternal iron supplementation as a risk factor for neonatal hyperbilirubinemia. **Methods:** In this prospective cohort study, using convenience sampling women with prenatal appointments during the first trimester of their pregnancies were evaluated and placed on therapeutic and prophylactic iron supplementation. Women were grouped on basis of serum ferritin level. Injectable Iron were given to women not improving with oral iron. The primary outcome was proportion of neonates developing hyperbilirubinemia during the first week of life. Data analysis was done using SPSS version 23.0. Normality of the data was checked by Shapiro-Wilk test. Chi-squared test was applied to compare variables between groups. Regression analysis was conducted to find the association between maternal iron supplementation and neonatal hyperbilirubinemia. **Results:** A sample of 176 mothers participated in the study. The overall frequency of newborn hyperbilirubinemia was 50.6%. The odds of having hyperbilirubinemia were 5.5 times higher with injectable iron. (aOR 5.5 95%CI:1.36-22.33). **Conclusion:** The outcome highlighted the potential connection between the iron supplementation of the mother during pregnancy and the development of neonatal jaundice suggesting the need to exercise early intervention in pregnant mothers who were at high risk of newborn jaundice.

INTRODUCTION

Neonatal hyperbilirubinemia (or neonatal jaundice) is a common condition that carries the risk of severe and life-threatening complications [1]. It is the most common cause of hospitalization in the neonatal period and affects up to 60% of neonates born at term [2, 3]. Although usually benign, hyperbilirubinemia results in significant neonatal morbidity and mortality, especially in low-income and middle-income countries [4, 5]. In Pakistan, the reported frequency of neonatal hyperbilirubinemia varies considerably and large-scale population-based studies are lacking. The latest available estimate comes from a population-based prospective study that reported a prevalence of 27.6% [6]. Maternal anemia, especially iron-deficiency anemia, is a significant concern in developing countries, including Pakistan, where it affects around 40-75% of women of reproductive age [7]. It is associated with several adverse neonatal outcomes, such as preterm birth, low birth weight, and perinatal mortality [8]. To decrease the risk of maternal anemia, the WHO recommends daily iron supplementation (30-60 mg of elemental iron) in pregnant women [9]. However, excessive iron supplementation can result in iron overload, which may negatively affect neonatal outcomes [10, 11]. Study have shown that higher iron intake in mothers can lead to increased incidence of neonatal jaundice [12]. Various risk factors for neonatal hyperbilirubinemia have been reported

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in the literature, including certain genetic diseases, inborn errors of metabolism, maternal diabetes, family history of jaundice, mode of delivery, delayed cord clamping, infections, sepsis, and prematurity [2, 13]. More recently, maternal iron supplementation has emerged as a potential risk factor for neonatal hyperbilirubinemia [14]. Recent studies have revealed associations between maternal and fetal hemogram aberrant maternal blood parameter levels as an indicators of newborn jaundice but the links and mechanism between maternal iron supplementation and neonatal jaundice is still poorly understood [15, 16]. Furthermore, research data supports the notion that sociocultural, seasonal, and ethnic variables also affect the development of neonatal jaundice [17]. To the best of our knowledge, this association has not been explored in our population yet.

Therefore, it was aimed to investigate the association of iron supplementation of pregnant females for both therapeutic and prophylactic purposes with neonatal hyperbilirubinemia.

METHODS

This was a prospective cohort study conducted at Darul Sehat Hospital for a period of 6 months (March 2022 to Aug 2022) after the approval from institutional review board, DSH/IRB/2022/0013. Women coming for antenatal visit in the first trimester of pregnancy and delivering at term were included in the study. Women with comorbidities (hypertension, diabetes, renal and liver disorders), blood transfusion in pregnancy and Rh negative women were excluded. Babies of mothers with Rh and ABO incompatibility, G6PD deficiency, and those delivering <35 weeks were also excluded. Women who attended prenatal appointments during the first trimester of their pregnancies were recruited using convenience sampling and evaluated by sending Complete blood counts during first trimester. Women with Hemoglobin less than 11 gm/dl were placed on therapeutic oral iron while mothers with Hemoglobin >11 gm/dl were placed on prophylactic oral iron supplementation according to the guidelines [9]. At 36 weeks of gestation, a repeat complete blood count was performed along with serum ferritin levels. Women were grouped on basis of serum ferritin level < 15 microgram per liter and serum ferritin level > 15-30 microgram per liter. Injectable Iron were given to women not responding to oral iron. Maternal anemia was classified as mild, moderate, and severe as per WHO classification [18]. The primary outcome was proportion of neonates developing hyperbilirubinemia during the first week of life. The bilirubin levels were interpreted in accordance with the neonate's age in hours according to the current guidelines [19]. Data were collected by trained junior doctors, after taking verbal informed consent on a pretested structured questionnaire based on literature review which included sections on maternal demographics, medical history, iron supplementation details (including type, dosage, frequency, and duration), and neonatal outcomes. Maternal investigations included complete blood count (1st trimester and 36 weeks) and serum ferritin levels. Neonatal outcome included were gestational age, mode of delivery, birth weight, and APGAR score. Content validity was assessed by having a panel of experts from Gynaecology and Pediatrics to evaluate the questionnaire to ensure that it adequately covered all aspects. Face validity was evaluated by piloting the questionnaire with a small sample of 20 pregnant women similar to the study population. It was carefully considered potential confounders and biases to ensure the validity of our findings. To address confounding factors, it was recognized that pre-existing maternal health conditions, such as diabetes, hypertension, and hypothyroidism, which could influence both the need for iron supplementation and the risk of neonatal jaundice. These conditions were meticulously recorded at the study's outset, and were excluded. Additionally, gestational age and birth weight, known risk factors for neonatal jaundice, were included as covariates, with subgroup analyses conducted to explore their specific effects. To minimize biases, it took several precautions. Information bias was mitigated by verifying iron supplementation through prescription records and diagnosing neonatal jaundice using standardized clinical criteria. It was also reduced recall bias by collecting data prospectively during routine antenatal visits, rather than relying on retrospective self-reporting. These comprehensive measures ensured that our study findings were both robust and reliable, providing valuable insights into the potential link between maternal iron supplementation and neonatal jaundice. It was hypothesized that there was a significant association of maternal iron supplementation on neonatal bilirubin levels. The minimum sample size n = 84 was calculated by the WHO sample size calculator 2.0, using two sample situations: 2.2b hypothesis test for two populations proportions, with a 95% confidence interval, with 27.6% prevalence of iron supplementation in cases and 8.5% in control in pregnant females of Pakistan [6]. A total of 176 mothers and their neonates were included in the study based on eligibility criteria. Data analysis was done using SPSS version 23.0. Normality of the data was checked by Shapiro-Wilk test. Due to non-normal distribution of all continuous variables, they were presented as median (interquartile ranges) while categorical variables were presented as frequencies (percentages). Mann-Whitney U test and Chi-squared test were applied to compare variables between groups. Regression analysis was conducted to find the association of neonatal hyperbilirubinemia and maternal supplementation. P-value<0.05 was considered to be statistically significant.

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RESULTS

A total 176 pregnant women participated in the study with a median age of 30 years (25-33). More than half of mothers were mild anemic 99(56.2%) and 12 (6.8%) were moderately anemic as shown in figure 1.

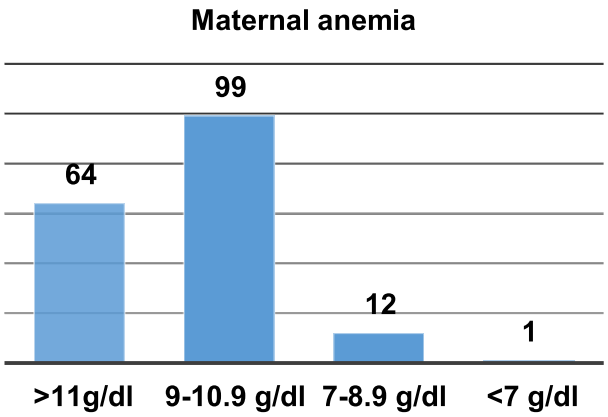

Figure 1: Distribution of study participants according to Maternal Anemia

Table 1 showed association of serum ferritin levels of women with their baseline characteristics and biochemical parameters. Maternal age was significantly lower among those with ferritin level 15-30 mcg/L (p-value<0.05) whereas, hemoglobin, hematocrit, and MCHC of women at 3rd trimester was significantly higher in women with ferritin level 15-30 mcg/L (P-value<0.05). Moreover, significant association was found between maternal serum ferritin and the type of iron supplements. A significantly higher proportion of women with serum ferritin <15 mcg/L received injectable iron supplements (29.9%) compared to those with ferritin level 15-30 mcg/L (12.4%). Data presented as n (%) or median (interquartile range): p-value<0.05 considered to be statistically significant.

Table 1: Association of Maternal Serum Ferritin Level with Baseline Characteristics and Biochemical Parameters

Variables	Serum Ferritin <15 mcg/L N (%)	Serum Ferritin 15-30 mcg/L N (%)	p-Value	Overall
n	87	89	-	176
Maternal Age	30 (27-34)	29 (25-32)	0.005	30 (25-33)
Gravida	3 (2-4)	2 (1-4)	0.15	2 (1-4)
Hemoglobin at Booking Visit	10 (9.5-11)	10.5 (9.7-11.65)	0.149	10 (9.6-11.2)
Hemoglobin in 3rd Trimester	10.2 (9.7-11.2)	10.8 (10.2-11.45)	<0.0001	10.5 (9.925-11.3)
Hematocrit in 3rd Trimester	32 (30-33)	33 (31-35)	0.032	32 (31-34)
MCV in 3rd Trimester	82 (75-87)	84 (80-88)	0.07	82.5 (79-87)
Peripheral Film in 3rd Trimester				
Normocytic Normochromic	50 (57.5%)	67 (75.3%)	0.057	117 (66.5%)
Normocytic Hypochromic	2 (2.3%)	3 (3.4%)		5 (2.8%)
Microcytic Hypochromic	29 (33.3%)	13 (14.6%)		42 (23.9%)
Normochromic Anisocytosis	5 (5.7%)	4 (4.5%)		9 (5.1%)
Mode of Delivery				
Normal Vaginal Delivery	32 (36.8%)	29 (32.6%)	0.954	61 (34.7%)
Instrumental VaginalDelivery	1 (1.1%)	1 (1.1%)		2 (1.1%)
Elective LSCS	34 (39.1%)	38 (42.7%)		72 (40.9%)
Emergency LSCS	19 (21.8%)	19 (21.3%)		38 (21.6%)
VBAC	1 (1.1%)	2 (2.2%)		3 (1.7%)
Iron Supplementation				
Oral Iron	61 (70.1%)	78 (87.6%)	0.004	139 (79%)
Injectable Iron	26 (29.9%)	11 (12.4%)		37 (21%)

Table 2 highlighted 64 (36.3%) mother with no anemia were receiving oral iron and 25 (67.5%) mothers who were mildly anemic received injectable iron.

Table 2: Association of Maternal Anemia with Iron Supplementation

Maternal Hemoglobin	Iron Supplementation N (%)		p-Value	Overall N (%)
	Oral Iron	Injectable Iron		
>11	62 (44.6%)	2 (5.4%)	<0.001	64 (36.3%)
9-10.9	74 (53.2%)	25 (67.5%)		99 (56.2%)
7-8.9	2 (1.4%)	10 (27.0%)		12 (6.8%)
≤7	1	0		1
Total	139 (79%)	37 (21%)		176

Table 3 signified that 37 (21%) neonates developed substantial Jaundice but statistically not significant p value > 0.05, whereas 13 (79%) babies were born with normal weight and 157 (89.2%) babies has good apgar.

Table 3: Effect of Maternal Hemoglobin on Neonatal Outcome

Neonatal Outcomes		Mother Hemoglobin in 3rd Trimester mg/dL				Total
		>11	9-10.9	7-8.9	<7	
Total Bilirubin of Neonates N (%)	<9.9	28	38	0	0	66(37.5%)
	10-15.9	24	41	7	1	73(41.5%)
	16-19.9	10	18	5	0	33 (18.8%)
	>20	2	2	0	0	4 (2.3%)
Total	-	64	99	12	1	176
p-value	-	0.220				-
Weight of Baby at Birth N (%)	<1.5	0	2	1	0	3 (1.7%)
	1.6-2.4	8	14	2	1	25 (14.2%)
	2.5-3.5	55	75	9	0	139 (79.0%)
	>3.5	1	8	0	0	9 (5.1%)
Total	-	64	99	12	1	176
p-value	-	0.094				-
Apgar Score of Baby N (%)	4-6	6	12	1	0	19 (10.7%)
	>7	58	87	11	1	157 (89.2%)
Total	-	64	99	12	1	176
p-value	-	0.450				-

Overall, the frequency of neonatal hyperbilirubinemia was found to be 89(50.6%) while 83 (47.2%) neonates were admitted to NICU as showed in figure 2.

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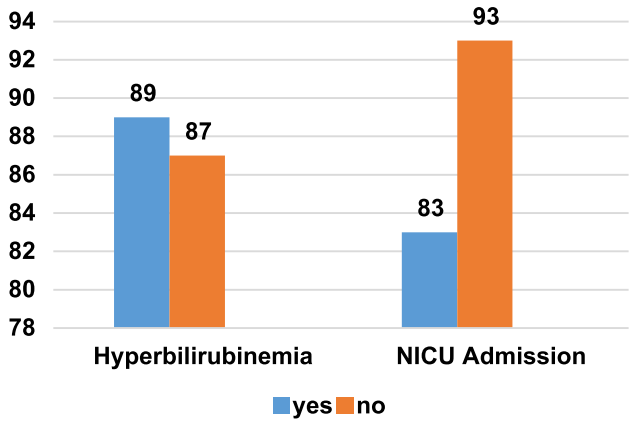

Figure 2: Frequency of Neonatal Hyperbilirubinemia and Neonatal Admission

Table 4 presented the frequency of neonatal hyperbilirubinemia among women using oral iron supplements or injectable iron supplements. The incidence of neonatal hyperbilirubinemia was notably higher among women using injectable iron supplements compared to those who received oral iron supplements (83.8% versus 41.7%; P-value <0.001). Data presented as n (%): p-value<0.05 considered to be statistically significant

Table 4: Frequency of Neonatal Hyperbilirubinemia among Women Receiving Oral Iron or Injectable Iron Supplements

Maternal Hemoglobin	Oral iron N (%)	Injectable iron N (%)	p-Value	Overall N (%)
n	139	37	-	176
Hyperbilirubinemia				
No	81 (58.3%)	6 (16.2%)	<0.001	87 (49.4%)
Yes	58 (41.7%)	31 (83.8%)		89 (50.6%)

Regression analysis (table 5) shows a significant association between neonatal hyperbilirubinemia and maternal iron supplementation. Initially, there was a robust association (crude odd ratio of 7.22), which remained statistically significant after adjusting for various parameters (adjusted odds ratio of 5.5). The odds of having hyperbilirubinemia with injectable iron supplements was 5.5 times higher than those receiving oral iron supplements (Table 4)(OR 5.5 95% CI 1.36-22.33, p = 0.017). CI: confidence interval; adjusted for ferritin, maternal age, gravidity, parity, Hb at booking visit, Hct at booking visit, MCV at booking visit, Hb at 3rd trimester, Hct at 3rd trimester, MCV at 3rd trimester.p-Value<0.05 considered to be statistically significant.

Table 5: Association of Maternal Iron Supplements and Neonatal Hyperbilirubinemia

Iron Supplements	Crude OR (95% CI)	p-Value	Adjusted OR (95% CI)	p-Value
Oral Iron	1	-	1	-
Injectable Iron	7.22 (2.83-18.42)	<0.001	5.5 (1.36-22.33)	0.017

DISCUSSION

The frequency of neonatal hyperbilirubinemia in our study was around 50%, which was similar to the results of a hospital-based cross-sectional study from Ethiopia where the prevalence of neonatal hyperbilirubinemia was 42.3% [20]. However, it was considerably higher (27.6%) than that reported by Tikmani SS *et al.*, in their population-based prospective study from Pakistan [6]. The difference could be due to different set of population, study design, sampling size, and methodology. Our hospital-based study allowed us to monitor the newborns for jaundice because the mothers received regular prenatal care up until delivery and were followed thereafter on post-natal visits. Iron supplementation to prevent the risk of anemia in pregnant women has been a concern as maternal anemia has several adverse consequences in infants, including low birth weight, preterm delivery, and increased susceptibility to infections. However, recently concerns have been raised regarding the adverse effects of iatrogenic iron overload [10, 21]. A nested case-control study by Mohammad Ali Moghimi MA *et al.*, compared excess iron supplementation may be associated with neonatal hyperbilirubinemia and jaundice [12]. The underlying pathophysiology was believed to be related to the alteration of heme metabolism due to iatrogenic overload as a result of iron supplementation [22]. Our study highlighted those 61 (34.6%) babies of mothers with mild anemia experienced considerable jaundice, with two of them developed severe jaundice. The reason could be attributed to use of injectables iron in mildly anemic mothers when oral iron can easily be used along with dietary modifications. Other minerals such as zinc have also been reported to influence bilirubin levels. Zinc inhibits heme oxygenase, resulting in decreased bilirubin levels [23]. Iron, on the other hand, increases the expression of heme oxygenase, which may result in hyperbilirubinemia [22]. Our study showed a strong association between neonatal hyperbilirubinemia and iron supplementation. This finding was also corroborated by the results of a randomized double-blind trial, which studied birth outcomes of iron supplementation in mothers and showed a higher incidence of neonatal jaundice in those that had received supplementation compared to those that had not. It should, however, be noted that this trial included women with a high baseline hemoglobin (>13.2 g/dL). Moreover, only the incidence of physiologic jaundice was noted and neonates with pathologic jaundice were excluded [14]. Our study was one of the first local study to explore the association between iron supplementation and neonatal hyperbilirubinemia. However, a few limitations should be noted. It was a single-center study and hence the findings may not be generalizable to other populations. Other potential risk factors like socioeconomic condition, parent's income and maternal weight/BMI were not included in the study. Moreover, we could not establish causality as it was a cohort study.

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CONCLUSIONS

The outcome highlighted the potential connection between the iron supplementation of the mother during pregnancy and the development of neonatal jaundice and suggests the need to exercise caution when prescribing iron supplements to pregnant women. Pregnant mothers who were at high risk of newborn jaundice should receive early intervention. Multi-center, larger-scale studies should be conducted to further investigate and validate our findings.

Authors Contribution

Conceptualization: SQB, SAM
Methodology: SQB, SAM, ANA, NS
Formal analysis: SQB, SAM
Writing, review and editing: SQB, SAM, ANA, NS

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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Assessing Interpersonal and Intrapersonal Emotional Insights in Undergraduate Medical Students

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ABSTRACT

Emotional intelligence (EI) plays a vital role in professional competence and psychological well-being, especially in healthcare. It significantly impacts how effective practitioners are and the outcomes for patients. In medical education, nurturing emotional intelligence is crucial because clinical practice often involves intense emotional experiences. **Objective:** To evaluate emotional understanding at both the interpersonal and intrapersonal levels among medical students. **Methods:** A Descriptive cross-sectional study was conducted at Sialkot Medical College, from August 23, 2023, and culminating on November 23, 2023 of three months' duration after taking IRB from Sialkot Medical College, Sialkot IRB no. (MRC/IRB/23019). The selection of participants was conducted utilizing a convenience sampling approach. The study included students across all academic years of the MBBS program, with the exclusion criteria being individuals diagnosed with anxiety or depression. Data were collected via a Google Forms questionnaire and analyzed using SPSS Version 23.0. **Results:** The study encompassed a total of 298 medical students, with an average age of 20.4 ± 1.77 years. The demographic breakdown revealed 143 (48%) male participants and 155 (52%) female participants. The findings underscored a prevalent understanding among students regarding their emotions and the significance of emotional awareness in their daily lives. Moreover, the research identified obstacles related to emotional expression and heightened sensitivity to external stimuli. **Conclusions:** This study concluded that brings substantial diversities in emotional and social-emotional acumen within the medical student cohort, underscoring the necessity for augmented emotional intelligence training in medical curricula to fortify self-awareness and interpersonal efficacy.

INTRODUCTION

Emotional intelligence (EI) plays a vital role in professional competence and psychological well-being, especially in healthcare. It significantly impacts how effective practitioners are and the outcomes for patients [1]. In medical education, nurturing emotional intelligence is crucial because clinical practice often involves intense emotional experiences. Medical students who excel in understanding and managing both their own emotions (self-awareness and emotional regulation) and those of others (social sensitivity, empathy, and communication skills) are better prepared to navigate patient interactions and the high-pressure demands of a medical career [2]. Training medical professionals involves not only the acquisition of theoretical knowledge and practical skills but also the cultivation of a professional attitude marked by empathy, resilience, and emotional stability [3]. These qualities are crucial for good patient care and are strongly tied to emotional intelligence. Studies have found that medical students with higher emotional intelligence have better communication skills, more satisfied patients, and

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improved personal well-being. Additionally, emotionally intelligent medical students are more likely to become skilled doctors who can manage their own emotions and understand the emotions of their patients and coworkers [4]. Emotional intelligence encompasses several key areas, including the ability to identify and manage one's own emotions (intrapersonal skills), and the ability to recognize, understand, and influence the emotions of others (interpersonal skills). These competencies are vital in medical settings where the ability to make rapid, yet compassionate decisions can significantly affect patient outcomes. In addition, the interpersonal component of emotional intelligence is crucial for teamwork and communication within multi-disciplinary healthcare teams, a common scenario in modern medical practice [5]. While numerous studies have explored the implications of emotional intelligence in healthcare, the focus has predominantly been on practicing healthcare professionals. Medical students, especially during their formative years, have received less attention. Studies that do focus on this group often view emotional intelligence as a fixed trait, overlooking its development throughout medical training [6, 7]. Additionally, existing research often relies on broad assessments of emotional intelligence, which may fail to capture the unique challenges and situations encountered by medical students [8]. This leads to a significant gap in the literature: the need for targeted research exploring both interpersonal and intrapersonal aspects of emotional intelligence within medical student populations. The reason for focusing on medical students instead of practicing professionals is because medical school is a key time for developing their professional identities. During this period, students shape the personal and professional qualities that will define their careers. By understanding and improving emotional intelligence in these early years, educators can greatly impact the quality of future medical practice. This study aims to fill a gap in research and serves an educational purpose, aiming to help create a more empathetic, aware, and emotionally skilled medical workforce.

This study aimed to fill these gaps by looking at how medical students understand their own emotions and those of others. The goal is to use the findings to improve medical training programs to better address the emotional and social needs of students.

METHODS

A descriptive cross-sectional study was conducted at a medical college, spanning three months from August 23, 2023, to November 23, 2023 after taking IRB from Sialkot Medical College, Sialkot IRB no. (MRC/IRB/23019). The expected prevalence of emotional intelligence attributes (20%), the total population of the medical college (500 students), desired confidence level (95%, Z-1.96), and margin of error (5%, E-0.05). Applying the finite population correction (FPC) formula resulted in a required sample size of 183. To ensure adequate power (80%, power=0.80) and account for possible non-response or incomplete data, the sample size was increased to 298 participants. A convenience sampling method was utilized, where participants were selected based on availability and willingness to participate. While this method allowed efficient data collection within the study timeframe, it may introduce selection bias. All students enrolled from the first to the final year of the MBBS program were eligible, excluded were the diagnosed with anxiety or depression, as these conditions might affect their emotional intelligence scores. Students unwilling to participate were also excluded. Data were collected through a validated questionnaire designed to evaluate social skills, empathy, and motivation. The questionnaire was sourced from an open-access study conducted in Chennai, India, ensuring relevance and adaptability to our study population [9]. It was disseminated via Google Forms, facilitating broad access and ease of use for participants and included items structured on a Likert scale. The study protocol received approval from the Institutional Review Board of the medical college. Ethical standards were strictly followed, with informed consent obtained electronically before participation. The consent form clarified the study's purpose, the voluntary nature of participation, the confidentiality of responses, and the participants' right to withdraw at any time without consequences. Responses were analyzed using statistical software (SPSS version 23.0). Descriptive statistics summarized the demographic data and emotional intelligence scores.

RESULTS

In this study, 298 students were enrolled. The mean age of students was 20.4 ± 1.77. Among the 298 students participated in the research, 143 (48%) were male and 155 (52%) were female. The majority of respondents (48.7%) were in their first study year, followed by a smaller proportion in subsequent years: 9.1% in the second year, 18.1% in the third year, 10.4% in the fourth year, and 13.8% in the fifth year in table 1.

Table 1: Sociodemographic Characteristics of Study Respondents n=298

Questions		Frequency (%)
Age in years	18 to 22	253 (84.9)
	22 to 26	45 (15.1)
Gender	Male	143 (47.8)
	Female	155 (52.2)
Year of MBBS study	1st year	145 (48.5)
	2nd year	27 (9.0)
	3rd year	53 (18.1)
	4th year	32 (10.7)
	Final year	41 (13.7)
	Total	298 (100)

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Emotional Awareness reveals a spectrum of responses indicating varying levels of emotional self-awareness among respondents. Key findings include that a majority (57.7%) often feel clear about their emotions, while a significant portion (51.7%) always acknowledge the importance of emotions in their lives. Additionally, a notable percentage (43.3%) sometimes experience their moods impacting others, highlighting a moderate awareness of interpersonal emotional dynamics. Challenges in emotional expression are evident, with a considerable portion (34.6%) rarely finding it easy to articulate their feelings. Moreover, a majority (52.7%) always feel their moods are easily influenced by external events, underscoring a heightened sensitivity to environmental stimuli. While a minority (22.1%) always sense impending anger, a substantial portion (49.0%) sometimes share their true feelings with others, indicating a varied inclination towards emotional transparency. Verbalizing emotions remains a struggle for many (36.9%), and yet, a significant majority (47.3%) always stay aware of their emotional state even when upset, demonstrating a strong self-awareness during distress. Lastly, a moderate percentage (37.6%) sometimes possess the ability to detach from thoughts and feelings for introspection, reflecting a nuanced capacity for self-reflection among respondents (Table 2).

Table 2: Response of the Study Participants Related to Emotional Awareness Domain (Intrapersonal Domain)

Emotional Awareness n (%)	Never	Rarely	Some-times	Often	Always	Total
My feelings are clear to me at any given moment	0 (0.0%)	27 (9.1%)	54 (18.1%)	172 (57.7%)	45 (15.1%)	298 (100.0%)
Emotions play an important part in my life	0 (0.0%)	3 (1.0%)	46 (15.4%)	95 (31.9%)	154 (51.7%)	298 (100.0%)
My moods impact the people around me	29 (9.7%)	62 (20.8%)	129 (43.3%)	61 (20.5%)	17 (5.7%)	298 (100.0%)
I find it easy to put words to my feelings	7 (2.3%)	103 (34.6%)	70 (23.5%)	80 (26.8%)	38 (12.8%)	298 (100.0%)
My moods are easily affected by external events	0 (0.0%)	0 (0.0%)	31 (10.4%)	110 (36.9%)	157 (52.7%)	298 (100.0%)
I can easily sense when I am going to be angry	35 (11.7%)	64 (21.5%)	76 (25.5%)	57 (19.1%)	66 (22.1%)	298 (100.0%)
I readily tell others my true feelings	21 (7.0%)	65 (21.8%)	146 (49.0%)	57 (19.1%)	9 (3.0%)	298 (100.0%)
I find it easy to describe my feelings	61 (20.5%)	110 (36.9%)	103 (34.6%)	21 (7.0%)	3 (1.0%)	298 (100.0%)
Even when I'm upset, I'm aware of what is happening to me	0 (0.0%)	28 (9.4%)	72 (24.2%)	57 (19.1%)	141 (47.3%)	298 (100.0%)
I can easily sense when I am going to be angry	32 (10.7%)	50 (16.8%)	112 (37.6%)	63 (21.1%)	41 (13.8%)	298 (100.0%)

Social Emotional Awareness presents data on respondents' perceptions of their ability to understand and navigate social interactions and emotions. It reveals varying levels of awareness and sensitivity to others' emotions and behaviors across different scenarios. A majority (53.0%) always consider the impact of their decisions on other people, indicating a high level of social awareness and empathy. Similarly, a significant percentage (54.0%) always sense when people around them are becoming annoyed, demonstrating a keen sensitivity to emotional cues. Furthermore, a substantial proportion (55.0%) always sense when a person's mood changes, indicating a strong ability to perceive and respond to shifts in emotional states. Additionally, a majority (48.0%) always feel able to be supportive when delivering bad news, highlighting a capacity for empathy and compassion. Moreover, a majority (53.7%) generally understand the way other people feel, suggesting a high level of emotional intelligence in interpersonal interactions. However, notable variations exist, such as a significant percentage (39.6%) reporting that their friends can tell them intimate things about themselves, indicating varying degrees of trust and openness in relationships. A majority (59.1%) always indicated that it genuinely bothers them to see other people suffer, indicating a high level of empathy and emotional sensitivity towards the well-being of others. A significant percentage (47.0%) always reported knowing when to speak and when to be silent, demonstrating a strong sense of social awareness and appropriate communication skills in various social situations (Table 3).

Table 3: Response of the Study Participants Related to Social Emotional Awareness Domain (Interpersonal Domain)

Social Emotional Awareness n (%)	Never	Rarely	Some-times	Often	Always	Total
I consider the impact of my decisions on the other people	0 (0.0%)	0 (0.0%)	20 (6.7%)	120 (40.3%)	158 (53.0%)	298 (100.0%)
I can easily tell if the people around me are becoming annoyed	0 (0.0%)	0 (0.0%)	14 (4.7%)	123 (41.3)	161 (54.0%)	298 (100.0%)
I sense it when a person's mood changes	0 (0.0%)	8 (2.7%)	46 (15.4)	80 (26.8%)	164 (55.0%)	298 (100.0%)
I am able to be supportive when giving bad news to others	0 (0.0%)	4 (1.3%)	42 (14.1%)	109 (36.6%)	143 (48.0%)	298 (100.0%)
I am generally able to understand the way other people feel	0 (0.0%)	0 (0.0%)	26 (8.7%)	112 (37.6%)	160 (53.7%)	298 (100.0%)
My friends can tell me intimate things about themselves	42 (14.1%)	129 (43.3%)	118 (39.6%)	9 (3.0%)	0 (0.0%)	298 (100.0%)
It genuinely bothers me to see other people suffer	0 (0.0%)	0 (0.0%)	25 (8.4%)	97 (32.6%)	176 (59.1%)	298 (100.0%)
I usually know when to speak and when to be silent	0 (0.0%)	28 (9.4%)	84 (28.2%)	140 (47.0%)	46 (15.4%)	298 (100.0%)

Relationship Management provides insights into respondents' perceptions of their abilities to manage and foster positive relationships. Findings reveal varying levels of comfort, communication, and support within interpersonal connections. A majority (53.7%) always consider their relationships as safe places, indicating a strong foundation of trust and security in their

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interactions. Additionally, while a significant portion (35.6%) sometimes find it easy to share deep feelings, there are also instances where respondents (14.8%) rarely or never do, suggesting varying levels of emotional vulnerability and openness. Moreover, a notable percentage (47.3%) often demonstrate proficiency in motivating others, showcasing leadership and interpersonal influence skills. Furthermore, respondents generally find it relatively easy to make friends (30.2% often, 35.9% sometimes), underscoring their sociability and ability to initiate and maintain connections. Additionally, a majority (56.0%) enjoy helping others, reflecting altruistic tendencies and a desire for social contribution. Furthermore, respondents (38.3% often, 47.7% sometimes) demonstrate a strong ability to offer support by engaging in conversations with individuals when they are very upset, indicating empathetic communication and active listening skills in nurturing relationships. Overall, the table highlights a diverse range of relationship management skills among respondents, encompassing trust-building, emotional expression, leadership, sociability, altruism, and supportiveness in fostering positive interpersonal connections (Table 4).

Table 4: Response of the study participants related to Relationship Management domain (Interpersonal Domain)

Relationship Management n (%)	Never	Rarely	Some-times	Often	Always	Total
My relationships are safe places for me	0 (0.0)	0 (0.0%)	34 (11.4%)	104 (34.9%)	160 (53.7%)	298 (100.0%)
I find it easy to share my deep feelings with others	7 (2.3)	44 (14.8)	106 (35.6%)	97 (32.6%)	44 (14.8%)	298 (100.0%)
I am good at motivating others	0 (0.0)	7 (2.3%)	33 (11.1%)	117 (39.3%)	141 (47.3%)	298 (100.0%)
It is easy for me to make friends	4 (1.3)	28 (9.4%)	69 (23.2%)	107 (35.9%)	90 (30.2%)	298 (100.0%)
I am fairly cheerful person	4 (1.3)	36 (12.1%)	93 (31.2%)	103 (34.6%)	62 (20.8%)	298 (100.0%)
I like helping people	0 (0.0)	0 (0.0%)	26 (8.7%)	105 (35.2%)	167 (56.0%)	298 (100.0%)
I am able to talk to someone when they are very upset	0 (0.0)	4 (1.3%)	38 (12.8%)	114 (38.3%)	142 (47.7%)	298 (100.0%)

DISCUSSION

This study aimed to assess the emotional and social emotional awareness among medical students at a medical college, enrolling a diverse cohort of 298. The majority of participants were first-year students, suggesting a youthful demographic which could influence the emotional maturity and awareness observed in the results. The findings from the Emotional Awareness domain reflect a broad spectrum of self-awareness and emotional expression among the participants. A significant majority often felt clear about their emotions (57.7%), and a majority also acknowledged the importance of emotions in their lives (51.7%). These results are encouraging as they indicate a high level of intrinsic emotional understanding, which is critical in the medical field for both self-management and patient care [9, 10]. However, the data also highlighted areas for improvement. A considerable number of students (34.6%) rarely found it easy to articulate their feelings, and a similar percentage (36.9%) struggled to describe their emotions. This difficulty in verbalizing emotions could hinder effective communication with peers and patients, potentially impacting clinical outcomes and personal well-being [10]. Interestingly, 52.7% of the students felt their moods were easily influenced by external events, which might suggest a vulnerability to environmental stressors—a common challenge in medical settings. This sensitivity, while enhancing empathy and responsiveness, might also necessitate targeted interventions to strengthen emotional resilience [11]. The Social Emotional Awareness responses illustrate a generally high level of interpersonal sensitivity and empathy. Notably, a majority of students consistently considered the impact of their decisions on others (53.0%) and were adept at recognizing when others were annoyed (54.0%) or when their moods changed (55.0%). These competencies are invaluable in medical practice, where understanding and reacting appropriately to patient and colleague emotions can significantly enhance collaborative efforts and patient care [12]. Despite these strengths, the data revealed areas of potential concern. Although many students felt capable of being supportive when delivering bad news (48.0%), a significant portion (39.6%) indicated that their friends rarely tell them intimate things, suggesting possible barriers to deeper emotional connections or trust [13]. Responses related to relationship management skills further underscored the students' capacity for interpersonal interaction and support. A majority viewed their relationships as safe spaces (53.7%), which is crucial for emotional support during the demanding medical training. The ability to engage effectively and supportively in emotionally charged situations was evident, with (47.7%) able to converse effectively with someone very upset. However, challenges in sharing deep feelings (14.8% rarely or never) point to a reticence that could impede deeper interpersonal connections and personal growth. Developing these areas could enhance students' overall emotional intelligence, benefiting their professional and personal lives [14-16]. An interventional study conducted in US for over two years revealed that, 70 medical students participated in an EI-Resilience elective focusing on skills such as positive thinking and gratitude, taught over six sessions. Post-elective evaluations using the EQ-i 2.0 showed a significant improvement in emotional intelligence scores from an average of 100.05 to 108.14. The majority of students (over 93%) found the elective beneficial and recommended its continuation for future students [17]. A newly introduced EI-Resilience curriculum significantly benefits preclinical medical students by

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instilling emotional intelligence and resilience strategies through a well-defined program. Introducing this type of educational intervention during the preclinical phase is both opportune and effective [18, 19]. These findings underline the importance of integrating emotional intelligence training into medical curricula. Programs focusing on enhancing emotional articulation skills, resilience to external stressors, and deepening interpersonal trust could be beneficial [20]. Future research should explore longitudinal studies to track emotional intelligence development throughout medical training and its impact on clinical efficacy and satisfaction. Overall, this study contributes valuable insights into the emotional and social emotional landscapes of medical students, offering a foundation for enhancing educational strategies to support the development of well-rounded, emotionally intelligent medical professionals.

CONCLUSIONS

This study concluded that a broad range of emotional and social-emotional awareness among medical students revealing both strengths in self-awareness, empathy and challenges in emotional expression and resilience. The findings emphasize the need for targeted emotional intelligence training in medical education to enhance interpersonal skills and emotional articulation.

Authors Contribution

Conceptualization: SZ

Methodology: AM, AS, MA

Formal analysis: NB, FU

Writing-review and editing: SZ

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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Frequency of Placenta Previa among Women with Previous Cesarean-Section

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ABSTRACT

Placenta Previa was defined as when the placenta was attached to the lower uterine segment, poses significant risks, including antepartum hemorrhage and maternal mortality. The incidence was rising, attributed partly to increased cesarean sections and advanced maternal age. **Objective:** To determine the frequency of placenta Previa among women with previous cesarean-sections. **Methods:** This cross sectional study was carried out at a Teaching Hospital of Sialkot, from June to December 2021. The sample size was 147 pregnant females. These pregnant females have a history of cesarean section. The non-probability Consecutive sampling technique was used, and data were analyzed by using SPSS version 25.0. **Results:** Among those, 16.3% had placenta Previa, which increased significantly in women with >2 previous cesarean sections to 26.4% (p = 0.003). Regarding parity, the increase in the risk of placenta Previa was not significant: 12.8% for parity < 3 and 20.3% for parity ≥ 3 (p = 0.087). However, in the stratified analysis by BMI, this became significant: 11.0% for normal-weight, 18.6% for overweight, and 66.7% for obese women (p = 0.001). There was no significant difference concerning age groups, p = 0.177. Such findings of the significant associations of placenta Previa with such factors as BMI and number of cesarean sections indicate that great attention to monitoring should be paid. **Conclusions:** Hence concluded that previous cesarean sections strongly correlate with placenta previa in subsequent pregnancies. Such findings underscore the need for rigorous monitoring and proactive measures, especially in cases of multiple cesarean deliveries in the management of associated complications.

INTRODUCTION

Placenta Previa is an implantation, either partially or totally, of the placenta into the lower uterine segment and is normally diagnosed in the second and third trimester, although it can be as early as the first trimester. It accounts for most cases of antepartum hemorrhage, as well as vaginal bleeding, and complicates about 1 in 200 deliveries worldwide; prevalence is on the rise with ever-growing rates of cesarean sections [1]. In some regional studies, as in the Provincial General Hospital of Kananga, the prevalence of the placenta Previa among women with a history of cesarean section was as high as 26.86% [2]. This agrees with the prevalence rate of 13.3%, which was reported in studies done at Lady Willingdon Hospital in Lahore, Pakistan [3]. The prevalence of placenta Previa in the world is from 0.26% to 2.00% of all pregnancies, being higher in some regions. In Indonesia, for example, the prevalence reported is between 2.4% and 3.56% of pregnancies [4]. One Iraqi study estimated the prevalence of placenta Previa among pregnant women as 0.21%, with advanced maternal age, high parity, and previous cesarean section being the major significant risk factors for the condition [5]. In Sudan, the condition has been reported at 1.4%, while in Libya, it has been variously reported at 1% [6]. In some developing countries like Pakistan, it was as high as 5.78%, especially among women with a previous history of cesarean sections [7]. In Nigeria, there is a tertiary hospital in Port Harcourt that recorded a prevalence rate of 0.97%, indicating a trend of decline in recent years [8]. The risk factors for placenta Previa include smoking, numerous gestations, high parity, and advanced maternal age. For example, the incidence is increasing in correlation with higher birth rates among mothers between 35 to 45 years of

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age worldwide [9]. This increase is closely related to an increase in the rates of cesarean sections and attendant complications, including morbidly adherent placenta and postpartum hemorrhage [10]. A study showed that placenta Previa accounted significantly to the indications of cesarean hysterectomy as 79.04% of the cases from post-cesarean patients resulted in hysterectomy [11]. Serious consequences for both mother and baby increase the global burden attributed to placenta Previa, including increased risks of maternal and neonatal mortality, fetal growth restriction, preterm labor, and significant hemorrhage in the antenatal and intrapartum periods. These events may necessitate invasive procedures such as hysterectomy or, in some instances, blood transfusion, especially in extremely critical cases [12]. The chances of such complications are much greater when placenta Previa is associated with a history of cesarean sections, especially when the placenta has been located on the anterior uterine wall, enhancing the chance of placenta and other complications [13]. The exact cause of placenta Previa remains unknown, but its strong association with previous cesarean deliveries suggests that damage to the myometrium may play a significant role [12]. This further complicates the understanding of the predisposing factors to it. Early diagnosis and proper management are the hallmarks of the reduction of morbidity and mortality for both the neonate and the mother. The incidence of placenta previa has been established by various studies as being higher in subsequent pregnancies following a cesarean section [14]. Thus, early diagnosis offers an opportunity to manage the associated risks effectively for both mother and child. In Pakistan, however, there remains a significant gap in the comprehensive understanding of this condition's prevalence and risk factors, particularly in subsequent pregnancies following a cesarean section.

This study aimed to address this gap by determining the frequency of placenta Previa in such cases within our population.

METHODS

This study has a cross sectional study design. The study was carried out at the Obstetrics and Gynecology department of a teaching hospital in Sialkot from June-2021 to December-2021 after institutional review board approval with a reference no.146/REC/KMSMC. Non-probability consecutive sampling was utilized for participant selection. With a 95% confidence level, a 5% margin of error, and an anticipated prevalence of placenta previa of 10.7% among women with a history of cesarean section, the sample size was calculated as147 participants. The current study recruited pregnant women aged 20-40 years with a history of cesarean section and at least 30 weeks' gestation based on Last Menstrual Period (LMP). The study excluded participants with a history of dilatation and curettage (D and C), a history of thyroid problems, pregnancy-induced hypertension, diabetes mellitus, and lack of informed consent. The 147 pregnant patients were included following written informed permission from patients and clearance from the hospital's ethical committee. Every patient received an explanation of the goal of the study. Demographic data were gathered while the patient was lying supine and had an empty bladder. Grayscale imaging was used to observe the placenta in real time. The questionnaire comprises two sections. The first section collected information on socio-demographic data, while the second section focused on details related to placenta Previa. The questionnaire was validated on 50 participants. Cronbach's alpha coefficient was 0.82, which was considered a good value for a questionnaire used in data collection. Three well-qualified researchers reviewed the entire questionnaire for validity. The index of item-objective congruence was 0.85 for each question, which was considered a satisfactory value. SPSS version 25.0 was utilized for data entry and analysis. For qualitative factors such as placenta Previa and parity, frequencies and percentages were utilized, whilst Mean ± SD was employed for the quantitative variable of age. To account for putative effect modifiers, stratification was used for age, parity, number of cesarean sections and BMI. The Chi-square test was used after stratification, with a p-value of ≤0.05 being regarded as significant.

RESULTS

In terms of parity, the prevalence of placenta Previa was 12.8% for less than three parity and 20.3% for three or more parity. Though the trend in relation to parity was not statistically significant (p = 0.087), there was a suggestion from these data of an increased risk with rising parity. Table 1 showed the age distribution of the patients, 48 (32.7%) patients were in the 20-30 years' age group and 99(67.3%) in the 31-40 years' age group. According to parity distribution, 78(53.1%) had parity <3, while 69(46.9%) had ≥3.

Table 1: Distribution of Frequency Related to Age and Parity

Age Groups	Frequency (%)	Parity	Frequency (%)	Prevalence of Placenta Previa	p-Value
20-30 Years	48(32.7%)	<3	78(53.1%)	12.8%	0.087
31-40 Years	99(67.3%)	≥3	59(46.9%)	20.3%	
Total	147(100.0%)	Total	147(100.0%)	-	

Results of the women with a previous cesarean delivery, 16.3% were found to have placenta Previa. Interestingly, the rate of placenta Previa was significantly higher for women who have had over two cesarean deliveries, at 26.4%, than it was for those who have had fewer than two cesarean deliveries, at 10.6% (p = 0.003). It also reveals a positive association between the number of previous cesarean sections and the risk of placenta Previa, signifying that the more cesarean sections performed, the higher and the risk. Table 2 showed the number of previous C-section distributions, 94(63.9%) had <2, while 53(36.1%) had ≥2.

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According to stratification of placenta Previa with respect to age, no significant difference was observed between age groups(p>0.05).

Table 2: Frequency Distribution of Number of Previous C-Section and Placenta Previa

Number of Previous C-Section	Frequency (%)	Placenta Previa	Frequency (%)	p-Value
<2	94 (63.9%)	Yes	24 (16.3%)	0.003
≥2	53 (36.1%)	No	133 (83.7%)	
Total	147 (100.0%)	Total	147 (100.0%)	

In this study, age did not statistically significantly influence the prevalence of placenta Previa; rates were 10.4% for women aged 20-30 years and 19.2% for women aged 31-40 years (p = 0.177). That means that advanced maternal age, though generally considered a risk factor, may not play such a major role in this population. Table 3 showed stratification of placenta Previa with respect to age, no significant difference was observed between age groups (p>0.05).

Table 3: Stratification of Placenta Previa with Respect to Age

Age Groups	Placenta Previa		Total Frequency (%)	p-Value
	Yes Frequency (%)	No Frequency (%)		
20-30 Years	5 (10.4%)	43 (89.6%)	48 (100.0%)	0.177
31-45 Years	19 (19.2%)	80 (80.8%)	99 (100.0%)	
Total	24 (16.3%)	123 (83.7%)	147 (100.0%)	

Stratification according to BMI also showed significant results. The prevalence of placenta Previa was 11.0% in normal weight women, 18.6% in overweight women, and as high as 66.7% in obese women (p = 0.001). Thus, the association was directly related: the higher the BMI, the greater the risk of placenta Previa, and thus obesity was a major risk factor (Table 4). Table 4 shows stratification of placenta Previa with respect to BMI, significant difference was observed between BMI groups(p<0.05).

Table 4: Stratification of Placenta Previa with Respect to BMI

Age Groups	Placenta Previa		Total Frequency (%)	p-Value
	Yes Frequency (%)	No Frequency (%)		
Normal	9 (11.0%)	73 (89.0%)	82 (100.0%)	0.001
Overweight	11 (18.6%)	48 (81.4%)	59 (100.0%)	
Obese	4 (66.7%)	2 (33.3%)	6 (100.0%)	
Total	24 (16.3%)	123 (83.7%)	147 (100.0%)	

DISCUSSION

This study underscores a significant association between previous cesarean sections and the increased risk of placenta Previa in subsequent pregnancies. To provide a comprehensive analysis, it is important to explore alternative explanations, potential biases, and limitations of the study. The observed increase in the incidence of placenta Previa with a higher number of cesarean sections (26.4% in women with more than two cesarean sections versus 10.6% in those with fewer than two) suggests a strong correlation with cumulative uterine scarring. Repeated cesarean sections can disrupt the endometrial lining and cause myometrial damage, creating an environment predisposed to abnormal placental implantation in future pregnancies. This finding aligns with studies showing that the risk of placenta Previa and placenta accreta spectrum disorders increases with the number of prior cesarean deliveries [14]. Furthermore, maternal age was another critical risk factor for placenta Previa. Advanced maternal age, particularly in women aged 40 years or older, significantly increases the likelihood of placenta Previa, as these pregnancies often present with additional complications such as uterine atony and prolonged labor [15, 16]. This was corroborated by other research demonstrating that maternal age and a history of cesarean sections were significant predictors of adverse pregnancy outcomes, including placenta Previa and its associated complications [17, 18]. Stratification by BMI in our study revealed a significant association between obesity and placenta Previa, with a prevalence of 66.7% in obese women compared to 11.0% in those with normal weight. Obesity may contribute to the risk of placenta Previa due to systemic inflammation, altered hemodynamics, and impaired angiogenesis that affect placental development [19, 20]. These findings underscore the importance of weight management and monitoring in pregnant women with high BMI to mitigate the risk of placenta Previa and associated complications. While parity showed a trend towards a higher risk of placenta Previa (20.3% in women with parity ≥ 3 compared to 12.8% in those with parity < 3), the association was not statistically significant (p = 0.087). However, other studies have shown a stronger association between higher parity and increased risk of placenta Previa, likely due to cumulative uterine changes over multiple pregnancies [21]. The lack of significance in our study could be attributed to the relatively small sample size or differences in population characteristics. Confounding factors such as lifestyle, genetic predisposition, and socio-economic status were not accounted for, potentially affecting the results. Future research should incorporate longitudinal designs with more comprehensive data collection to adjust for these potential confounders and provide more definitive conclusions. Moreover, retrospective data collection can introduce recall bias, particularly regarding the accurate reporting of obstetric history. Prospective data collection methods in future studies could enhance the reliability of these findings and better elucidate the relationship between previous cesarean sections, BMI, parity, maternal age, and placenta Previa.

CONCLUSIONS

This study demonstrates a significant association between previous cesarean sections and the occurrence of placenta Previa in subsequent pregnancies, with the risk notably increasing in women with more than two prior

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cesarean deliveries. The findings highlight the impact of maternal obesity and advanced maternal age as important risk factors contributing to the incidence of placenta Previa. These results have both practical and theoretical implications. Early identification and proactive management of placenta Previa should be done by the health provider, especially in high-risk women with multiple cesarean deliveries or higher BMI. A well-defined, individualized monitoring plan and prevention strategy can reduce the risk of adverse maternal and neonatal outcomes associated with placenta Previa, inclusive of lifestyle approaches for weight management, judicious planning of route of delivery.

Authors Contribution

Conceptualization: UM
Methodology: UM, NS
Formal analysis: SK
Writing, review and editing: JL, SS, SN

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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Micro Marsupialization Versus Modified Micro Marsupialization in The Management of Mucocoele of Lower Lip

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ABSTRACT

The most prevalent kind of soft-tissue cyst of the small salivary glands in the lower lip is called a mucocele. It usually manifests as a fluctuating, bluish, not tendering sub-mucosal swelling with a usual overlying mucosa. The lower lip is where mucoceles are most frequently found, despite the fact that small salivary glands are present in most areas of the oral cavity with the exception of the gingiva, Anterior hardpalate and tip of the tongue. This is most likely because this area experiences more mechanical trauma than other locations. **Objective:** To compare the outcomes of surgical technique between micro- marsupialization and modified micro marsupialization in treatment of mucocele of lower lip. **Methods:** Experimental study was conducted at Department of OMFS, LUMHS, Jamshoro, by convenience sampling technique in time frame of Six months. Patients were called into two groups at random. Patients in group A were managed by micro-marsupialization and in group B by modified micro-marsupialization. All the patients were followed till one week to assess wound healing time and pain. The analysis of data was conducted using SPSS version 26.0. **Results:** In comparison of group A and B, wound healing time was noted as 9.7 ± 3.1 and 10.9 ± 4.01 days (P=0.180), duration of surgery 30.2 ± 3.7 and 29.9 ± 3.6 minutes (P=0.727) and postoperative pain at 7th day was noted 2.7 ± 1.8 and 2.17 ± 1.7(P=0.257), respectively. **Conclusion:** It was concluded that insignificant difference was noted between micro-marsupialization and modified micro-marsupialization in outcomes of surgical technique in treatment of mucocele of lower lip.

INTRODUCTION

Usually resulting from mechanical trauma to the small salivary glands, mucocoeles are common lesions of the oral mucosa that accumulate mucus [1]. These often affect both adults and children, and they can develop at any location where the oral mucosa contains small salivary glands. The most frequently impacted area by mucoceles is the lower lip [2, 3]. Although they often don't create major issues, mucocoeles can cause troubles with eating or drinking, masticating, and talking. In accordance with the positioning and extent of the mucocele, discomfort may arise [4]. Extravasation mucoceles make up more than 80% of all mucoceles and are more common in people under 30 years old. With varying degrees of success, a number of treatment options, including excision, excision combined with surgical removal of a minor salivary gland, micro- marsupialization, cryosurgery and steroid injection have been suggested for the management of mucocele [5-7]. The best course of treatment is surgical removal of the mucocele and the related salivary gland. Recurrence, however, may result from the partial excision or severance

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of nearby small salivary glands. One potential therapeutic option for mucoceles is micro-marsupialization [8, 9]. Micro-marsupialization is effortless to carry out, reasonably a traumatic, and patient-accepted [10]. With varying degrees of efficacy, managing mucoceles in pediatric patients with micromarsupialization of lesions smaller than 1 cm in diameter has been documented. The act of introducing sutures is thought to preserve an epithelial tract that separates the glandular tissue under the surface and stops fluid concentration [11, 12]. This approach has also been documented to cause recurrence. It is proposed that the number of epithelized drainage channels increases with an increase of sutures, and that the precise number of sutures may vary depending on the size of the lesion [13-15]. This study is designed to compare the outcomes of surgical technique between micro-marsupialization versus modified micro-marsupialization in treatment of mucocele of lower lip. This study tested the hypothesis that modified micro-marsupialization is better technique than micro-marsupialization in treatment of mucocele of lower lip. Thus, in order to gather local data, this study aims to determine whether there is a statistically significant difference between the two approaches' outcomes. Based on this, additional approaches might be developed to enhance the outcomes for these patients by making the superior approach their first option for treatment.

METHODS

Experimental study was conducted at Department of OMFS, LUMHS, Jamshoro, Pakistan by non-probability convenience sampling method in time frame of six months i.e. from 1stJune, 2021 To 30th November 2021 after approval by the Institutional Research Ethics Committee of LUMHS (NO. LUMHS/REC/-95). Informed consent was taken after explaining the procedure. Two groups of patients were randomly assigned. Patients in group A were managed by micro-marsupialization and in group B by modified micro-marsupialization. All the patients were followed till one week to assess wound healing time and pain. Patients between age of 18 to 50 years, either gender and Patients presented with mucocele of lower lip were included and patients found with the lesions found on palate, buccal mucosa, tongue, floor of the mouth, Immunocompromised patients were expelled from the study. By using Open-Epi sample size calculator taken mean healing time of micro marsupialization and modified micro marsupialization technique as (7.47±0.64 versus 9.87±1.88 days) [7], Confidence level (C.I)=95%, Power of test (1-β)=80% then the estimated sample size came out to be n=60.To fulfill the statistical assumption of both groups took n=30 in each group. 5% povidone iodine and 2% xylocaine jelly topical anesthetic were applied to the surgical site and left on for five minutes. Group A received a 4-0 silk suture into the internal lesion at its widest diameter. On the seventh day in both groups, the suture was taken out. Group B underwent the largest number of 4-0 silk sutures (3–5 in our study) while keeping the gap between entry and exit as short as possible. In order to prevent necrosis and suture loss, caution was exercised during tying the knot in both groups to prevent strangulation of the mucosa. Following surgery, all groups were advised to apply 2% xylocaine jelly topical anesthetic preparation three times a day for five days at the surgical site. All the procedure was done by researcher himself under the supervision of consultant. SPSS version 26.0 was employed to analyze the data. Independent t-test was applied to compare the wound healing time and duration of surgery and comparison of postoperative pain on 7th day between the groups. At the $p < 0.05$ threshold, statistical significance was established.

RESULTS

Table 1 indicated demographics information of patients. Where most of the patients belongs to age group >30, 42 (70%) followed by 18-30, 18 (30%) respectively. And gender distribution displays male were in preponderance 36 (60%) than female 24 (40%) mean ± SD of Group A presented 37.7 ± 8.4 and Group B 33.8 ± 10.1 respectively. Mean ± SD postoperative 1st day was 8.2 ± 1.1, postoperative 3rd day 6.2 ± 1.4 in group A while in group B postoperative 1st day mean ± SD was 7.8 ± 1.2 and postoperative 3rd day indicates 5.7 ± 1.7 (pain was assessed by visual analogue scale).

Table 1: Demographic Information of Patients and Postoperative Pain at Follow Ups

Age (Years)	Group A N (%) / Mean ± SD	Group B N (%) / Mean ± SD
18-30	7 (23.33)	11 (36.67)
>30	23 (76.67)	19 (63.33)
Mean	37.7 ± 8.4	33.8 ± 10.1
Gender		
Male	19 (63.33)	17 (56.67)
Female	11 (36.67)	13 (43.33)
Pain Score at 1st Day	8.2 ± 1.1	7.8 ± 1.2
Pain Score at 3rd Day	6.2 ± 1.4	5.7 ± 1.7

Table 2 showed stratification of age groups and gender association age group of 18-30 years in group A indicated mean ± SD of 3.71 ± 1.79 whereas, age group >30 showed 2.39 ± 1.82 (p=0.129) and in group B 18-30 years showed mean ± SD of 2.27 ± 1.90 while in > 30 years it showed 2.11 ± 1.66 (p=0.602). Gender stratification showed insignificant values in male (p=0.682) while in female (0.194). Independent t-test was applied on variables of table 2. No any significant association was observed in age or gender.

Table 2: Stratification of Age Group and Gender

Age	Groups	Postoperative Pain (7th Day) Mean ± SD	p-Value
18 -30	Group A	3.71 ± 1.79	11 (36.67)
	Group B	2.27 ± 1.90	19 (63.33)

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>30	Group A	2.39 ± 1.82	0.602
	Group B	2.11 ± 1.66	
Gender	**Groups**	**Postoperative Pain (7th Day) Mean ± SD**	**p-Value**
Male	Group A	2.42 ± 1.67	0.682
	Group B	2.18 ± 1.87	
Female	Group A	3.18 ± 2.18	0.194
	Group B	2.15 ± 1.57	

Table 3 showed comparative statistics of wound healing time, duration of surgery and postoperative pain at 7th day. Mean ± SD of wound healing time between groups was noted as (9.7 ± 3.17 versus 10.9 ± 4.01) with a non-significant P-value (P=0.180). Mean ± SD of duration of surgery was noted between groups as (30.23 ± 3.71 versus 29.90 ± 3.64) having a non-significant P-value (P=0.727). Mean ± SD of postoperative pain score at 7th day was noted as (2.70 ± 1.87 versus 2.17 ± 1.72) having a non-significant P-value (P=0.257) as indicated in table 3.

Table 3: Comparative Statistic of Wound Healing, Duration of Surgery and Postoperative Pain

Groups	Mean ± SD	p-Value
Wound Healing Time (Days)		
Group A	9.70 ± 3.17	0.180
Group B	10.97 ± 4.01	
Duration of Surgery (Minutes)		
Group A	30.23 ± 3.71	0.727
Group B	29.90 ± 3.64	
Postoperative Pain at 7th Day		
Group A	2.70 ± 1.87	0.257
Group B	2.17 ± 1.72	

DISCUSSION

While mucous retention cysts are caused by blockage of the duct of a minor or auxiliary salivary gland, mucous extravasation cysts are typically thought to have a traumatic origin, such as lip biting. Over 80% of all mucoceles are extravasation mucoceles, which are more prevalent in people under 30. Retention mucoceles, on the contrary, are not as common and more common in elderly people [16]. Evolution of mucoceles was rapid or slow and painless, with periods of remission and exacerbation. If the lesion was localized superficially, it presents a bluish coloring due to the superficial capillary network that appears through it. When located more deeply in tissues, its color is similar to that of the mucosa. Prognosis of the lesion was favorable and was conventionally treated by excision of the gland along with the associated overlying mucosa and glandular tissue down to the muscle layer [17]. The surgical procedure has a high rate of morbidity with risk of injury to the submandibular duct and lingual nerve. Mucocele is a common oral mucosal lesion that occurs more frequently in children and adolescents, which originates from the minor salivary glands [18]. These lesions resulting from either trauma or change in the drainage system of the salivary glands resulting in mucous accumulation. The primary risk factors include oral trauma, which includes lip and cheek biting, piercings, and unintentional salivary gland rupture. The duct's dilatation is a result of an etiologic component other than its obstruction, which can be a sialolith or dense mucosa [19, 20]. These lesions are benign, generally painless, depending on the location, can cause discomfort and create trouble, especially in pediatric population. Lesions are most commonly affected with equal gender predilection and with a clinical history of a painless swelling. However, lesions are often recurrent in nature that may present for months or even years before the patient seek treatment. According to the microscopic features, oral mucoceles can be classified as "mucus retention", which occurs due to ductal obstruction with subsequent retention of saliva within the ducts, whereas "extravasation" occurs due to trauma to the salivary duct and pooling of mucus into the connective tissue [19]. The findings of our study are comparable with multiple studies conducted worldwide. Few of which were discussed here. In this study, mean age in group A (micro-marsupialization) was 37.7 ± 8.4 and group B (modified micro marsupialization) was 35.5 ± 10.1 years. In another study, the mean age of the patients in group 1 (micro marsupialization) was 19.6 ± 9.6 years while in group 2 (surgical excision) it was 21.9 ± 11 years [4]. A study reported the mean healing time and duration of surgery in micro-marsupialization and modified micro-marsupialization technique as (7.47 ± 0.64 versus 9.87 ± 1.88) days and (4.10 ± 0.39 versus 5.33 ± 0.72) minutes respectively while no pain was noted in both group at 7th day of treatment [7]. In this study, in group wise distribution of gender, 19 (63.3%) males and 11 (36.7%) females were included in group A while 17 (56.7%) males and 13 (43.3%) females were included in group B. In present study, in group A and B, wound healing time 9.7 ± 3.1 and 10.9 ± 4.01 days, duration of surgery 30.2 ± 3.7 and 29.9 ± 3.6 minutes and postoperative pain score at 1st day 8.2 ± 1.1 and 7.8 ± 1.2, at 3rd day 6.2 ± 1.4 and 7th day 2.7 ± 1.87 and 2.17 ± 1.72, respectively. The oral trauma was the main predisposing factors such as lip biting, cheek biting, piercings, and accidental rupture of salivary gland. The dilation of the duct was secondary to its obstruction caused by dense mucosa or a sialolith was another etiologic factor [21].

CONCLUSIONS

One of the more established techniques, marsupialization, was typically used on significant mucoceles to prevent harm to nearby anatomy structures that have differing rates of recurrence. In addition, it causes a great deal of discomfort and necessitates cleanliness to avoid infections in the area. It seemed that modified micromarsupialization is a safe method for treating

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mucoceles. However, it requires more time during surgery and causes more discomfort afterward than micromarsupialization. It was concluded that insignificant difference was noted between micro-marsupialization and modified micro-marsupialization in outcomes of surgical technique in treatment of mucocele of lower lip.

Authors Contribution

Conceptualization: A
Methodology: A, LMA
Formal analysis: SS
Writing, review and editing: AAK, THS, FL

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

Conflicts of Interest

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Comparison of Pain, Facial Swelling and Mouth Opening of Single Versus Multiple Suture Technique After Third Molar Extraction

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ABSTRACT

Extraction of the third molar is a common technique. Pain, swelling and trismus are common signs of local inflammation during the postoperative phase. Moreover, opinions are divided when it comes to the mucosal closure phase of impacted mandibular third molar **Objective:** To compare the pain, facial swelling and mouth opening of single versus multiple suture techniques after third molar extraction. **Methods:** This quasi-experimental study included 54 patients aged 18-35 requiring mesioangular mandibular third molar extraction. Participants were non-randomly assigned to Group A (single suture) or Group B (multiple suture). Exclusions were based on suture allergies, chronic conditions, pregnancy, lactation, or acute infections. Impacted molars were classified using the Pell-Gregory system, and radiographs assessed impaction. Participants were instructed to return on the 1st, 3rd, and 7th postoperative days for assessment of Pain, swelling, and mouth opening, and comparisons between the two groups were made using the Student's t-test. **Results:** Patients in groups A and B had mean and standard deviation pain levels of 6.9 ± 0.9 and 6.4 ± 0.9 post-operatively on Day 1 and 2.0 ± 2.1 and 2.5 ± 2.7 on Day 7. Post-operative facial swelling measured 15.4 ± 2.4 and 17.0 ± 3.4 mm on Day 1, 14.8 ± 2.4 and 4 ± 2.7 mm on Day 7 in groups A and B. Mean and standard deviation of mouth opening in groups A and B were 26.5 ± 3.6 and 23.7 ± 2.8 mm post-operatively at Day 1, 29.6 ± 3.6 and 27.2 ± 3.0 mm at Day 7. **Conclusions:** It was concluded that based on post-operative pain, swelling, mouth opening, and trismus following third molar extraction, single suture approach was somewhat better than multiple suture.

INTRODUCTION

Eruption of wisdom tooth normally occurs around the age of 17-21 years [1]. A tooth that does not erupt into its functional state of occlusion is termed as "impacted tooth" [2]. The removal of third molar is a common and frequently done oral surgical procedure performed in oral and maxillofacial surgery [3]. Based on the location, depth, angulation and density of bone extractions may vary from easy to extremely difficult procedure [4]. Symptoms related to impaction of third molars usually arise from pericoronitis and its sequelae. Some of the patients may also face these symptoms related to pathological conditions occurring as a result of impaction of the third molar [5]. The third molar extraction's most often reported side effects include trismus, pain, and swelling [6]. During the postoperative phase, an inflammatory response is predicted despite the expert surgeon using a precise surgical procedure [7]. A number of experimental studies have been focusing on different methods to reduce these complications which includes single and multiple suture techniques with or without placement of drains and giving

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incision in the mucosa distal to second molar to create a window for inflammatory exudates to let out. Suture less techniques related to third molar surgery are gaining fast worldwide recognition [8]. The variance of opinion concerning wound closure technique after the extraction of the third molar has different beliefs related to the merit and demerit of primary versus secondary wound closure [9]. Primary wound closure is carried out by covering and sealing the socket with the help of an air-tight mucosal flap. The secondary wound closure involves a 5-6 mm thick wedge of mucosa removed from the distal aspect of the second molar and the flap is repositioned. A triangular opening is made distal to the second molar with the help of interrupted sutures to create a passive outlet for inflammatory exudates and avoid the incorporation of drains [10]. In contrast to first-intention healing, second-intention healing results in a better outflow of the inflammatory exudate, which lowers edema [11]. There is a paucity of local studies about the use of single and multiple suture techniques in removing impacted mandibular significantly decreased postoperative inflammatory complications i.e., pain, swelling and trismus. The single suture technique involves using one long, continuous stitch to close the site after removing a third molar. It's quicker and simpler, with even tension along the incision, but if something goes wrong, it's harder to adjust. On the other hand, the multiple suture technique uses several individual stitches, giving the surgeon more control and allowing for precise adjustments if needed. This method can improve the way the tissue heals but takes more time and involves more knots. Generally, the single suture is used for straightforward cases, while the multiple suture technique is preferred for more complex or irregular wounds [12]. Through this study, we can bring out data that which technique is better in controlling inflammatory complications postoperatively. There is limited local research comparing pain, facial swelling, and mouth opening between single and multiple suture techniques after third molar extraction.

This study aimed to provide clinicians with evidence to choose the most effective and convenient suturing method for optimal patient outcomes and to compare the pain, facial swelling and mouth opening of single versus multiple suture techniques after third molar extraction.

METHODS

This quasi-experimental study used a non-probability consecutive sampling method and was conducted from January 2022 to December 2022 at the Department of Oral and Maxillofacial Surgery, Liaquat University of Medical and Health Sciences, Jamshoro. The sample was calculated through open epi at 90% power of the test and 95% confidence level using mean swelling of 1.2 ± 0.113 from the multiple suture group and 1 ± 0.107 from single suture group on Day 1 of the third molar surgery from the previous study [8]. Patients aged 18-35 years irrespective of any gender and requiring surgical extraction of mesioangular mandibular third molar were included in the study. Patients who were allergic to suture material, medically compromised patients i.e., Chronic Liver Disease (CLD), Diabetes, Pregnant and Lactating Patients and Acute Infection (pericoronitis) were excluded from the study. The study was carried out with permission from the Liaquat University of Medical and Health Sciences' research ethics committee in Jamshoro (LUMHS/REC/- 154). Patients who met the eligibility requirements and those who expressed interest in participating were added to the research, and they were told of its purpose and the benefits of participating. Before study enrolment, a signed permission was obtained in good faith. Each suspected patient was assessed carefully. Complete history and examination were done to preclude any systemic disease. The patient's whole medical history, including name, age, gender, and hospital registration number, as well as any current complaints and any clinical characteristics like pain, swelling, or mouth opening was documented on a proforma. The Pell-Gregory classification was used to assess the third molar that was affected. Every patient had an OPG and periapical radiograph to determine the class of impaction [13]. Following the patient's non-randomized allocation, they were assigned to either Group A (single suture) or Group B (multiple suture). All surgeries were carried out under the supervision of a supervisor and local anesthesia using the conventional nerve block anesthesia technique of the lingual, buccal, and inferior alveolar nerves. Two 1.8 mL cartridges containing 2% xylocaine with epinephrine 1: 100,000 (Medicine; made in Korea) were administered. Using blade number 15, a three-sided mucoperiosteal flap was elevated. The incision was made at the spot where the second molar's middle and posterior thirds converge (approximately 6 mm down the buccal sulcus), and it continued upward to the tooth's distobuccal angle. The incision was expanded laterally and distally along the external oblique ridge after continuing along the gingival sulcus to a location somewhat distal to the third molar. Neither a lingual retractor nor a lingual flap were used. The bone was removed utilizing the buccal guttering method on a rotator hand piece with a fissure bur while being continuously irrigated with regular saline. Following extensive irrigation and debridement, the tooth was raised using an elevator and straight pair. The flaps were then closed by the treatment group. A single 3-0 silk suture was positioned at the distal relieving incision in Group A. Multiple 3-0 silk sutures were positioned at the distal relieving incision and at the interdental papilla, which is the space between the second and third molars, for the Group B patient. Oral antibiotics, analgesics, and instructions to use a warm saline rinse were given to both treatment

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groups. We took care to exclude any elements or substances that may have an impact on the research's variables. This includes applying cold packs and using steroids. Post-operative guidelines were given to each patient. Measurements of facial swelling were taken before the procedure as well as on the 1st, 3rd, and 7th Day after the procedure. To quantify facial swelling, three measures were obtained for the gonion angle-lateral canthal of the eye, tragus-commissure of the mouth, and tragus-pogonium. Before the procedure and on the 1st, 3rd, and 7th Day after the procedure, trismus measurements were made using a millimeter ruler (which measures the greatest distance between the maxillary and mandibular central incisor). Mouth opening less than 25 mm was considered trismus. SPSS version 21.0 was used for data analysis. The mean and standard deviation were calculated for the quantitative variables, which included age, pain score, trismus, and swelling. The frequency and percentage of the qualitative variable, such as gender, were calculated. To determine the significance of the differences between the two groups, student t-test was used. P<0.05 was a significant level.

RESULTS

To assess the level of pain, swelling and mouth opening restriction, the patients were instructed to return to the clinic on the 1st, 3rd, and 7th postoperative days. If the patients had any unexpected pain, they were also instructed to visit the clinic on any day. Each patient received a form, on which to enter their visual analog scale (VAS) values for pain assessment [14, 15]. Prior to surgery as well as the 1st, 3rd, and 7th Day after surgery, VAS scores were gathered (Figure 1).

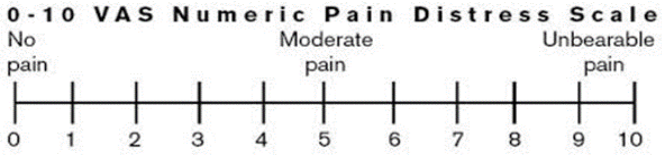

Figure 1: Visual Analogue Scale Rating

The age range of participants in both groups was 23 to 35 years. The mean age for the first single suture group was 31.4 ± 4.6 years, while the mean age for the second single suture group was 31.2 ± 4.3 years. Out of 54 patients, male patients were 12 (44.4%) and 10 (37.0%) and female patients were 15 (55.56%) and 17 (62.96%) in Group A (single suture) and B (multiple suture) respectively (Table 1).

Table 1: Distribution of Age of the Participants in Both Groups (n=54)

Variable	Characteristics	Single Suture (n=27)	Multiple Suture (n=27)
Age (Years)	Range	23-35	23-35
	Mean ± S.D	31.4 ± 4.6	31.2 ± 4.3
Gender n (%)	Male	10 (37.03%)	12 (44.44%)
	Female	17 (62.96%)	15 (55.56%)

*student t-test

The mean preoperative pain scores were similar between the single suture (7.3 ± 1.2) and multiple suture groups (7.6 ± 1.2), with no significant difference (p-0.30). On postoperative Day 1, mean pain scores were slightly higher in the single suture group (6.9 ± 0.9) compared to the multiple suture group (6.4 ± 0.9), but this difference was not statistically significant (p-0.063). On Day 3, pain scores had decreased in both groups (single suture mean 5.1 ± 1.4; multiple sutures mean 4.9 ± 0.9) with no significant difference (p-0.48). On day 7, mean pain scores further decreased (single suture 2.0 ± 2.1; multiple sutures 2.5 ± 2.7) with no significant difference between the groups (p-0.39) (Table 2).

Table 2: Comparison of Pain Score at Preoperative, and Various Time Points Between Two Interventions (n=54)

Pain	Single Suture Mean ± S.D (95% CI)	Multiple Suture Mean ± S.D (95% CI)	P-Value*
Pre-Operative	7.3 ± 1.2 (5.0-10.0)	7.6 ± 1.2 (5.0-9.0)	0.302
Post-Operative			
Day 1	6.9 ± 0.9 (5.0-8.0)	6.4 ± 0.9 (5.0-8.0)	0.063
Day 3	5.1 ± 1.4 (2.0-8.0)	4.9 ± 0.9 (4.0-7.0)	0.482
Day 7	2.0 ± 2.1 (0.0-6.0)	2.5 ± 2.7 (0.0-9.0)	0.399

*student t-test

Preoperative facial swelling was similar between the single suture (14.3 ± 2.4 mm) and multiple suture groups (mean 15.5 ± 3.3 mm), with no significant difference (p-0.128). On postoperative Day 1, facial swelling was slightly higher in the multiple suture group (17.0 ± 3.4 mm) compared to the single suture group (15.4 ± 2.4 mm), approaching statistical significance (p-0.050). By Day 3, facial swelling remained higher in the multiple suture group (16.8 ± 3.0 mm) compared to the single suture group (15.1 ± 2.7 mm), with a significant difference (p-0.034). By Day 7, the trend continued, with the multiple suture group having higher facial swelling (16.4 ± 2.7 mm) compared to the single suture group (14.8 ± 2.4 mm), also showing a significant difference (p-0.027) (Table 3).

Table 3: Comparison of Facial Swelling (mm) at Preoperative and Various Time Point Between Two Interventions (n=54)

Facial Swelling	Single Suture Mean ± S.D (95% CI)	Multiple Suture Mean ± S.D (95% CI)	P-Value*
Pre-Operative	14.3 ± 2.4 (12.0-21.7)	15.5 ± 3.3 (10.7-21)	0.128
Post-Operative			
Day 1	15.4 ± 2.4 (13.0-23.7)	17.0 ± 3.4 (12.0-23.3)	0.050
Day 3	15.1 ± 2.7 (12.3-24.3)	16.8 ± 3.0 (11.7-22.7)	0.034
Day 7	14.8 ± 2.4 (12.0-23.0)	16.4 ± 2.7 (10.7-21.7)	0.027

*student t-test

Preoperative mouth opening was greater in the single suture group (29.9 ± 3.7 mm) compared to the multiple suture group (26.6 ± 3.9 mm), and this difference was significant (p-0.002). On postoperative Day 1, mouth opening remained significantly greater in the single suture group (26.5 ± 3.6 mm) compared to the multiple suture

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group (23.7 ± 2.8 mm), with a statistically significant difference (p-0.002). By Day 3, mouth opening increased in both groups, but the single suture group (27.4 ± 3.6 mm) still showed significantly greater mouth opening than the multiple suture group (25.3 ± 2.6 mm, p-0.016). By Day 7, the single suture group (29.6 ± 3.6 mm) continued to have significantly greater mouth opening compared to the multiple sutures group (27.2 ± 3.0 mm) (p-0.011) (Table 4).

Table 4: Comparison of Mouth Opening (mm) at Preoperative, and Various Time Point Between Two Interventions (n=54)

Mouth Opening	Single Suture Mean ± S.D (95% CI)	Multiple Suture Mean ± S.D (95% CI)	P-Value*
Pre-Operative	14.3 ± 2.4 (12.0-21.7)	15.5 ± 3.3 (10.7-21)	0.128
Post-Operative			
Day 1	26.5 ± 3.6 (21.0-35.0)	23.7 ± 2.8 (17.0-29.0)	0.002
Day 3	27.4 ± 3.6 (22.0-36.0)	25.3 ± 2.6 (18.0-30.0)	0.016
Day 7	29.6 ± 3.6 (25.0-40.0)	27.2 ± 3.0 (22.0-33.0)	0.011

*student t-test

DISCUSSION

An impacted lower third molar removal results in pain swelling, and difficulty opening the mouth. Submucosal dexamethasone is an accessible route of steroid administration in patients [14]. The duration of the surgical intervention, the kind of suturing method used, and the type of wound closure all influence the prevalence of such postoperative issues [15, 16]. Our results showed that age and gender were not different statistically between groups. This shows that randomization eliminates these two confounders. Post-operative pain in this study decreased continuously from Day 1, 3, and 7 in both group patients. In the multiple suture group pain level was low on Days 1 and 3 as compared to single suture group whereas pain level on Day 7 was low in single suture group as compared to multiple suture group. According to Osunde OD's research [3], there was a statistically significant difference in pain on postoperative Days 1, 2, and 3 ($P<0.05$), but no significant changes were seen between the two groups on Days 5 and 7. Since Shuja and Maria effectively removed the inflammatory exudates through their closure techniques, they also reported reduced discomfort [17-19]. In this research post-operative assessment of facial swelling after third molar extraction shows a significant difference in facial swelling on Day 1 (p-value = 0.050) 15.4 ± 2.4 and 17.0 ± 3.4 mm, facial swelling at Day 3 (p-value = 0.034) 15.1 ± 2.7 and 16.8 ± 3.0 mm and facial swelling at Day 7 (p-value = 0.027) 14.8 ± 2.4 and 16.4 ± 2.7 mm in Group A (single suture) and Group B (multiple suture) respectively. Post-operative swelling decreased continuously from Day 1, 3 and 7 in both group patients. In single suture group swelling level was low on Day 1, 3 and 7 as compared to multiple suture group. Similarly, a study carried out by Mahat showed that facial swelling on 7th postoperative day was significantly higher in the multiple suture group [19].

One of the frequent side effects that accompany the extraction of mandibular impacted third molars is trismus. In addition to other factors, low-grade infections and repetitive muscular stimulation are the usual causes of this [20]. Post-operatively, trismus in our study was almost similar from Day 1, 3 and 7 in both group patients. Other studies have shown a reduction in trismus when using a method of closure that allows for the outflow of inflammatory exudates. These outcomes were likewise comparable to those previous investigations [16, 17].

CONCLUSIONS

This study concluded that both single and multiple suture techniques are effective in managing postoperative pain, the single suture technique may offer advantages in terms of reducing postoperative facial swelling and improving mouth opening. These benefits could lead to enhanced patient comfort and faster functional recovery.

Authors Contribution

Conceptualization: KAC
Methodology: BB, SUR
Formal analysis: SM, SH
Writing-review and editing: SARS, SS

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

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Original Article

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Comparison of Prognostic Value of Predictors of Mortality in Patients with Cirrhosis and Refractory Ascites

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ABSTRACT

The Model for End-Stage Liver Disease-Sodium score (MELDNa) has been developed that has a better prognostic value to predict early mortality but has not been frequently used in cirrhotic and refractory ascites patients with recurrent incidences of severe hyponatremia. **Objective:** To compare the prognostic value of severe hyponatremia, Child-Pugh score, and the model for end-stage liver disease-sodium score in cirrhotic and refractory ascitic patients. **Methods:** A prospective, observational study was conducted at the Hepatology Department, Bakhtawar Amin Trust Hospital, Multan from March 2023 to March 2024. A total of 200 patients with cirrhosis and refractory ascites undergoing albumin paracentesis twice a month were selected for the study. The 135 patients (after exclusion of preexisting ascites patients) were administered diuretics symmetrically; 50 mg spironolactone and 40 mg furosemide in patients who did not have renal failure and severe hyponatremia. Prognostic scores were recorded and patients were followed up for minimum 3 months. **Results:** The area under the curve of the Child-Pugh score (0.90, 95% CI: 0.87-0.96) was significantly higher than the MELD score (0.60, 95 CI: 0.51-0.70) and MELDNa (0.75, 95% CI: 0.65-0.79) as a predictor of mortality (p<0.0001). With respect to the etiology of refractory ascites being an independent risk factor of mortality, the cumulative incidence function was highest in patients with hyponatremia (79%; 95% CI: 79-80%) followed by renal failure patients (55%; 95 CI: 54-56%) and patients receiving maximum dose of treatment (28%; 95% CI: 27-29%) (p<0.001). **Conclusions:** Severe hyponatremia, ineffective diuretic treatment, and Child-Pugh score were risk factors of death in cirrhotic and refractory ascitic patients.

INTRODUCTION

Cirrhotic patients often suffer serious complications including ascites. This condition is commonly managed by diuretics and sodium restriction [1]. Resistance to the diuretic medication or unchanged status after diuretic treatment can be regarded as refractory ascites. Refractory ascites can only be treated definitively by a liver transplant [2]. Several tools called predictors of mortality are used to predict the patient prognosis and outcomes of patients with liver diseases. Model for End-Stage Liver Disease (MELD) score is used to diagnose end-stage liver disease and predict its prognosis and 3-month survival. United Network for Organ Sharing had adopted it to test donor livers due to its objectivity and ability to predict risk of mortality. Child-Pugh score is also a prognostic tool for liver cirrhosis patients based upon ascites, hepatic encephalopathy, International Normalized Ratio, albumin and total bilirubin levels. Some studies have argued that MELD is a better predictor of mortality while some report comparable prognostic accuracy of both [3, 4]. Patients are referred for liver transplants by assessing them by end-stage liver disease score only. However, the MELD score cannot accurately assess the risk of mortality in cirrhotic and refractory ascitic patients [5]. Studies have shown that transplant patients with MELD scores less than 20

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were at high risk of mortality and were independently associated with the incidence of hyponatremia and refractory ascites [6, 7]. An improved version of the MELD score, the model for end-stage liver disease-sodium score has been developed that has a better prognostic value to predict early mortality [8]. The score assesses the severity of liver cirrhosis by using serum sodium values ranging from 125 mmol/L and 140 mmol/L. However, this score has not been frequently used in cirrhotic and refractory ascites patients with recurrent incidences of severe hyponatremia. It was conducted that the present study to evaluate the incidence and risk factors of low serum sodium in patients with cirrhosis and refractory ascites.

The aim of this study was to compare the prognostic value of severe hyponatremia, Child-Pugh score, and the model for end-stage liver disease-sodium score in cirrhotic and refractory ascitic patients.

METHODS

A prospective, observational study was conducted at the Medicine Department, Bakhtawar Amin Trust Hospital, Multan from March 2023 to March 2024. A total of 200 patients with cirrhosis and refractory ascites undergoing albumin paracentesis twice a month were selected for the study by consecutive sampling. The sample size was calculated by EpiInfo keeping 5% margin of error, 95% confidence interval and 50% population proportion. Patients who died during 1st month of the follow-up, who did not undergo a minimum of two large volume paracentesis, who had a transplant history, and patients with trans jugular intrahepatic portosystemic shunt were excluded. All patients provided their consent to become a part of the study. The ethical board of the hospital approved the study by Ref No.186/23.EC/BAM and DC. Refractory ascites patients were classified according to International Ascites Club, 30 patients had tense ascites and severe hyponatremia and 35 patients had renal failure without diuretics [9]. Patients were divided into classifications based on the etiology of refractory ascites; diuretic resistant ascites, diuretic intractable ascites caused by renal failure, and one caused by severe hyponatremia. These patients did not receive diuretic therapy. These patients were treated with 40 mg propranolol once a day. After excluding the refractory ascites patients, 135 patients were administered diuretics symmetrically; 50 mg spironolactone and 40 mg furosemide in patients who did not have renal failure and severe hyponatremia. These doses were increased per week by 50mg for spironolactone and 20mg for furosemide with a maximum dose administered of 400mg and 160 mg, respectively. A total of 62 patients were administered the maximum dosage of medication and were deemed to have diuretic-resistant ascites, 40 patients experienced severe hyponatremia when the dose was increased and were deemed to have diuretic intractable ascites by hyponatremia (cut-off sodium value during treatment: 125 mmol/L) and 33 patients had renal failure during treatment and were deemed to have diuretic intractable ascites by renal failure (cut-off serum creatinine: 1.5 mg/L). the effective dosage of medication in these patients was contraindicated so they were administered at low dosages while closely observing metabolic disturbances. A minimum 3-month follow-up was done (unless patients died before it) when the maximum dosage of medication started being ineffective or when limited diuretics were started. Transplant patients were followed up till transplant day and non-transplanted ones were follow up till last visit and survival data were noted. Sodium and creatinine values were measured by blood test when patients were divided into categories. Patients were divided into Group A (those with sodium level less than 130 mmol/L) and Group B (those with sodium levels more than 130 mmol/L). Patients' data including demographics, cause of cirrhosis (by lab tests, blood count, radiological assessment and hepatitis screening), prognostic scores (MELD, MELDNa, and Child-Pugh), physical exam were recorded at admission and information about biochemical test results, the incidence of diabetes, and treatment details (diuretics or betablockers) was extracted from patient records. MELD was measured by online Medscape calculator [10]. MELDNa was calculated by the formula used in Kim WR et al [11]. Child-Pugh score was calculated by MdCalc online calculator [12]. The frequency of large-volume paracenteses was recorded after satisfying the inclusion criteria. Patient outcomes i.e. transplant or mortality were recorded in 3-month follow-up. Cardiac output and cardiac index were measured by thermodilution and standard formula, respectively to check cardiac function. All the data were analyzed by SPSS version 24.0. Results of all patient groups were compared to assess predictors of low sodium by t-test or Wilcoxon Rank test in case of continuous data and by chi-squared or Fisher's test in case of categorical data. Binary logistic regression analysis was performed of these variables. The patients in whom the transplant was carried out and were discharged were at lower risk of mortality so transplantation defined the competing risk of death before discharge. The risk of mortality was defined by cumulative incidence competing risk estimate with transplant being the competing risk of the outcome. Gray's test was performed to assess cause-specific death (calculated by cumulative incidence function) differences. Univariate and multivariate analyses were performed to assess predictors of mortality by using the Fine-Gray hazards model. The area under the receiver operating characteristic curve was used to determine the prognostic value of predictors of mortality. A two-tailed p-value <5% was taken significant.

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RESULTS

Patients' characteristics were shown in table 1. With respect to the etiology of refractory ascites, 66 (33%) patients had renal failure, and 70 (35%) patients had severe hyponatremia. Seventy-six patients had low sodium levels. The average MELDNa score was 22 and 92 (46%) had a score below this median. Patients were followed up for a median duration of 9 months during which 135 (65%) patients died. 40 patients (20%) had a transplant with 54% (95% CI: 54-55%) cumulative incidence of death after one year and 66% (95% CI: 66-67%) after two years (Gray's test). Major causes of death were sepsis, hepatocellular carcinoma, and spontaneous bacterial peritonitis. Patients were categorized according to serum sodium levels which revealed that group B had a lower Child-Pugh score but higher albumin and protein levels. MELDNa scores were lower in high sodium patients with high creatinine levels (Table 1).

Table 1: Patient's Variables with Respect to Sodium Concentrations(n=200)

Variables	Group A Na <130 mmol / L N (%) / (Mean ± SD)	Group B Na >130 mmol / L N (%) / (Mean ± SD)	p-Value
Male	61 (80.3%)	98 (79.1%)	0.42
Age	61.8 ± 12.5	57.1 ± 12.4	0.27
Weight	79 (51-112)	75 (41-133)	0.89
Child-Pugh Class C	65 (85.6%)	69 (55.7%)	<0.001
MELD Score	18.8 ± 5.0	20.3 ± 5.3	0.070
MELDNa	26.9 ± 3.0	22 ± 4.5	<0.001
			0.30
Etiology of Cirrhosis			
Hepatitis C (by Hepatitis Screening)	40 (52.7%)	100 (80.7%)	-
Hepatitis B (by Hepatitis Screening)	36 (47.3%)	24 (19.3%)	-
Hepatocellular Carcionoma (Triphasic MSCT)	23 (30.3%)	36 (29.1%)	0.55
Hepatic Encephalopathy (Liver Function Test)	34 (44.8%)	41 (33.1%)	0.09
Diabetes (Patient Records)	19 (25%)	23 (18.6%)	0.25
INR (Blood Test)	2.0 (1.4-2.7)	1.9 (1.2-2.8)	0.09
Creatinine (Blood Test)	80 (50-250)	99 (43-319)	0.001
Sodium (Blood Test)	125 (115-130)	135 (129-147)	<0.001
Total Bilirubin (Blood Test)	65 (20-345)	49 (9-160)	0.28
Albumin (Blood Test)	27 (20-39)	30 (20-48)	0.020
HVPG	17.5 ± 8.0	18.0 ± 7.1	0.80
Cardiac Index	3.6 (2.8-9.0)	3.9 (2.6-6.8)	0.74
LVPs	2.0 (0.8-7.2)	2.0 (0.8-11.3)	0.56
Protein Concentration in Ascitic Fluid	11 (2-24)	13 (1-26)	0.001
Diuretics at Admission (Obtained from Patient Records)	44 (58%)	93 (75%)	0.015

According to multi-variable analysis a low sodium was independently related to low dosage diuretic treatment, high Child-Pugh score and low MELD score. The groups did not differ with respect to cause of mortality (86.6% vs 70%). The cumulative risk of mortality at one year was 80% and 39%, respectively (p<0.001). The difference between cumulative incidence at 125, 130, and 135 mmol/L of sodium was significant between both groups. The predictors were mortality were shown in table 2.

Table 2: Univariate Analysis of Predictors of Mortality in Entire Study Population

Variables	Crude Hazards Ratio (Before Adjustment of Variables)	Minimum	Maximum	p-Value
Male	1.05	0.72	1.56	0.910
Age	1.05	1.05	1.06	<0.001
Systolic Blood Pressure	1.03	1.01	1.03	0.051
Child-Pugh Class C	1.49	1.41	1.74	<0.001
MELD Score	1.06	1.03	1.12	0.072
MELD Na	1.15	1.11	1.22	<0.001
HCC	1.79	1.32	2.56	<0.001
Diabetes	1.11	0.76	1.59	0.67
Renal Failure	2.19	1.44	3.58	<0.001
Hepatic Encephalopathy	1.42	0.98	2.03	0.083
Esophageal Varices	1.42	1.15	1.71	0.001
Maximum Dose of Diuretics	**Reference**			
Severe Hyponatremia	4.36	2.76	6.85	<0.001
INR	2.07	1.35	3.42	0.002
Creatinine	0.97	1.01	0.98	0.36
Sodium	0.95	0.99	0.97	<0.001
Total Bilirubin	0.97	0.97	1.05	0.003
Albumin	1.00	0.92	0.96	0.092
HVPG	1.04	0.95	1.13	0.38
Cardiac Index	1.22	0.72	2.10	0.57
LVPs	1.45	1.27	1.58	<0.001
Protein Concentration in Ascitic Fluid	0.96	0.93	1.02	0.009
Beta-blockers at Admission	2.53	0.75	3.62	<0.001
Diuretics at Admission	0.66	0.47	0.96	0.019

The independent predictors of mortality were shown in table 3. No significant association between beta-blockers and LVPs was noted in relation to the risk of mortality in patients without beta blockers. (HR: 1.20, p=0.3). Hyponatremia, renal failure, and high Child-Pugh score were independent predictors of death in these patients.

Table 3: Multi-variate Analysis of Predictors of Death by Fine-Gray Model

Variables	Patients without HCC				Patients without Beta-Blocker Therapy at Admission			
	aHR	Minimum	Maximum	p-Value	aHR	Minimum	Maximum	p-Value
Etiology of Refractory Ascites								
Hyponatremia	2.19	1.20	4.16	0.01	4.38	1.92	10.10	<0.001
Renal Failure	1.8	0.88	2.90	0.2	2.45	1.18	4.91	0.02
Beta-Blockers	1.98	1.18	3.35	0.009	-	-	-	-
LVPs	1.68	1.29	2.08	<0.001	1.40	1.19	1.61	<0.001
Child-Pugh Score	1.51	1.29	1.68	<0.001	1.56	1.28	1.77	<0.001

The prognostic accuracy of predictors of mortality is shown in table 4. The area under the curve of the Child-

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Pugh score (0.90, 95% CI: 0.87-0.96) was significantly higher than the MELD score (0.60, 95 CI: 0.51-0.70) and MELDNa (0.75, 95% CI: 0.65-0.79) as a predictor of mortality (p<0.0001). With respect to the etiology of refractory ascites being an independent risk factor of mortality, the cumulative incidence function was highest in patients with hyponatremia (79%; 95% CI: 79-80%) followed by renal failure patients (55%; 95 CI: 54-56%) and patients receiving maximum dose of treatment (28%; 95% CI: 27-29%)(p<0.001).

Table 4: Prognostic Accuracy of Independent Predictors of Mortality Calculated the Area Under ROC Curve

Variables	Sensitivity	Specificity	PPV	NPV
Hyponatremia	50%	90%	90%	89%
Child-Pugh Class C	80%	65%	80%	66%
Beta-Blockers	60%	69%	78%	51%
LVPs	55%	49%	74%	40%

DISCUSSION

It was conducted that this study to compare the prognostic accuracy of predictors of mortality in cirrhotic and refractory ascites patients. The results demonstrated Child-Pugh score and severe hyponatremia as etiology of ascites were accurate predictors as compared to the MELDNa score. A low sodium level was frequent in these patients with a 38% incidence in the total population. Hyponatremia was diagnosed in 35% of patients due to which effective treatment course could not be followed. This incidence of severe hyponatremia was significantly higher than as recorded before [13, 14]. A poor prognosis was seen in patients with low sodium and refractory ascites as compared to patients with higher sodium levels [15, 16]. Literature has shown the association between hyponatremia and the degree of cirrhosis, the present study results also showed that low sodium levels were strongly related to the degree of cirrhosis evaluated by the Child-Pugh score [17, 18]. Hyponatremia was also an independent risk factor of mortality, as backed by other studies [19, 20]. This implies that hyponatremia and ascites play an important role in the disease outcome of cirrhotic patients besides adjustment of the MELD score. There were conflicting views regarding the reason for the association between hyponatremia and poor patient outcomes [21, 22]. Our study was unique as we selected patients consecutively and disregarded their position on the waiting list for transplants. Other studies conducted on the association between hyponatremia and cirrhosis followed distinctively different study designs [23]. In the current study, the prognostic accuracy of the MELDNa score in the prediction of mortality was not higher than the Child-Pugh score in refractory ascites and cirrhosis patients so it may not be an appropriate predictor of early mortality in this population. 38% of the population in the present study had low sodium levels <130 mmol/L as it was followed that the criteria of International Ascites Club to diagnose refractory ascites. Kim WR et al., reported that sodium levels in MELDNa were better predictors of prognosis when capped between levels <125 and >140mmol/L [11]. Zhang QK also supported these results [24]. However, some studies disagree with using sodium levels in these ranges when applying MELDNa scores although lower levels were common in refractory ascites patients [25]. Beta-blockers use was a strong riskfactor for mortality in ascitic patients. This was supported by other studies and may be due to the fact that beta-blockers alter survival in patients receiving frequent paracentesis by inducing circulatory dysfunctions [26]. In the current study, LVPs were an independent risk factor of mortality irrespective of treatment with beta-blockers.

CONCLUSIONS

Severe hyponatremia, ineffective diuretic treatment, and Child-Pugh score were risk factors of death in cirrhotic and refractory ascitic patients.

Authors Contribution

Conceptualization: MA, MM
Methodology: HA
Formal analysis: NU, MA
Writing, review and editing: MM, MA, SM, MAC

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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Issues in Clinical Learning Environment Faced by Female Nursing Students at Jamshoro, Pakistan

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ABSTRACT

Hospital-based education provides a supportive environment for nursing students who accept challenges for their profession. Although nursing is primarily a skill-based profession, clinical training is an important component of the growing nursing field. This empowers nursing students to integrate theoretical information into their psychomotor abilities, which they may then use in patient care. **Objective:** To identify issues in the clinical learning environment faced by female nursing students at Jamshoro. **Methods:** A descriptive cross-sectional study was directed at the public sector Liaquat College of Nursing attached to Liaquat University Hospital in Jamshoro from November 2023 to April 2024. A convenience sampling technique was utilized, and the research tool was adopted with some modifications and expert consultations to collect the data. Nursing students enrolled in clinical practice for six months and performed data analysis using IBM SPSS version 25.0. **Results:** The mean age of the participants in this study was evaluated at 21.5 years, with a standard deviation of 0.664 years. According to our findings, 24.6% of participants assigned their duties to the pediatric ward. 82.4% of participants were overseen by a single teacher, 78.3% lacked personal protection equipment, and 72.5% reported a lack of cooperation between the College of Nursing and the hospital. **Conclusions:** It was concluded that most participants are dissatisfied with clinical education, thus, reducing the shortage of clinical faculty, providing personal protective equipment, and developing good coordination between nursing colleges and hospitals can reduce issues faced by nursing students in clinical settings, thereby improving patient care.

INTRODUCTION

The clinical learning environment (CLE) is an essential component of nursing education, allowing students to apply theoretical knowledge in real-world settings [1]. However, CLE refers to the space where learners develop their clinical skills, encompassing the physical surroundings, teaching staff, nurses, and other healthcare professionals [2]. Gender dynamics, cultural norms, and professional expectations can all provide distinct challenges for female students [3]. Undergraduate nursing students face several important issues in their clinical settings, which have an influence on their training to provide patient care [4]. Inadequate staffing in hospitals is one of the most persistent concerns that female nursing students face. [5]. A lack of resources, increases workloads, requiring nurses to hurry through patient care, compromising the quality of treatment offered. Nursing students confront a variety of job dangers, such as infectious illness exposure and physical assault from patients or visitors [6]. As a result, the CLE is more challenging and includes anxiety about unanticipated events, dealing with new equipment, staff and faculty impoliteness, a theory and practice gap, and a lack of confidence in communicating with healthcare workers and patients in clinical settings [7]. Moreover, the administrative burdens and communication breakdowns experienced by nursing students during clinical rotation reduce the quality of patient care [8]. Nursing students claim a lack of support from hospital management in terms of working conditions and professional growth [9]. However, many nurses report a lack of chances for

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professional development, which might impede their growth and capacity to offer high-quality care and teaching-learning processes [10]. These challenges can affect the competencies and learning of nursing students, which eventually compromises the quality of patient care [11]. Thus, learning in a clinical setting presents difficulties in the integration of continuous healthcare delivery, the student-supervisor connection is widely accepted as critical to the learning experience and accomplishment of learning goals [12]. Students face a variety of problems during clinical rotations, which arise from both clinical settings and educational institutions. Moreover, nursing students frequently confront substantial issues in hospital settings, such as high patient-to-nurse ratios, insufficient supervision, and little practical experience, hence high workloads can cause stress and burnout, affecting both student learning and patient care [1]. However, nursing colleges encounter a variety of problems that impact the quality of education they deliver to students. Issues like as ineffective curriculum, a lack of faculty support, and insufficient resources might influence students' readiness for clinical practice [13]. Therefore, healthcare providers play an important part in nursing students' clinical learning experiences [14]. A major obstacle to nursing education is a lack of relevant learning opportunities in clinical environments. This involves insufficient exposure to a wide range of clinical events, as well as a lack of practical expertise [15]. The emotional demands of nursing can worsen stress and feelings of isolation, emphasizing the need for mental health assistance. Understanding these problems allows healthcare organizations and educators to develop ways to improve the clinical learning environment while fostering fairness and inclusion in nursing education. This study aimed to identify issues in the clinical learning environment faced by female nursing students at Jamshoro.

METHODS

A descriptive cross-sectional study was directed to determine the issues in the clinical learning environment faced by female nursing students at Liaquat College of Nursing Female Jamshoro, Pakistan. The target population consists of 69 undergraduate nursing students, 34 from the second year and 35 from the third year. There were 45 students in each batch that are 2nd year and 3rd year in total 90 students' population. The required sample size was 74, with a 95% confidence interval and 5% margin of error However, only 69 students voluntarily participated in the research. Calculator.net was used to calculate the sample size. The research tool was adopted with the permission of the author [16]. Some modifications were done with the experts' consultations. Moreover, the questionnaire was divided into two parts. The first section comprises demographic statistics, while the second section offers various clinical learning environment-related issues in the form of different statements. To simplify the analysis, closed-ended questions were distributed among the enrolled participants, which contained 21 items. The questionnaire used in the study has been reviewed for content validity and pilot-tested on 10% of the population. (Cronbach's alpha coefficient = 0.78) was found to be significant, allowing for measurement of consistency. The study utilized a convenient sampling technique, with inclusion criteria limited to willing second- and third-year students while excluding those who did not consent or were absent during the study. The analysis was performed using SPSS version 25.0. In descriptive statistics, frequencies and percentages were calculated for categorical variables, while means and standard deviation were calculated for continuous variables., with a confidence level of 95% and statistical significance set at $p<0.005$, employing chi-squared tests for categorical variables. Each participant ensured privacy and confidentiality throughout the research process.

RESULTS

In total (n=69) nursing students had a mean age (in years) of 21.55, with a standard deviation of 0.664 years. Participants who completed the questionnaire aged 18 to 26 years were identified and were allocated to different wards based on a clinical rotation method for detecting clinical-related issues. The results are presented in a tabulated format, with descriptions provided below each table. The majority of participants were third-year students, followed by second-year students. Furthermore, huge numbers of participants were placed in clinical placement in the pediatric ward, followed by the medical ward, and then the surgical and endocrinology wards. Age, year of education, and clinical placement of participants were the study's quantitative variables, so their mean and standard deviation were calculated in table 1.

Table 1: Demographic Data Related to Age, Year of Education and Clinical Placement of Participants

Variables	Categories	Frequency (%)	Mean ± SD
Age in (Years)	18	1 (1.4)	21.5 ± 0.66
	20	15 (21.7)	
	21	18 (26.1)	
	22	20 (29)	
	23	11 (15.9)	
	24	3 (4.3)	
	26	1 (1.4)	
Year of Education	Second year	34 (49.3)	1.51 ± 0.504
	Third year	35 (50.7)	
Clinical Placement of Participants	Medical ward	16 (23.2)	4.57 ± 2.714
	Orthopedic ward	5 (7.2)	
	Surgical ward	7 (10.1)	
	Urology ward	5 (7.2)	
	Endocrinology	7 (10.1)	
	Operation Theater	3 (4.3)	

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	Pediatrics	17 (24.6)	
	Gynaecology	5 (7.2)	
	Oncology	4 (5.8)	

That is the gender and marital status. Frequencies and percentages were calculated for all the qualitative variables as shown in table 2. This study found all participants were female and unmarried. All the qualitative demographic variables are presented in table 2.

Table 2: Demographic Data Related to Gender and Marital Status

Variable	Categories	Frequency (%)
Gender	Female	69 (100)
Marital Status	Single	69 (100)

These variables were: (I) Hospital-related issues; and (II) Departmental- or institutional-related issues. (III) Healthcare provider's related issues; and (IV) Lack of learning opportunities faced by undergraduate female nursing students at CLE. Each of these categories is subdivided into different statements in the form of questions, which were asked of participants. The majority 82.4% of participants reported that many students were supervised by a single clinical instructor or (none) in a clinical setting leading to dissatisfaction with learning in clinical areas. Nearly 80% of participants stated a lack of proper PPE in clinical areas, which could have exposed students to infection. Therefore, most students did not participate in nursing procedures and performing skills, which hindered their skill development.

However, 72.5% of participants highlighted healthcare workers as a significant barrier to improved learning. The p-value was found to be statistically significant (p = 0.012). More than 71% of nursing students perceived a lack of collaboration from other medical students during clinical rotations as a difficulty in clinical practice. The p-value was determined to be statistically significant (p = 0.006). About 70% of respondents expressed feeling overwhelmed by written assignments, leading to anxiety, and time-consuming which impacts performing nursing procedures in clinical areas the p-value was found statistically significant (p = 0.001). Moreover, 69% of participants experienced fear of criticism from clinical teachers during practical sessions, which prevented them from seeking guidance in clinical settings and engaging in real-life medical practice. While 68.1% of respondents indicated a lack of clinical instructors or mentors to guide them in clinical settings which developed low confidence in performing clinical skills. It was found that 62.3% of respondents stated that clinical instructors infrequently visit the students in the clinical setting, this lack of interaction led to feelings of isolation in the clinical environment and a subsequent impact on the learning process, the p-value was found to be statistically significant (p = 0.058). While over 60% of respondents were inspired by healthcare workers for clinical learning, factors like time limitations, patient overload, shortage of clinical teachers and a disconnect between institutions hinder their ability to develop their skills. On the other hand, about 39.1% of participants stated that the p-value was found statistically significant (p = 0.001). Besides on above results, students seemed dissatisfied with their clinical learning environment because of various challenges found during this study and these issues became alarming for students' nurses. Moreover, all of the clinical learning environment issues were equally present in the mentioned population. The p-value was determined to evaluate the statistical significance of the data and identify factors influencing nursing students in their clinical learning experiences [17]. The frequency and percentage of each question for identifying alarming variables were discussed in table 3.

Table 3: Clinical Issues Faced by Female Nursing Students in Frequency and Percentage

Central Thought	Clinical Issues	Response		p-value
		Frequency (%) (YES)	Frequency (%) (NO)	2nd year/3rd year
Hospital-related issues Faced by undergraduate Female nursing students At clinical learning Environment (cle)	Adequate equipment available in your area	39 (56.5)	30 (43.5)	0.387
	The hospital environment was clean?	30 (43.5)	39 (43.5)	0.020
	Inadequate PPE exposed to infection in the clinical areas.	54 (78.3)	15 (21.7)	0.819
	Less clinical teachers or someone to guide	47 (68.1)	22 (31.9)	0.934
Departmental issues Faced by undergraduate Female nursing Students at cle.	College of Nursing and the hospital have less coordination.	50 (72.5)	19 (27.5)	0.012
	Inadequate teaching and skill training in the college to prepare us for clinical	37 (53.6)	32 (32.4)	0.281
	Lack of supervision from the instructors to contribute to increased learning	31 (44.9)	19 (55.1)	0.726
	Clinical teachers rarely visited students in the clinical area.	43 (62.3)	26 (37.7)	0.058
	A single instructor had to monitor far too many pupils.	57 (82.4)	12 (17.6)	0.185
	Students were overloaded with too many written assignments by the clinical teacher.	48 (69.6)	21 (30.4)	0.001
	The hospital staff did not provide accurate information about the ward	34 (49.3)	35 (40.7)	0.398
	Inappropriate behaviour by doctors and nurses toward nursing students in clinical settings made them lose confidence.	29 (42)	40 (58)	0.070

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Healthcare providers Related issues faced By undergraduate Female nursing Students at cle.	Nursing staffs did not supervise undergraduate Female nursing students comfortably at the clinical area.	33 (47.8)	36 (52.2)	0.543
	Hospital staff discouraged you from seeking guidance from them in clinical duration.	27 (39.1)	42 (60.9)	0.001
	The students were assigned inappropriate and heavy workload by the hospital staff.	23 (33.3)	46 (46.7)	0.733
Lack of learning Opportunities at cle Faced by undergraduate Female nursing Students.	Felt the anxiety to perform the wrong procedure.	48 (69.6)	21 (30.4)	0.219
	Lack of opportunities to practice or not allowed taking part in practice according to objectives.	34 (49.3)	35 (50.7)	0.398
	Non non-supportive environment due to many patients in the clinical areas	38 (55.1)	31 (44.9)	0.894
	There was a lack of cooperation from other students in the clinical area.	49 (71.0)	20 (29)	0.006
	The students were afraid of criticism by clinical teachers.	48 (69.6)	21 (30.4)	0.165
	Lack of guidelines for nursing practice or uneasiness in the working climate.	39 (56.5)	30 (43.5)	0.066

*Significant with a p-value of less than < 0.05

DISCUSSION

According to the current study's findings, the majority of students identified the presence of issues in clinical settings, indicating an overall feeling of dissatisfaction. Clinical experiences vary depending on organizational management, supervisory interactions, and students' expectations. According to previous research, second-year nursing students had the most clinical problems as compared to third and final years, due to initial days in the hospital and inadequate clinical exposure of patients, resulting in lower satisfaction [18]. Moreover, 78.3% of participants agreed they face a shortage in hospital work facilities which it makes difficult for student nurses to learn, Similarly, a study revealed that a shortage of material resources contributed to severe issues in nursing education, impeding nursing students' learning [19]. Thus, nursing students' confidence and competence would be lowered, which is critical for their professional growth. While 68% of participants in this study stated that a lack of clinical teachers in the clinical area leads to learning difficulties in clinical settings, this was supported by the shortage of clinical instructors and healthcare workers in clinical settings is producing major issues among nursing students, specifically fear and incompetency in female nursing students [20]. Approximately 70% of participants reported concern about their anxiety about conducting procedures and their fear of being criticized by healthcare staff while attending the procedure. This study's findings are similar to those reported that nursing students in clinical settings are afraid of making mistakes, which might hurt patients [21]. Similarly observed that nursing students' lack of self-confidence inhibits the practical learning process [22]. While 60% of participants stated that there was insufficient teaching and training in clinical settings and that clinical instructors seldom visited students in the clinical areas, that negative impact on nursing students' interest in their clinical learning. The findings of this study were similar and revealed that registered nurses have challenges in educating nursing students due to shortages, heavy workloads, and a lack of motivation in teaching [23].

Over 72% of nursing participants in this study highlighted a lack of cooperation between the college of nursing and hospitals in which nursing students are poorly placed in clinical areas, resulting in learning difficulties in contrast proposed that clinical education should carefully arrange the number of nursing students whose rotations are as well-planned as they acquire an enthusiasm in learning [24]. Furthermore, 82% of participants reported that the majority of students were supervised by a single instructor in clinical settings, which had a detrimental influence on student learning. A good clinical teacher is ready to make clinical learning pleasurable, encourage and engage students in learning, provide students with learning opportunities, and make the clinical atmosphere attractive [25]. In this study, 70% of participants reported inadequate PPE exposure to infection in the clinical areas. Further, all healthcare workers must utilize personal protection equipment (PPE) effectively when treating patients in critical care areas [26, 27] Another study found that a lack of PPE in clinical settings contributes to the spread of illness in the clinical learning environment, leading to a loss of motivation for learning among students. Another study indicated that female nursing students encounter unique challenges in the clinical learning setting compared to their male students [28]. Therefore, gender has a substantial impact on students' perspectives and clinical practice experiences. Female students frequently encounter gender prejudice, stereotyping, and labelling, which can influence their learning experiences and relationships with patients. Extensive study is needed, particularly interventional to have a better awareness of the underlying issues in the clinical learning setting. This would contribute to improving the existing situation and producing trained, qualified, and professional nurses [29].

CONCLUSIONS

This study concluded that undergraduate nursing students expressed dissatisfaction with clinical education, which makes nursing students disappointed in the clinical

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learning environment. Nursing students encounter numerous challenges that affect their education and clinical practice. Addressing hospital-related issues, enhancing nursing institute curricula, fostering collaboration with healthcare providers, and improving clinical learning opportunities are crucial steps in preparing competent nursing professionals. Future interventions should focus on improving supervision, safety concerns, better coordination, and collaboration between the nursing institute and the hospital. If the necessary steps are not taken, the likelihood of training and producing nurses who are highly skilled, knowledgeable, and professional may decrease.

Authors Contribution

Conceptualization: IAC
Methodology: IAC, HBC, SA[1]
Formal analysis: IAC, ZA, SA[2]
Writing review and editing: JK, IAC, HBC

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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Hemodynamic Instability during Intermittent Hemodialysis in ICU Patients with Abnormal Capillary Refill Time

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ABSTRACT

Intradialytic Hemodynamic Instability (IHI) may cause delay in renal recovery and also increases risk of mortality. Capillary Refill Time (CRT) was a stress free method used for peripheral perfusion that becomes worse during circulatory failure. **Objective:** To determine Hemodynamic Instability during Intermittent Hemodialysis in ICU Patients with Abnormal Capillary Refill Time at a tertiary care hospital, Karachi, Pakistan. **Methods:** This was the 06 months' data collection, 1-year prospective observational study. Overall 137 patients were evaluated via sampling technique of non-probability consecutive sampling technique. For each intermittent hemodialysis session, index CRT was recorded. IHI was noted down 30 minutes before the beginning of intermittent hemodialysis and then 60 minutes, 120 minutes and 180 minutes. Entire data were recorded as a predesigned proforma. The natural distribution of patients into subgroups was done using Chi Square test considering p-value ≤0.05 as significant **Results:** The total population was 98 men (71.5%) and 39 women (28.5%) Average age was 61.51 ± 15.37 years. 45(17.5%) patients observed abnormal Capillary refill time. 20(14.6%) patients experienced intradialytic hemodynamic instability. Among patients diagnosed with intradialytic hemodynamic instability, 9(45%) had abnormal CRT. Compared to patients with normal CRT, individuals with aberrant CRT had a higher risk of hemodynamic instability (OR = 5.564, p < 0.001). **Conclusions:** IHI was most at risk when it comes to initiating intermittent hemodialysis, especially in the first hour of the first session. The increase in index capillary refill time was linked to IHI.

INTRODUCTION

Chronic Kidney Disease (CKD) represents a critical global public health challenge, frequently progressing to End-Stage Renal Disease (ESRD), which necessitates dialysis or kidney transplantation. The prevalence of hypertension rises as Glomerular Filtration Rate (GFR) declines, making it a common comorbidity in both CKD and ESRD. Intradialytic Hypotension (IDH) is a prevalent complication during intermittent hemodialysis, primarily due to the need for rapid fluid removal over short treatment periods. Reported rates of IDH in ESRD patients vary widely, ranging from 5% to 40% across different patient populations [1]. IDH is linked to a range of severe complications, including disabling symptoms, inadequate dialysis, vascular access thrombosis, accelerated kidney function decline, cardiovascular events, and increased mortality. The prevalence of IDH varies depending on the definitions applied, as there is no universally accepted "safe" blood pressure range for dialysis patients. This makes defining IDH particularly challenging. Most definitions incorporate one or more of the following criteria: a drop in blood pressure below a specific threshold or nadir, a decline in blood pressure during dialysis, patient-reported symptoms occurring during dialysis, and medical interventions during dialysis aimed at restoring blood volume [1]. ESRD can further complicate the relationship between blood pressure and tissue perfusion due to factors such as

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upstream vascular stenosis, endothelial dysfunction, and capillary rarefaction. While it is typically assumed that these limits are reached when mean arterial pressure drops below 60 mm Hg, a recent study in dialysis patients found the mean limit to be 74 mm Hg, with a significant range from 39 to 103 mm Hg. [2]. Some studies have employed alternative threshold values to characterize IDH was 68% based on these cut-off values [3]. Because of the comparatively short treatment durations that require quick volume clearance of excess fluid gains, IDH is a commonly encountered consequence of intermittent hemodialysis [4]. Remarkably, immediate Renal Replacement Treatment (RRT) is needed for 10–20% of AKI patients in the ICU, and their predicted death rate is close to 50% [5]. However, RRT is linked to a significant death rate and is necessary for 5-20% of patients. [6-9]. In the absence of emergent criteria, identifying individuals in whom the commencement of RRT should be reevaluated could be facilitated by the identification of risk factors for IHI by physicians [10]. In response to circulatory dysfunction, the body's compensatory mechanisms prioritize blood flow to vital organs, reducing circulation to non-essential areas like the skin. This shift makes the skin a valuable area for clinical assessment of circulatory issues. Bedside evaluation of peripheral perfusion parameters is straightforward and often used to determine the need for fluid resuscitation in patients with sepsis-induced acute circulatory dysfunction [11]. Capillary Refill Time (CRT), an inexpensive and readily accessible tool, has gained attention as a promising target for guiding resuscitation efforts in septic shock [12]. CRT is convenient-to-use bedside indicator of the perfusion in the periphery. Its applicability in pre- hospital patient triage has been established as well as in the emergency room [13-15]. An earlier clinical study involving adult patients with septic shock compared two resuscitation strategies: one aimed at normalizing CRT and the other focused on serum lactate levels. The results showed comparable effectiveness in reducing 28-day mortality rates. However, a more recent meta-analysis of 10 studies, encompassing 917 septic shock patients, identified a weak inverse relationship between Mean Arterial Pressure (MAP) and CRT [15]. In order to find out the intradialytic hemodynamic instability by abnormal CRT in order to maintain the hemodynamic stability among ICU patients.

As a secondary objective this study defined CRT in IDH future management strategies which should be can be formed for better management of patients who need intermittent hemodialysis.

METHODS

This cross-sectional study was conducted over six months, from August 2022 to January 2023, within the Intensive Care Unit of Ziauddin Hospital in Karachi, Pakistan. With ethical approval secured from Ziauddin University Hospital (Ref code: 5660622AJCCM), all eligible patients were thoroughly briefed on the study's goals, potential benefits, and any associated risks. Informed written consent was obtained, ensuring that each participant's privacy was protected by assigning them a unique encrypted code. Participants were selected using a non-probability consecutive sampling method. The data gathered will be kept strictly confidential, shared only with authorized personnel and the study's principal investigators. Patients undergoing IHD at the ICU and met the following criteria were included in this study: they were 18 years of age or older, of any gender, and undergoing intermittent hemodialysis. Patients were excluded from the study if they refused to provide consent or if CRT could not be assessed due to conditions such as Raynaud syndrome or severe hypothermia. Prior to inclusion the purpose, procedure, risk and benefits of the study was explained to all participants. Demographic profile of the patients was recorded like gender and age. History of the patients was taken regarding hypertension, diabetes mellitus and noted in predesigned proforma. All IHD must be advised by consultant nephrologist of experience more than 5 years. It usually occurs at the initiation of intermittent hemodialysis during the first hour of the first session despite the absence of fluid removal. It was found that there was association of Index CRT ≥ 3 s with the occurrence of IHI. Taking SOCRATE study [16, 17], first and later sessions made up the 211 sessions, with 72 (34%) being first sessions and 139 (66%) later sessions, sample size of this study was 137, with a 95% confidence interval and a 5% margin of error. Non-probability, Consecutive Sampling technique was used for data collection. In the absence of strong evidence supporting the use of one modality of RRT over the other, guidelines from both national and international organizations recommended IHD to maximize hemodynamic tolerance. The occurrence of an IHI was b recorded 30 minutes just before started IHD and after 60 minutes, 120 minutes and 180 minute intervals. For each IHD session, the index CRT was recorded just before the start of the session (T0). The cut-off values defining tissue hypoperfusion were based on previously published studies, with an index CRT of ≥ 3 seconds. The index CRT was measured 30 minutes before the hemodialysis by applying firm pressure to the distal phalanx of the right index finger for 10 seconds. The time for the normal colour to return to the ventral surface was recorded using a mobile phone chronometer. The selected cut-off value for CRT was ≥ 3 seconds, and all measurements were performed by the principal investigator to ensure consistency and avoid variability. Confounding variables and biasness was controlled by strictly adhering to inclusion and exclusion criteria and stratification. Patient information will be kept secured and available to authorized person only. Only

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authorized individuals had access to patient information, which was maintained safely. SPSS version-21.0 (IBM Corp., 2012) was used for data entry and analysis. IBM SPSS Statistics, Version 21.0, for Windows. IBM Corp., Armonk, NY. For quantitative (continuous) characteristic like age (years) and descriptive statistics like mean ± SD, skewness, median (IQR) and for the accurate computation of maximum and minimum values, the Shapiro-Wilk test was utilized to validate the hypothesis of normality. Frequency and percentages will be computed for categorical variables like age, gender, hypertension, type 2 diabetes, aberrant CRT time, and hemodynamic instability. Using stratification, effect modifiers including age groups, type 2 diabetes and hypertension were managed. Applications included the Fisher Exact Test and the Post-Stratification Chi-Square Test. The significant level was set at the level of less than 0.05.

RESULTS

Out of 137 patients, there were 28.5% women and 71.5% men with an average age was 61.51 ± 15.37 years, however the majority 110 (80.3%) were over 50 years. 75 (54.7%) patients diagnosed with diabetes mellitus and 98 (71.5%) with hypertension. Total 45 (17.5%) patients observed abnormal capillary refill time. In our study, 20 (14.6%) patients experienced intradialytic hemodynamic instability (Table 1).

Table 1: Descriptive Data for the Population under Investigation (n = 137)

Variables	N (%) / Mean ± SD
Gender	
Males	98 (71.5%)
Females	39 (28.5%)
Age (Years)	
Mean ± S.D	61.51 ± 15.37
Groups	
≤50 Years	27 (19.7%)
>50 Years	110 (80.3%)
Diabetes Mellitus	
Yes	75 (54.7%)
No	62 (45.3%)
Hypertension	
Yes	98 (71.5%)
No	39 (28.5%)
Abnormal CRT	
Yes	24 (17.5%)
No	113 (82.5%)
Intradialytic Hemodynamic Instability	
Yes	20 (14.6%)
No	117 (85.4%)

Fifteen patients (75%) among 20 intradialytic hemodynamic instability patients were discovered in the first hour, while 3 (15%) in the second hour, and 2 (10%) in the third hour (Figure 1).

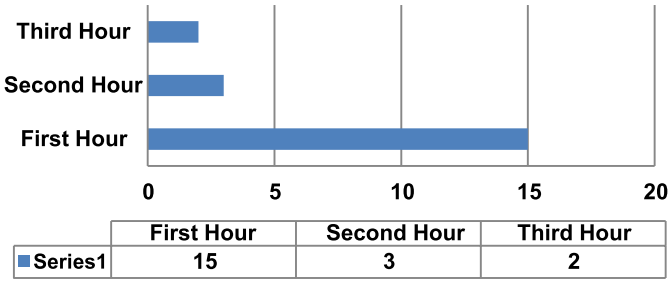

Figure 1: Intradialytic Hemodynamic Instability during Hour

Ninety- five percent of the 19 patients were older than 50. Among these, 11 (55%) of the patients have diabetes mellitus, 13 (65%) have hypertension, and 9 (45%) have abnormal CRT. Intradialytic hemodynamic instability was shown to be significantly associated with abnormal CRT (p = 0.002), but not with gender (p = 0.484), age group (p = 0.107), diabetes mellitus (p = 0.980) or hypertension (p = 0.484) (Table 2).

Table 2: Association of Intradialytic Hemodynamic Instability with Demographic Profile and Co-Morbid

Variables	Intradialytic Hemodynamic Instability N (%)		p-Value
	Yes	No	
Gender			
Male	13 (65%)	85 (72.6%)	0.484
Female	7 (35%)	32 (27.4%)	
Age Groups			
≤50 Years	1 (5%)	26 (22.2%)	0.124
>50 Years	19 (95%)	91 (77.8%)	
Diabetes Mellitus			
Yes	11 (55%)	64 (54.7%)	0.980
No	9 (45%)	53 (45.3%)	
Hypertension			
Yes	13 (65%)	85 (72.6%)	0.484
No	7 (35%)	32 (27.4%)	
Abnormal CRT			
Yes	9 (45%)	15 (12.8%)	0.002*
No	11 (55%)	102 (87.2%)	

A chi-square or Fisher exact test was applied. Significant at 0.05 levels IHD instability was less common in male patients than in female patients (OR = 0.699, p = 0.485). Patients under 50 were less likely to experience intradialytic hemodynamic instability compared to those over 50 (OR = 0.184, p = 0.107). Compared to patients with normal CRT, individuals with aberrant CRT had a higher risk of hemodynamic instability (OR = 5.564, p < 0.001) (Table 3).

Table 3: Odds Ratio for Intradialytic Hemodynamic Instability

Variables	Odds Ratio (95% CI)	p-Value
Gender		
Male	0.699 (0.256 - 1.910)	0.485
Female	1.000	
Age Groups		
≤50 Years	0.184 (0.024 - 1.442)	0.107

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>50 Years	1.000	
Diabetes Mellitus		
Yes	1.012 (0.390 - 2.625)	0.980
No[c/o]	1.000	
Hypertension		
Yes	0.699 (0.256 - 1.910)	0.485
No[c/o]	1.000	
Abnormal CRT		
Yes	5.564 (1.978 - 15.652)	0.001*
No[c/o]	1.000	

[c/o:] Reference Category
Binary logistic regression was applied
*Significant at 0.05` level

DISCUSSION

Despite optimization through protocols, IHI was still a common problem in critically ill patients. In our study 14.6% patients experienced Intradialytic Hemodynamic Instability (IHI) and among them IHI was observed 75% in first hour, 15% in the second hour and 10% in the third hour. Furthermore, among 20 patients diagnosed with IHI, 65% were male and 35% were female. 95% patients were over the age of fifty years. According to Bangash IA *et al.*, the frequency of IHI was quite significant and it varies between 10% and 50% due to the significant variations in its description [17]. In contrast, a different study found that the first 25% of the session was when IHI frequency was highest [18-20]. We observed that patients with abnormal CRT were significantly more likely to experience IHI compared to those with normal CRT ($p = 0.002$). Additionally, female patients and those aged 50 years or older were at a higher risk for developing IHI. Moreover, the development of IHI was documented within the first 30 minutes of the hemodialysis session, highlighting the importance of early monitoring and intervention. Similar to our findings, the SOCRATE Study identified CRT as a significant predictor of IHI. This study further emphasized the role of cardiovascular parameters, such as the SOFA score and lactate levels, in predicting hemodynamic instability, which aligns with our observation that abnormal CRT was a critical marker for IHI [16]. Unlike our study, which did not focus on PRR, Wang AY and Bellomo R highlighted PRR as a crucial factor influencing IHI. This study found that a high PRR at the start of dialysis was protective, while a consistently high PRR during dialysis increased the risk of hypotension. This suggests that, in addition to CRT, PRR could be another valuable marker for predicting IHI risk [5]. Flythe JE *et al.*, found that the prevalence of IHI varied greatly. Consequently, they demonstrated that when the cut-off value of IHI was defined as a drop in systolic blood pressure of greater than 20 mmHg, 68% of the patients experienced IHI during dialysis [20]. Contrary to our findings, Islam F *et al.*, indicated that the frequency of IHI during dialysis was approximately 12%. IHI frequency was observed to be similar in both genders in the Bangash IA *et al.*, study (23.2% in males versus 26.3% in females) [17, 21]. Contrary to our findings, previous studies have identified female sex as a significant risk factor for developing Intradialytic Hemodynamic Instability (IHI) [22]. This discrepancy may be attributed to variations in the study populations and methodologies. Moreover, it was logical to anticipate an increased incidence of IHI with advancing age, given the higher prevalence of comorbid conditions that were known to elevate the risk of IHI [23]. However, our results challenge this assumption, as we found no significant correlation between age and the frequency of IHI. IHI was associated with significant morbidity and mortality, underscoring the necessity for effective preventative strategies [24]. In a prospective study conducted in an intensive care unit, Bige N *et al.*, identified that IHI frequently occurred within the first hour of intermittent hemodialysis, even in the absence of fluid loss. This instability was significantly associated with two measures of tissue hypoperfusion: A Capillary Refill Time (CRT) of ≥3 seconds and a lactate level >2 mmol/L, alongside a cardiovascular SOFA score of ≥1 [17]. The risk of IHI increased proportionally with the number of abnormal parameters observed. In another cohort study, the incidence of IHI was reported to be 23% while Monnet X *et al.*, documented a higher incidence rate of 33%, albeit in a population where all patients underwent fluid removal [25]. The convergence of results across multiple studies suggests that a multifaceted approach, incorporating early detection markers like CRT and PRR along with adherence to practice guidelines, may enhance patient outcomes during hemodialysis.

CONCLUSIONS

The findings indicate that the incidence of Intradialytic Hemodynamic Instability (IHI) in individuals undergoing hemodialysis was relatively low. However, dialysis remains an essential intervention for critically ill patients suffering from Acute Kidney Injury (AKI), despite the inherent concerns regarding its frequency, as it was a non-negotiable treatment for these patients. The commencement of intermittent hemodialysis presents the highest risk for IHI, particularly within the first hour of the initial sessions. This increased risk was significantly associated with prolonged index capillary refill times. Therefore, early and vigilant monitoring during the initial phases of dialysis was crucial to reduce the risk of IHI and its associated complications.

Authors Contribution

Conceptualization: MH
Methodology: SM
Formal analysis: GR
Writing, review and editing: AJ, BA, SA

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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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Comparison of Effectiveness of Conventional Polypectomy with Functional Endoscopic Sinus Surgery

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ABSTRACT

It is common for rhinologists to face nasal polyposis. When other treatments have failed, patients must undergo Functional Endoscopic Sinus Surgery (FESS) with a microdebrider or traditional equipment to clear out their sinuses and restore normal airflow. **Objective:** To compare the effectiveness of conventional polypectomy with functional endoscopic sinus surgery in patients presenting to tertiary level care hospital in Islamabad, Pakistan. **Methods:** This study was conducted at Department of ENT Head and Neck Surgery, Pakistan Institute of Medical Sciences, Islamabad from November 2017 to December 2018. Eighty-eight patients were enrolled and they were randomly into group A and group B assigned for conventional polypectomy and functional endoscopic sinus surgery, respectively. **Results:** There were 27 (61.4%) males and 17 (38.6%) females and mean age was 34.59 ± 12.00 years in conventional polypectomy and 28 (63.6%) males and 16 (36.5%) females and mean age was 36.64 ± 10.76 years in function endoscopic sinus surgery. The recurrence rate after 6 months in patients underwent conventional polypectomy was 18 (40.9%) and functional endoscopic sinus surgery was 2 (4.5%). **Conclusions:** The frequency of recurrence of nasal polyps after conventional polypectomy was more than in patients receiving functional endoscopic sinus surgery procedure.

INTRODUCTION

Edematous mucosal outpouchings of the nasal and paranasal sinuses, known as sinonasal polyps, can be observed in the nasal cavity or isolated in the sinuses, typically in the early stages of the disease. Allergies and asthma are common causes of sinonasal polyps. When they're little, they might not create any problems, but when they grow, they clog the nose and prevent the sinuses from draining properly [1]. The recurrence rate, chronicity, and severity of sinonasal polyposis make it a significant issue for clinicians. This widespread condition affects about 4% of the global population at some point in their lives. It may be the only issue or a symptom of other serious conditions, such as asthma or aspirin idiosyncrasy [2]. Restoring nasal breathing and preventing its recurrence are both achieved via appropriate management and therapy of this condition [1, 3]. For smaller nasal polyps, medical therapy often consists of systemic and local steroids; however, surgery is sometimes necessary for bigger polyps [4]. In contrast to FESS, which necessitates a skilled surgeon, endoscopes of varying diameters and angles, and extensive sedation, conventional polypectomy makes use of standard devices that are readily available in even small-setup hospitals. The high upfront cost and recurring expense of bits, tips, and blades make microdebriders an inefficient instrument [3-

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6]. Hereditary predisposition and persistent nasal mucosal irritation are common causes of polyp development. They are associated with nonallergic conditions more frequently than allergic ones. Inflammatory alterations were characterized by Gohar MS et al., as the pathophysiology of nasal polyps [7]. Airflow turbulence and polyps typically originate in the ethmoidal area's narrowed spaces, which are narrowed due to mucosal inflammation. An increase in sodium intake, water retention, and polyp development are all outcomes of fibroblasts' effects on the bioelectric integrity of sodium channels. The primary method of medically treating nasal polyp(s) is with topical or oral nasal steroids. When administered alone, immunotherapy fails to eradicate polyps [8]. When other forms of therapy have failed, surgical intervention may be necessary. When it comes to nasal symptoms, polypectomy is most effective in relieving them. Nevertheless, there is a greater recurrence incidence after polypectomy for numerous nasal polyps. Some surgical procedures include Functional Endoscopic Sinus Surgery and snare and forceps removal of a polyp (polypectomy). Constant sinusitis, brought on by an obstructive blockage in the outflow system, makes breathing painful and difficult. Citations [9, 10]. The high recurrence rate of conventional nasal polypectomy has rendered treatment unappealing. Patients with nasal polyposis and chronic rhinosinusitis were less likely to need sinus surgery after 12 weeks of therapy with fluticasone propionate nasal drops, according to Galletti C et al [11]. However, 14 out of 27 patients still needed surgery. When conventional medical methods fail to alleviate symptoms of nasal polyposis or chronic rhino sinusitis, FESS has recently been the therapy of choice. After an average of 31.7 years of follow-up, Zong H and Lou Z found that 85 percent of patients' quality of life improved [12]. The restriction of having to use just one hand for everything became apparent as endoscopes became standard equipment for surgery. The necessity for a multi-function surgical tool was an inevitable consequence of this fact. A number of decades ago, with the advent of the microdebrider, powered sinus devices became commonplace. In 1969, Urban developed a "vacuum rotary dissector" the precursor of the modern microdebrider. In 1970, the House group began using it for arthroscopy and then for morselizing auditory neuromas. In 1994, Setliff and Parsons introduced these devices for use in nasal surgery [13]. Recurrence of illness is one of the most common serious consequences following this operation. Another author found that recurrence rates were 36% for individuals who underwent conventional polypectomy and 8% for people who had functional endoscopic sinus surgery.

The purpose of this study was to compare the recurrence rates of nasal polyps after FESS and conventional polypectomy. By comparing the two, we can improve patient care by increasing access to endoscopes and microdebriders, which will reduce the need for patients to undergo multiple surgeries to address the same problem.

METHODS

This Quantitative experimental was conducted at Department of ENT Head and Neck Surgery, Pakistan Institute of Medical Sciences, Islamabad (Ref# F.1-1/2015/ERB/SZABMU) from November 2017 to December 2018 and 88 patients were enrolled. They were divided in two groups; each group comprised 44 patients. With level of significance as 5%, power of the test as 80%, P1 as 125 and P2 as 365, N was 44 in each group. Sample size came to be 88. Probability simple random sampling technique with lottery method was utilized. All patients undergoing polypectomy in ENT department between 18 to 60 years of age, both genders were included. All patients with acute infection of the nose, upper respiratory tract and paranasal sinuses assessed by clinical examination and radiological findings as acute ENT infections are relative contraindication for polypectomy due to increased chances of infection and post-operative complications, not fit for surgery, general anesthesia, bleeding diathesis and deranged coagulation profile due to increased risk of bleeding and pregnant ladies which is relative contraindication for polypectomy were excluded. Patients were collected and admitted from the outdoor department of the ENT department, Pakistan Institute of Medical Sciences Islamabad. Group A treated by conventional intranasal polypectomy method and group B was treated by Functional Endoscopic Sinus Surgery (FESS). Patient demographic data along with registration number was noted. Informed written consent with research inclusion consent was taken from all patients preoperatively. Detailed history was taken and clinical and ENT examination was done and findings were noted. Baseline investigations and pre-operative anesthesia fitness for surgery was done. Patients underwent the procedure by expert surgeon. General anesthesia was used during the surgery, which also included thoracotomy and endotracheal intubation. Group A underwent endoscopy with the assistance of a magnum microdebrider. Group B, the conventional endoscopic group, used the traditional endoscopic surgical equipment and the typical Messerklinger procedure as described by Stammberger. The duration of the operation, which began with the insertion of the vasoconstrictor nasal pack and ended with the insertion of the antibiotic-impregnated nasal pack, was meticulously recorded by an impartial intern doctor stationed in the ENT department. In both groups A and B cases were kept on follow up after 6months; anterior and posterior rhinoscopy was done so that we can be able to look for any recurrence and to compare the recurrence of both groups. Data were then analyzed using SPSS version 24.0. Comparison in the recurrence after 6 months in both

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groups was done by using Chi-square test considering p-value <0.05 as significant.

RESULTS

Mean age of the study participants was 34.59 ± 12.00 in conventional polypectomy and 36.64 ± 10.76 years in functional endoscopic sinus surgery (Table 1).

Table 1: Descriptive Statistics of Age of Patients (n=88)

Age (Years)	Conventional Polypectomy Mean ± SD	Functional Endoscopic Sinus Surgery Mean ± SD
	34.59 ± 12.00	36.64 ± 10.76

There were 27 (61.4%) males and 17 (38.6%) females in conventional polypectomy and 28 (63.6%) males and 16 (36.5%) females in function endoscopic sinus surgery (Table 2).

Table 2: Frequency of Genders (n=88)

Gender	Conventional Polypectomy N (%)	Functional Endoscopic Sinus Surgery N (%)
Male	27 (61.4%)	28 (63.6%)
Female	17 (38.6%)	16 (36.4%)

The recurrence rate after 6 months, patients underwent conventional polypectomy and functional endoscopic sinus surgery (FESS) was 18 (40.9%) and 2 (4.5%). Statistically the significant (P<0.05) was difference between the groups (Table 3).

Table 3: Comparison of Recurrence Rate after 6 Months (n=88)

Recurrence	Conventional Polypectomy N (%)	Functional Endoscopic Sinus Surgery N (%)	p-Value
Yes	18 (40.9%)	2 (4.5%)	<0.05
No	26 (59.1%)	42 (95.5%)	

Note: 2= 16.565, df = 1, P-value = 0.000

DISCUSSION

Every day, doctors see cases of nasal polyposis, a condition characterized by the development of polyps inside the nasal cavity. The intensity, chronicity, and increased likelihood of recurrence make it a major problem for western nations [14]. Aspirin idiosyncrasy and asthma are two major medical conditions that might be causing this symptom or another one altogether. Nasal polyposis can be effectively treated and managed to restore normal nasal airflow and reduce the likelihood of recurrence [15]. Recurrence rates at 6 months were the primary endpoints for this study's design, which compared functional endoscopic sinus surgery to traditional polypectomy. The majority of polyps in patients are caused by anterior ethmoids. Polyps typically manifest in the ethmoidal space of the fundibulum, turbinates, and uncinate process. The anterior portion of the ethmoidal bulla is another, less common, location where polyps can originate, blocking the hiatus semilunaris channel Citations [16, 17]. When describing the endoscopic method of simus surgery for the treatment of nasal polyposis, a recent research adopted the name FESS [18]. The majority of infections affecting the frontal and maxillary sinuses, according to FESS, originate in the nose and anterior ethmoids. Clearing sick air cells and mucosal contact sites is a specific function of FESS in the osteomeatal area. The natural ostia of the maxillary and frontal sinuses are used to restore ventilation and drainage. Patients with severe illness who had a preoperative CT scan with FESS reported significant symptom relief, according to Galluzzi F et al [19]. In every patient except five, we were able to maintain the central turbinate. To improve access and visibility, we need to remove or cauterize the central turbinate in those five situations. Throughout the procedure, we had no significant complications. Prior research has shown that functional endoscopic sinus surgery has a very low complication risk of 0.5 percent. It has two possible treatments: medicine and surgery. For endoscopic surgery, the most important instrument is the microdebrider. Ultrasonic aspirators, coblators, and endosopic drills are only a few of the advanced instruments that have their roots in powdered sinus devices, which are in widespread usage [18]. The microdebrider is an electrically driven shaver with a cylindrical form that effectively protects the nasal mucosa while minimizing blood loss. The continual suction of the microdebrider, together with the short healing period and absence of damage, crusting and blockage, allows the nasal cavities to be repaired and resume normal functioning. In A total of 55 (62.5%) male and 33 (37.5%) female patients participated in our research. Likewise, in a research carried out by Calus L et al., there were 10 male patients (50%) and 10 female patients (50%) respectively [20]. After 6 months, patients who received Functional Endoscopic Sinus Surgery (FESS) had a recurrence rate of 4.5 percent, whereas those who underwent conventional polypectomy had a recurrence rate of 18. Similarly, Varman et al., found that recurrence occurred at a rate of 36% in patients who underwent traditional polypectomy and only 8% in individuals who had functional endoscopic sinus surgery [1]. A highly advantageous surgical technique for enhancing mucociliary transport by reducing inflammation, oedema, and polyp development is FESS, according to Dadgarnia M et al [21]. In order to improve patient care and reduce the need for recurrent surgeries, more research comparing FESS to traditional polypectomy is needed. This will help increase access to modern tools and knowledge, such as endoscopes and microdebriders, which in turn will improve patients' quality of life. The indications for sinus surgery have been broadened simultaneously by both FESS and CT technologies [22]. The If you're worried about problems with your brain, eyes, or major blood arteries, you may want to look into the emerging field of imageguided endoscopic surgery. When a patient has exceptionally atypical sinus architecture,

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severe chronic sinusitis, or a history of sinus surgery that left anatomical markings, this sort of surgery may be indicated.

CONCLUSIONS

The frequency of recurrence of nasal polyps after conventional polypectomy was more than in patients receiving functional endoscopic sinus surgery procedure.

Authors Contribution

Conceptualization: MZ

Methodology: AU

Formal analysis: MZ, WUD, SRM, MR

Writing, review and editing: MZ, MB, MR, MA

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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Prevalence of Depression, Anxiety, Stress, and Quality of Life among Individuals with Hemodialysis

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ABSTRACT

Hemodialysis was filtering the blood of a person whose kidneys were not working normally. **Objective:** To investigate the prevalence of depression, anxiety, stress, and quality of life among individuals with hemodialysis. **Methods:** A total of 134 patients were taken from the hospitals of Lahore. The participant's age ranges were between 20-60 years. A purposive sampling technique was used to collect the data. The following measures were used to assess the findings i.e., Demographic, Depression Anxiety Stress Scale (DASS), and World Health Organization Quality of Life Brief (WHOQOL). **Results:** The analyses revealed that the high prevalence of depression, anxiety, and stress in hemodialysis patients and significantly poor quality of life in hemodialysis patients. **Conclusions:** It was concluded that hemodialysis, the most common treatment for end stage renal disease, was a risk factor for psychological illnesses such as depression and anxiety. So, there was a need to develop a treatment strategy, including therapeutic invitations that eventually, improve quality of life.

INTRODUCTION

A patient with CKD has the following complications such as elevated blood pressure, anemia (low blood count), brittle bones, inadequate nourishment, and nerve damage could occur in the patient. Moreover, heart and blood vessel diseases are more likely to develop in those with kidney illness [1]. Diabetes, high blood pressure, and other conditions can lead to chronic kidney disease. In this disease, the kidneys lose their capacity to filter and eliminate waste and excess fluid from the body as a result of acute kidney injury and chronic kidney disease (also known as acute renal failure) [2]. Hemodialysis is a phrase that means filtering the blood. It accomplishes this by circulating a few ounces of blood through a filter to remove waste materials and excess fluid [3]. Psychosocial concerns are an understudied but significant concern in the overall health of hemodialysis patients. Stress is a byproduct of chronic illness and its treatment, and it can have significant effects on psychological and physical results [4]. Depression is the most common psychological complication that has a significant impact on the quality of life of patients and their careers, negatively affecting their social, economic, and psychological well-being [5]. Extreme nervousness and anxiety [6]. Renal failure patients may have somatic symptoms such as shortness of breath, palpitations, chest pain, sweating, and fear of death. Many times, these symptoms are unrelated to any stimuli and can arise suddenly. However, there are numerous reasons why anxiety may emerge. The dialysis process, as well as a slew of potential medical consequences, cause the patient to be concerned and

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anxious [7]. Depression has an important role in the evolution of chronic medical conditions. People suffering from depression lose hope and give up on life. Depression is the most significant and prevalent psychological condition among ESRD patients [8]. Depression in dialysis patients has an impact not only on mortality but also on hospitalization rates and dialysis withdrawal [9]. On the other hand, anxiety is also widespread in hemodialysis patients, with a 27% incidence among 70 urban HD patients, slightly higher than the 18% reported in a nationwide survey [10]. Health-related Quality of Life (QOL) is an important assessment of how a condition impacts patients' life. Physical, psychological, and social functioning, as well as overall life satisfaction, are among the dimensions of quality of life [11]. Depression is closely associated with lower health-related QOL, particularly in mental dimensions. Furthermore, multiple studies have found that individuals with inferior QOL had a higher prevalence of worry and weariness, as well as increased mortality over time [12].

Hence, the current study aimed to explore the prevalence of depression, anxiety, stress, and quality of life among individuals with hemodialysis

METHODS

In this research, a cross-sectional study was chosen to explore the prevalence of depression, anxiety, stress, and quality of life among individuals with hemodialysis. The sample size was calculated using G-Power software with effect size = 0.35, using α=0.05, and power = 0.90 (https://www.highyieldmed.org/sample-size-calculation-2/) structured sample of 129 and 134 participants were taken in this study. A purposive sampling technique was used to collect the data from hospitals in Lahore through a purposive sampling technique from September 2023 to March 2024. The inclusion criteria involved only adults aged 20-60 years who have been diagnosed with ESRD and were receiving regular hemodialysis treatment and had been on this treatment for a minimum duration, such as three months, to ensure stability and adaptation. Patients were taken from only the middle-class income group. Patients with medical and psychiatric comorbidity, and physical and intellectual disability were excluded. Patients with mild, moderate, and severe rage were taken but extremely severe cases were excluded. Personal Demographic sheet, personal information form comprised items related to the participant's name (optional), age, education, working/non-working, marital status, family structure, range of total family income, and duration of dialysis and comorbidities. The Depression Anxiety Stress Scale was developed by Lovibond PF and Lovibond SH in 1995 [13]. It consists of 42 items and has three subscales, depression, anxiety, and stress. Each subscale was based on 14 items. The questionnaire was a 4-point ranting scale. Response categories range from 0 does not apply at all, to 3 applies very strongly and all items were positively worded. Scoring categories for depression, 28+, for anxiety 20+ for stress 34+ were extremely severe. WHO's WHOQOL-BREF questionnaire (1997) was used to assess QOL in ESRD patients. The improved and clinically appropriate variant was designated WHOQOL-BREF. It has organized into four domains: physical, psychological, social relationships, and environment. The reliability ranged from .67 to .86 for all the domains of the instrument. A translation of WHOQOL-BREF in Urdu was carried out which established that it was a reliable (α = 0.86) and valid version for the Pakistani population. It consisted of 26 items which were scored on a 5-point scale that ranged from extremely satisfied to extremely dissatisfy [5, 1]. The study protocol was first submitted to the Ethical Research Committee (ERC) for review. After that, it received clearance from the Board of Studies (BOS). Finally, on 18-9-2023, the Institutional Review Board (IBR) (Reference Number: IHT/ADM/30) granted its final approval. The researcher provided a concise explanation to the participants regarding the study's objective. After taking informed consent, participants were requested to carefully review and sign it to indicate their willingness to participate in the study. It was guaranteed that the information you received would be kept confidential, and you would have the right to withdraw from the study at any time if you experienced any discomfort. All statistical computations were calculated by using Statistical Package for the Social Sciences (SPSS) version 27.0. Qualitative variables were presented with mean ± SD and qualitative variables were presented with frequency and percentage. One Way ANOVA was applied to see the WHO quality of life score in relation to anxiety depression and stress status of patients. Multiple comparison test Tukey (HSD) was applied to see the difference of WHO-QOL score in relation to anxiety, Depression and Stress status. P-value ± 0.05 was considered statistically significant

RESULTS

Table 1 shows that the sample included 13.4% of individuals in the age range 18 to 28 years, 14.2% 29 to 38 years, 22.4% 39 to 49 years, 50.0% of participants were age range 50 and above years 9.0% in participants were illiterate, 29.1% participants were under matric education level, 32.8% participants were matriculation, 17.2% participants had intermediate education level, 6.7% participants were bachelor and 5.2% did M.A and above of the participants, 82.8% were married, 11.9% were single, and 5.2% were widowed. Regarding family structure, 30.6% of the patients belonged to joint families, while 69.4% were part of nuclear families. Among the participants, 11.9% were employed, 32.1% were unemployed, 49.3% were housewives, 5.2% were retired, and 1.5% were students.

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Participants had monthly income in a range of 15,000 to 30,000 18.7%, and 56.0% had a range of 30,000 to 45,000. A total of 31.3% of participants had been undergoing dialysis for 6 months to 1 year, 17.2% had been on dialysis for 2 to 3 years, and 51.5% had been on dialysis for more than 3 years. Additionally, 32.1% of participants had diabetes as a comorbidity, 51.1% had hypertension, and 22.4% were affected by hepatitis B or C.

Table 1: Frequency and Percentage of Demographic Sample

Variables	N (%)
Gender	
Male	71 (53.0%)
Female	63 (47.0%)
Age	
20-30	18 (13.4%)
30-40	19 (14.2%)
40-50	30 (22.4%)
50-60	67 (50.0%)
Marital Status	
Married	16 (11.9%)
Unmarried	111 (82.8%)
Widow	7 (5.2%)
Education Level	
Illiterate	12 (9.0%)
Under Matric	39 (29.1%)
Matriculation	44 (32.8%)
Intermediate	23 (17.2%)
Bachelor	9 (6.7%)
MA and Above	7 (5.2%)
Family System	
Joint	41 (30.6%)
Nuclear	93 (69.4%)
Total Income	Total Income
15,000-30,000	25 (18.7%)
30,000-45,000	75 (56.0%)
45,000 and Above	34 (25.4%)
Employment Status	
Employed	16 (11.9%)
Unemployment	43 (32.1%)
Housewives	66 (49.3%)
Retired	7 (5.2%)
Student	2 (1.5%)
Average Year of Hemodialysis	
6 Months - 1 Year	42 (31.3%)
2 Years - 3 Years	23 (17.2%)
3 Years and Above	69 (51.5%)
Comorbidities	
Diabetes	43 (32.1%)
Hypertension	69 (51.5%)
Hypothesis B/C	30 (22.4%)

Note: f=frequency and %=Percentage

Table 2 showed that the greatest proportion of patients experience extreme severity in depression (35.8%) and severe stress (35.1%), with mean scores of 72.15 and 74.28, respectively. Anxiety was most widespread in the moderate group (35.1%), with an average score of 73.38. The table demonstrates the tremendous psychological burden in this patient population, with a high proportion of patients in the severe and extremely severe categories for all three illnesses.

Table 2: Frequency Distribution Mild to Extreme Severity of Depression, Anxiety and Stress among Patients with Hemodialysis

Variables	Categories	Mean ± SD	N (%)
Depression	Mild	88.722 ± 7.969	18 (13.4%)
	Mod	75.625 ± 9.640	24 (17.9%)
	Severe	70.545 ± 8.638	44 (32.8%)
	Extremely Severe	72.145 ± 7.682	48 (35.8%)
Anxiety	Mild	69.694 ± 15.036	36 (26.9%)
	Mod	73.383 ± 8.208	47 (35.1%)
	Severe	76.920 ± 4.725	25 (18.7%)
	Extremely Severe	80.692 ± 3.121	26 (19.4%)
Stress	Mild	68.400 ± 5.253	10 (7.5%)
	Mod	67.475 ± 6.332	40 (29.9%)
	Severe	74.276 ± 7.216	47 (35.1%)
	Extremely Severe	83.918 ± 10.523	37 (27.6%)

Table 3 displayed the mean and standard deviation of scores across the four dimensions of the World Health Organization Quality of Life BREF (WHOQOL), which were provided on a 4-20 and 0-100 scale. The Environmental domain has the greatest average score of 13.57 (60.06 on the 0-100 scale), while the Physical domain has the lowest average of 11.4 (44.68 on the 0-100 range). The Psychological and Social domains were in the middle, indicating differing levels of reported quality of life in many parts of patient's lives.

Table 3: Mean and Standard Deviation of Scores on World Health Organization Quality of Life BREF (WHOQOL)

Categories	Transformed (4-20) Mean ± SD	Transformed (0-100) Mean ± SD
Physical	11.4 ± 2.508	44.68 ± 15.499
Psychological	12.66 ± 2.152	54.21 ± 13.428
Social	12.49 ± 3.188	53.01 ± 19.963
Environmental	13.57 ± 2.140	60.06 ± 13.372

Note: Mean ± SD = Standard Deviation

Table 4 showed the findings of a one-way ANOVA comparing Quality of Life (QOL) across patients with varied degrees of depression, anxiety, and stress. There were significant variations across all three variables. Patients with mild depression had the highest mean QOL (M = 88.72), whereas those with severe and extremely severe depression had considerably lower QOL ratings (M = 70.55 and M = 72.15, respectively), with a f value of 21.78 and P =0.001. For anxiety, QOL dropped as severity rose, from light (M = 69.69) to extremely severe (M = 80.69), with substantial variation (f = 7.47, P <0.001). Stress had the greatest influence, with QOL scores ranging from 68.40 in

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mild situations to 83.92 in really severe cases, as indicated by a f value.

Table 4: One-Way ANOVA on the variable of Quality of Life with Mild to Extreme Severity of Depression, Anxiety and Stress among Patients with Hemodialysis

Grade	N	Mean ± SD	SE	95% CI		F	p-Value
				Lower Bound	Upper Bound		
Depression							
Mild	18	88.722 ± 7.969	1.878	84.759	92.685	21.78	0.001
Moderate	24	75.625 ± 9.640	1.967	71.554	79.695		
Severe	44	70.545 ± 8.638	1.302	67.919	73.171		
Extreme	48	72.145 ± 7.682	1.108	69.915	74.376		
Anxiety							
Mild	36	69.694 ± 15.036	2.506	64.606	74.782	7.47	0.001
Moderate	47	73.383 ± 8.208	1.197	70.973	75.792		
Severe	25	76.920 ± 4.725	0.945	74.969	78.870		
Extreme	26	80.692 ± 3.121	0.612	79.431	81.953		
Stress							
Mild	10	68.400 ± 5.253	1.661	64.641	72.158	29.77	0.001
Moderate	40	67.475 ± 6.332	1.001	65.449	69.500		
Severe	47	74.276 ± 7.216	1.052	72.157	76.395		
Extreme	37	83.918 ± 10.523	1.730	80.410	87.427		

Table 5 showed the findings of a Tukey-HSD post-hoc analysis that compared the quality of life (QOL) scores of patients with varying degrees of depression, anxiety, and stress. For depression, mild instances had considerably higher QOL scores than moderate, severe, and extremely severe cases ($P < 0.001$). However, there were no statistically significant differences between moderate, severe, or extremely severe instances. In terms of anxiety, light cases had significantly higher QOL scores than severe and extremely severe cases, while moderate cases had greater QOL than extremely severe cases, demonstrating a constant reduction in QOL as anxiety intensity increased. There were considerable changes in stress between mild and extremely severe.

Table 5: Tuckey-HSD Comparison Among Mild to Extreme Severity of Depression, Anxiety, And Stress On the Variable of Quality of Life Among Patients with Hemodialysis

(I) > (J)	Mean Difference (I-J)	SE	95% Confidence Interval		p-Value
			Lower Bound	Upper Bound	
Depression					
Mild > Moderate	13.097*	2.623	6.270	0.000	19.923
Mild > Severe	18.176*	2.353	12.051	0.000	24.302
Mild > Extreme	16.576*	2.325	10.525	0.000	22.627
Moderate > Severe	5.079	2.134	-0.476	0.086	10.635
Moderate > Extreme	3.479	2.103	-1.994	0.352	8.952
Severe > Extreme	-1.600	1.755	-6.169	0.799	2.969
Anxiety					
Mild > Moderate	-3.688	2.109	-9.178	0.303	1.801
Mild > Severe	-7.225*	2.479	-13.678	0.022	-0.772
Mild > Extreme	-10.997*	2.451	-17.377	0.000	-4.618
Moderate > Severe	-3.537	2.357	-9.672	0.440	2.598
Moderate > Extreme	-7.309*	2.327	-13.367	0.011	-1.251
Severe > Extreme	-3.772	2.667	-10.715	0.493	3.170
Stress					
Mild > Moderate	0.925	2.807	-6.380	0.988	8.230
Mild > Severe	-5.876	2.764	-13.072	0.151	1.3193
Mild > Extreme	-15.518*	2.829	-22.883	0.000	-8.154
Moderate > Severe	-6.801*	1.707	-11.246	0.001	-2.356
Moderate > Extreme	-16.443*	1.810	-21.157	0.000	-11.730
Severe > Extreme	-9.642*	1.744	-14.183	0.000	-5.101

DISCUSSION

The finding of the present research showed a high Prevalence of depression, anxiety, and stress in hemodialysis patients. In the present study, 42.5% were severe levels of depression. 26.5% of patients were found in extremely severe levels of depression 67.2% of patients had extremely severe levels of anxiety.18.7% of patients were found in severe levels of anxiety. 48.5% of patients reported severe levels of stress. 32.1%patients reported moderate levels of stress. Additionally, another study showed a prevalence incidence of 26.6% for depression and 45% for anxiety was found in individuals who were diagnosed with ESRD [14, 15]. On the other hand, the study found that the prevalence rate for anxiety was 45.7% and the prevalence rate for depression was 29% among patients with ESRD [16]. These findings highlight the significant burden of mental health concerns that persons who were having therapy for ESRD confront. Increased levels of psychological distress may be a result of the difficulties that were involved with the management of a chronic illness such as ESRD, which necessitates continuing medical interventions such as transplantation or dialysis [17]. This patient population may be more susceptible to developing melancholy and anxiety or experiencing an exacerbation of these conditions, due to many factors, including the impact of symptoms, changes in lifestyle, financial strain, and uncertainty about the future [18]. Additionally, the present study also indicates that patients with poor quality of life will have high levels of depression and anxiety. The ANOVA analysis supports this hypothesis, showing significant associations between depression and three out of the four domains of quality of life: physical health, psychological well-being, and the environment. Patients experiencing poor physical health often report feelings of helplessness and despair, which were core components of depression. Similarly, poor psychological well-being, characterized by negative emotions and cognitive dysfunction, is inherently linked to depressive symptoms. These findings were consistent with numerous studies that have documented the reciprocal relationship between poor quality of life and depression. For instance, Feijão and Freitas investigated depression in 150 hemodialysis patients and stated that non-adherence to medicine could be a possible explanation for high levels of depression, stress, and

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anxiety in hemodialysis patients [19]. However, the researchers found that adherence or non-adherence to the treatment regimen did not significantly correspond to quality of life across the two groups [20]. According to numerous studies, people confronted with challenges or coping with chronic conditions frequently experience a decline in their mental well-being. Some of the factors that might lead to feelings of sadness, stress, and anxiety include the burden of managing physical health conditions, living with pain or discomfort, and navigating complex healthcare systems [21]. Additionally, the influence that these disorders have on day-to-day functioning, social relationships, and general life satisfaction further exacerbates the effects of psychological discomfort [22]. An early diagnosis of depression in patients who were waiting for a kidney transplant, according to, may contribute to an increase in the quality of life of those patients[23].

CONCLUSIONS

Hemodialysis, the most common treatment for end-stage renal disease, was a risk factor for psychological illnesses such as depression, stress, anxiety, and poor QOL. There was a need to develop a treatment strategy, including therapeutic invitations that eventually, improve quality of life.

Authors Contribution

Conceptualization: ASH
Methodology: AU
Formal analysis: AU
Writing, review and editing: MS

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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Systematic Review

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Innovative Approaches to Stress Reduction: A Review of Virtual Reality Therapy in University-Going Students

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ABSTRACT

Students face unique challenges in terms of stress and Virtual Reality Technology (VRT) is emerging as a novel method for managing it. It has immersive and engaging nature that makes it potentially more effective stress management tool. **Objective:** To analyzed the effectiveness of VRT in managing stress among university students. It also evaluates student willingness to adopt these interventions compared to traditional methods. **Methods:** Narrative approach was used to review existing literature, focusing on studies that assessed the impact of VRT on student stress levels. Data were analyzed considering variations in VR content, delivery format, and participant demographics. **Results:** The review revealed that students generally show a willingness to use VRT for stress management but the effectiveness of these interventions was inconsistent. VRT using natural environments especially with greenery was more effective in reducing stress as compared to virtual settings. However, some studies reported no significant difference between VRT and traditional methods. **Conclusions:** VRT has potential in enhancing student well-being but its effectiveness was influenced by the type of VR content, delivery method, and individual characteristics. The limitations suggest that VRT was not a definitive solution to stress. This shows that further research was needed to optimize VRT interventions and to implement them to broader academic settings.

INTRODUCTION

Academic stressors such as fear of failure, time management, coursework, exams, and the challenge of balancing social life significantly affect university students [1]. The prevalence of stress within university going students ranges from 15% to 30% [2]. After COVID-19 pandemic, due to disruptions, uncertainty, and loss of social life the presence of psychiatric disorder has significantly elevated [3]. This has led to increased stress levels and depression among students [4]. The incidence of suicidal thoughts and attempts is higher among students than in older individuals i.e., nearly 5%-7% in males and females respectively [5]. It has been reported in the literature that stressful environment and suicidal behavior is associated [6]. Another factor that causes higher prevalence of stress in students is the urbanization, migrating from rural less densely populated areas to urban areas [7]. Due to this, students get isolated from their natural environments [8, 9]. College and university students around the world are compelled to live independently for the first time in their life for studies which can lead to a lot of stress [10]. Additionally, other academic stressors like financial pressures, high academic workload, performance pressure, lack of social support, poor time management, health issues, and access to academic resources further increase the stress levels among students. Every situation that leads to negative emotions such as anxiety, anger, sadness and fear can lead to stress. On the contrary interest contentment, joy and love are positive emotions which reduces the levels of stress. In this review stress among university students and the efficacy of Virtual Reality Therapy (VRT) to mitigate the levels of stress is discussed. VRT is a novel tool that uses

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computer-generated simulations to create immersive, interactive 3D environments. This allows individuals to engage with these environments as if they were real. It has potential in therapeutic applications such as stress management. Traditionally, stress management for students has relied on counseling, meditation, and exercise regimes [10]. These approaches are effective but have limitations like accessibility, affordability, and long term adherence [11]. Modern students are tech-savvy and their perceptions about traditional approaches is that they are outdated and efficient for older adults [12]. Furthermore, the traditional approaches for stress management may be unappealing and stigmatizing to the students. Also, they require time and financial resources which the students usually lack. The alarming levels of stress among students requires innovative approaches for stress reduction [13]. It is known that physical exercises prevent negative emotions and is beneficial for the physical and mental wellbeing of individuals [14]. The literature suggests that the psychological effects of physical exercise can be attained by manipulating the brain with environmental changes through VRT [15]. This approach helps in improving the ability to calm down and stimulating positive emotions thus resulting in better stress management [16]. The main advantage of VRT in contrast to the traditional approaches of mental health management is that it can be tailored according to the individual's needs and preferences.

The aim of this study was to review the efficacy of VRT as a stress management tool among students, specifically among university going students. Considering the high prevalence of stress among university students and the drawbacks of traditional approaches for stress management the need for affordable, appealing and innovative approach for this purpose was higher than ever before. The use of VRT in phobia, anxiety and PTSD has been studied extensively. Nevertheless, the use of VRT in the management of stress primarily in students was limited. This paper seeks to synthesize the existing literature on this topic and critically analyze the efficacy of VRT based interventions and opening a portal for future research.

METHODS

An extensively structured search was conducted in Pub Med database using the following keywords: "virtual reality therapy", "stress reduction", "students" and "university". The search strategy utilized in this review was influenced by a prior systematic investigation exploring the use of VRT in promoting the well-being of young adults [17]. The search had no time restrictions to include all the relevant studies. The inclusion criteria were as follows: (a) studies with college and university students as participants, (b) studies that evaluated the efficacy of virtual reality therapy for stress reduction, (c) studies published in English language and (d) publications of peer reviewed journals. The exclusion criteria were: (a) studies including participants other than students, (b) studies focusing on approaches for stress management other than VRT, (c) studies in which the assessment of efficacy of VRT was related to other psychological complications such as PTSD. We excluded studies focusing on PTSD because the primary aim was to evaluate the efficacy of VRT specifically for stress reduction. PTSD was related to stress but it represents a distinct clinical condition with specific therapeutic approaches and outcomes. Adding PTSD would have introduced variables not comparable to general stress management. This could potentially affect the results of specific impact of VRT on everyday stress experienced by students. The initial search resulted in the identification of 512 published articles. The titles and abstracts of all the articles were screened carefully by the principal author and resulted in the isolation of 12 studies. After a thorough full text study of these articles 4 studies were finalized that met the inclusion criteria. In the process of studying these articles 3 new studies were identified based on the citations. Majority of the studies were excluded because they focused on participants other than the students or the efficacy of VRT on stress reduction was not the objective of the studies. The complete process of screening was scrutinized by the corresponding author. For this purpose, Mendeley reference management was used. The data from the included studies was extracted regarding the names of the authors, year of study, study design, sample size, intervention, objectives and conclusions of the studies. An excel sheet was devised to record the data systematically (See supplementary material). For the data synthesis a narrative approach was used to qualitatively interpret the findings of the studies. Such approach was used in order to explain qualitatively the different methods, results and circumstances of the studies included in the analysis. This approach makes it possible to make a broader and more thorough assessment of VRT in different forms and in a variety of populations [18]. It was advantageous because studies on the topic are limited and also varied. Meta-analysis on the other hand, necessitates that studies are similar on a number of fronts while in this case the narrative synthesis can allow the differences in study and study outcomes. The studies published in high impact journals were focused more for the synthesis. The data synthesis was focused primarily on the use of VRT as a stress management tool among university students, its effectiveness, compliance and potential in the future research.

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RESULTS

Seven studies were shown to be satisfactory for the purpose of the review. Basic characteristics of these studies are set forth in table 1. These studies explore the use of Virtual Reality technology for stress management among various student populations. figure 1 Gao *et al.*, conducted a cross-sectional study with 120 college students and used the Profile of Mood States (POMS-SF) to assess changes in restorative states before and after VR visual stimulation [19]. Jo *et al.*, did a Randomized Controlled Trial (RCT) with 60 college students and examined the effect of VR-based forest videos on EEG outcomes [20]. Modrego-Alarcón *et al.*, targeted a total of 280 undergraduates and assessed response to a virtual reality-based mindfulness-based intervention [21]. FFMQ and SCS scales measuring perceived stress levels were also used and a significant reduction was seen. Plante *et al.*, conducted an experimental study with 112 psychology students [22]. They investigated the impact of physical activity and its adherence to the exercise combined with VR together with VR. AD-ACL, PACES and MC-SDS were some of the tools that had been utilized. Valtchanov *et al.*, did an RCT with 69 undergraduate students to compare physiological and affective responses to different VR environments [23]. They focused on nature versus urban settings and used the Zuckerman Inventory of Personal Reactions. Villani *et al.*, also evaluated to what extent VR technology was superior to more traditional approaches such as relaxation DVDs and audiotapes [24]. All 64 general students were involved in an experiment where the following scales were used: STAI-Trait, COPE, VAS, PANAS and STAI-State. Finally, Xu *et al.*, studied the feasibility of a 6-week VR exergame-based intervention for reducing anxiety, depression, and perceived stress among 15 university students [17]. Outcomes were rated using Perceived Stress Scale (PSS). These studies as a whole show that VRT is flexible tool in relieving stress in students. The outcomes of different VR treatments differ in various studies depending upon type of content used and type of format or participant's characteristics.

Table 1: Basic Attributes of the Studies Incorporated in this Review

S.No.	Authors	Method	Sample Size	Population	Tool	Objective
1	Gao *et al* [19]	Cross-Sectional	120	College Students	Profile of Mood States (POMS-SF)	To figure out the Difference in the Restorative State Before and After Visual Stimulation by Using VR Devices.
2	Jo *et al* [20]	RCT	60	College Students	Questionnaires	The effect of Watching Forest Videos using VR on the EEG.
3	Modrego-Alarcón *et al* [21]	RCT	280	University Students	FFMQ and SCS	To Investigate the Effectiveness of a MBP Delivered through Virtual Reality for Reducing Perceived Stress in University Students.
4	Plante *et al* [22]	Experimental	112	College Psychology Students	AD-ACL, PACES and MC-SDS	To Evaluate the Psychological Effects of Exercise when Paired with Virtual Reality.
5	Valtchanov *et al* [23]	RCT	69	Under-graduate Students	Zuckerman Inventory of Personal Reactions	To Investigate the Physiological and Affective Responses of Individuals when Immersed in different VR Environments, Specifically Comparing the Effects of Nature and Urban Settings.
6	Villani *et al* [24]	Experimental	64	Students in General	STAI-Trait, COPE, VAS, PANAS, STAI-State	To Evaluate the Effectiveness of Virtual Reality as a Tool for Relaxation Compared to DVD and Audiotape
7	Xu *et al* [25]	Experimental	15	University Students	Perceived Stress Scale (PSS)	To Explore the feasibility of a 6-week VR Exergame-Based Intervention in Reducing Anxiety, Depression, and Perceived Stress Among University Students and to Examine the Usability And Acceptability of Such Games.

[1]**Abbreviations:** RCT, randomized controlled trials; FFMQ, five facet mindfulness questionnaire; SCS, self-compassion scale; AD-ACL, activation deactivation adjective check list; PACES, protective and compensatory experiences; MC-SDS, Marlowe Crowne social desirability scale; STAI, state-trait anxiety inventory; COPE, coping orientation to problems experienced; VAS, visual analogue scale; PANAS, positive and negative affect schedule.

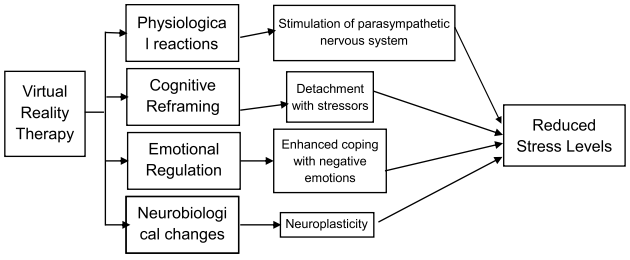

Figure 1: Potential Mechanisms Involved in Reduction of Stress Through Virtual Reality

The research findings on the effectiveness of VRT in stress management are presented in table 2. In all the studies included in this review the intervention of VRT somehow was effective in managing stress. Almost all the studies incorporated a control group to compare the intervention with. Notably the interventions were not significantly effective in all the reported studies in this review. Nonetheless, decreased negative emotions, increase in positive emotions and more relaxed state were reported in different studies. One of these studies reported no significant difference between mindfulness-based

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programs and VRT [19]. Another study suggested that the effect of VRT was increased if the individuals feel more engaged in the environment [22]. Most of the studies were conducted among university students but some were also conducted on undergraduate students, college students of nursing and medical backgrounds. The VRT interventions used in these studies varied. Panoramic VR based photographs, VR nature imagery, VR combined with MBP, VRT combined with exercise, VR visuals of urban, natural and geometrical visuals, VR with forest images, VR based boxing games were used as an intervention in the included studies. The data synthesis suggests that VRT with natural images and visuals particularly with greenery seems to be more effective for stress management as compared to other VRT interventions [19, 23]. The available evidence suggests that the VRT interventions tailored for individual's preference are more effective in managing stress [22]. The potential for VRT as a stress management tool lies in its general efficacy and the adaptability to the needs of student populations [26]. The review highlights the need to tailor VRT procedures to the individuals on whom it was applied. Such personalization can however be extended to cover other sociographic factors such as age, sex, socio-cultural factors and technological capabilities of the students. For instance, children or those who are not technology-oriented could be provided with primitive screens and orientation sessions. On the other hand, students who are more familiar with technology could be taken through the more sophisticated VRT sessions. Moreover, even though the choice of the virtual environment might be determined in terms of users social and cultural lines some cultural factors might also come in. For instance, the social setting that was preferred may be the one that matches the home atmosphere of the student. Different delivery formats can be used like one-on-one sessions, group interactions, or self-guided experiences. Based on student preferences alone an introvert student may do better with the self-guided or individual VRT sessions while an extrovert average better in VRT experiences which are group-based. VRT was capable of presenting any form of experience thus it was flexible. This flexibility provides a chance to come up with more universal measures of stress management based on the peculiarities present in the student samples [27]. Additionally, individual sessions with proper guidelines are seen to be more effective. It should be noted that the individual sessions and sessions with proper guidance give better results as compared to group sessions. However, they are costly and more time consuming which limits the use of VRT for stress reduction. We acknowledge that the data to compare the delivery formats was inadequate and more studies are needed to compare the delivery formats. The review regarding the use of VRT for stress management in students found studies involving students from different backgrounds as mentioned previously. Notably the studies of this review showed homogeneous results regardless of the academic background of students. It can be assumed that participants from higher education and female participants are more likely to benefit from VRT interventions for stress reduction [17]. Additionally, the students with high baseline levels of stress are more likely to experience positive effects of this intervention. Also, the students more inclined towards the use of technology are more likely to choose to experience this intervention. The authors acknowledge that the current literature was not adequate and further studies are required to evaluate the effectiveness of VRT among different groups of students based on demographics. The available literature further suggests that the university students are more willing to engage with the VRT interventions [25]. For the participants with currently enrolled in academic programs the use of VRT was not a complex or unpleasant to use process. The students were happy to complete the intervention-based programs. It should be noted that the effectiveness of VRT for the stress management was may not significantly higher than the traditional methods, but the adherence and acceptability was quite higher than the traditional approaches among college and university students [20]. The synthesis of the qualitative data indicated that this intervention was "easy to use, polished to a professional standard, fun and innovative" for students [28].

Table 2: Insights of the Studies Incorporated in this Review

S.No.	Authors	Intervention	Outcome
1	Gao *et al* [19]	VR Panoramic Photographs	While The Study Shows a Reduction in Negative Mood and Attentional Fatigue, Which are often Associated with Stress, it Doesn't Explicitly Conclude that these Environments Reduce Stress Overall.
2	Jo *et al* [19]	2D Videos and VRT	As a Result of the above, it was Investigated that Forest Videos using vr had a Positive Effect on the Physiological Stress on College Students. Therefore, it is Expected that a Positive effect will Occur if vr is used as an Alternative to Stress Management for College Students.
3	Modrego-Alarcón *et al* [21]	MBP and VRT	The Inclusion of VR Exposure Resulted in an Improved Adherence to the Mindfulness Program, although it did not Affect the Efficacy of the Intervention.
4	Plante *et al* [22]	Exercise, Exercise + VRT, VRT	Both Female and Male Participants walking in the Laboratory with the Virtual Reality were more Relaxed and Experienced the least Tension of the three Conditions.
5	Valtchanov *et al* [23]	VR Visuals of Nature, Urban and Geometric Shapes	Exposure to a Virtual Nature Environment led to Significantly Improved Affect and Reduced Stress Levels Compared to Exposure to an urban or Neutral Virtual Environment. This Suggests that Virtual Nature Experiences could have Restorative effects similar to real Nature, Potentially offering a Valuable Tool for Stress Reduction.
6	Villani *et al* [24]	VR, DVD Condition Audio Condition	More Immersed someone Feels in the Virtual Environment, the more effective the Relaxation Intervention will be.

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7	Xu *et al* [25]	Boxing-style VR Exergame called FitXR (FitXR Limited) Twice Per Week	The mean Perceived Stress Score for the Pretest was 16.87 (SD 4.88), and the mean Perceived stress score for the Posttest was 16.13 (SD 5.81). A 2-tailed Paired ttest showed that there was no significant difference between the Pretest and Posttest Scores (t14=0.564; P=.58)

[2]**Abbreviations:** VR, virtual reality; 2D, two dimensional; MBP, mindfulness-based program. SD, standard deviation.

DISCUSSION

The results of this review underscore the growing interest in Virtual Reality Technology (VRT) as a tool for stress management among students, with seven studies meeting the inclusion criteria. The diversity in study design, intervention types, and measurement tools reflects the exploratory nature of research in this area. Despite the variability in methodologies, several key themes and findings emerged that warrant discussion. First of all, the methodology through which VRT produces its effects is: The VRT can cause Physiological Relaxation, distract the individual from stressful environments, and can divert them from their stressful lives and provide more relaxed visuals. As outlined earlier in this review natural visuals are more effective in relaxing the participants thus coping with stress. Evidence exists that the sympathetic nervous system is responsible for stress in the body [25]. The diversion produced by VRT stimulates the parasympathetic nervous system, which is responsible for the relaxed state of the individuals. In more accessible terms the sympathetic nervous system and parasympathetic nervous system is responsible for 'fight or flight' and 'rest and digest' responses in the body, respectively [26]. The shift of body towards parasympathetic nervous system predominance results in the diminution of blood pressure, heart rate and muscle tension thereby eliciting relaxation [27]. It was also known that the phenomenon of stress is triggered by the external or internal events or situations known as stressors [29]. The individual's cognitive appraisal of stressors determines the levels of stress. For the management of stress, the cognition needs to be reconstructed. The VRT provides psychological detachment of the individual with the stressors and the visuals provided by the VRT can help them in reframing the cognition through providing relaxation stimuli [30-32]. The VRT visuals and even gaming equips the individuals to enable them to effectively confront the negative emotions and stress in real life [33]. Furthermore, the VRT experience may provide emotional regulation i.e., facilitating the ability to accept and regulate the emotions. It reduces the reactivity by providing an environment where instead of being overloaded by intense emotions in real life the person can relax and make better decisions about handling the situation [28]. Additionally, gaming in VRT has been shown to increase the mindfulness by detaching with stressful thoughts and engaging in the present. The visuals of VRT can empower the person experiencing it to cope with emotions. Virtual Reality Technology (VRT) facilitates stress management through a complex interaction between cognitive reframing, emotional regulation, and physiological changes. Cognitive reframing in VRT involves altering negative thought patterns by immersing individuals in controlled environments that challenge their perceptions and encourage positive reinterpretation of stressors [34]. This process was supported by the vivid, immersive nature of VRT, which allows users to experience and practice new ways of thinking in a safe, virtual space. Emotional regulation is another key component in this regard. VRT makes users able to manage their emotional responses by providing a buffer against overwhelming stressors [35]. Virtual environments are designed to reproduce the conditions that soothe individuals and assist them in practicing emotional self-regulation. The expectancy of stress response improves and the reactivity is improved. For instance, the capacity of the users to deal with stress in a build virtual environment can be transferred to affect the emotional stability in the actual world. Discussing the physiological aspects, the influence of VRT is such that it incorporates the working of the autonomic nervous system through the induction of relaxation by parasympathetic activity [36]. The physiological indicators of stress such as Heart Rate and Blood Pressure are seen to decrease as VRT transforms the status of the person from the state of 'fight or flight' to the state of 'rest and digest'. This change in physiology diminishes the stress factor and helps maintain the cognitive and emotional improvements achieved in VRT sessions. VRT stress relief is achieved through a combined action of cognitive dissonance, affective modulation, and bodily relaxation. Hence, it is a holistic approach to stress management and a powerful tool for improving mental well-being. Some neurobiological changes are also induced by VRT. Neuroplasticity is a process in which the brain adapts and modifies its structure and functions in response to experiences encountered by the body [37]. The VRT may stimulate this process to manage stress. The process involves decreased activity in the amygdala which is responsible for emotional responses to threats such as fear and anxiety [38]. Simultaneously, the prefrontal cortex of the brain which plays a role in the emotional regulation, decision making and cognitive functioning [39, 40]. The VRT induced neuroplasticity improves the ability of this region. Additionally, this process results in growth of new brain

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cells; neurogenesis which enables enhanced cognitive functioning and improving the mood. In conjunction with this, the activity of neurotransmitters is increased such as dopamine, serotonin and Gamma Amino Butyric acid (GABA) which are associated with motivation, feeling of happiness and a calming effect, respectively [41].The findings of most of the studies used in this review suggest that VRT is effective in stress management, although with varying levels of effectiveness. For example, Gao *et al.*, and Jo *et al.*, were able to investigate the effect of VRT on negative emotions and noted that it had a significant effect of improving emotions on the participants, particularly for interactive virtual environments despite the decoration of these environments. However, the authors also caution that not all studies showed any statistical significance results. For example, Xu *et al.*, work involving a study earning a VR exergame did appreciate or observe any changes in the level of stress of the participants following the change and so emphasizing the challenges that characterize the quest to possible find the suitable VRT techniques. The content type of the VR seems to be very important in determining the success of the intervention program [42]. In this case, natural environments, particularly green ones, were always more effective in helping the users to relieve stress than other virtual environments. Such findings are consistent with the evidence regarding the positive impact of nature on one's well-being and support the use of VRT as an alternative approach for achieving the same effects [43]. The findings from Valtchanov *et al.*, study, which highlighted the superior stress-reducing effects of virtual nature environments over urban or geometric visuals, further support this conclusion. Another aspect that stands out was the character and manner of delivery of VRT interventions. The review shows that VRT sessions that are oriented to individual needs and offered on a one to one basis are more effective. Such sessions although personalized are also costlier which may restrict their reach. It was therefore warranted that more research be carried out on the best model of delivery since the weight of the existing literature does not allow for any conclusion to be drawn. The characteristics of the participants also affected the results. It was noted in the review that it is more probable that higher education students, especially females, and those suffering from higher metrics of stress at baseline, would benefit more from VRT interventions. This correlates with the concept that stress affects the way one responds to the interventions given. In addition, the studies reviewed show that students who are more technology savvy are more likely to take interest and participate in VRT programs and this may affect the mode of the results. While VRT shows promise as a stress management tool, it is essential to recognize that its effectiveness may not significantly surpass that of traditional methods. However, the higher acceptability and engagement levels associated with VRT, particularly among university students, suggest that it could be a valuable complement to existing stress management strategies. It should be noted that the effectiveness of VRT for the stress management was may not significantly higher than the traditional methods, but the adherence and acceptability is quite higher than the traditional approaches among college and university students [22]. The synthesis of the qualitative data indicated that this intervention was "easy to use, polished to a professional standard, fun and innovative" for students [25]. VRT is dissimilar to the conventional types of stress relieving procedures such as counseling, meditation, and physical exercise in several ways. The first is the high level of immersion and engagement of the users. VRT Interest in adopting new technologies was highest for interactive 3D environment simulated placements [44]. Such interactivity adds to the VRT's capacity to reach out to users in a way that was not achieved by older methods. It also increases the level of engagement from users, especially the younger generation who tend to be more enthusiastic about such activities. VRT has also a high range of customization. It also considers the preferences of the person and therefore makes use of VRT more effective. For example, students may select certain environments instead of simply browsing, allowing for relaxation with a certain type of environment [45]. This level of adaptability is not possible with other, less recent techniques. Nevertheless, even though VRT does have its limitations. The technology is still nascent and while more research is being conducted, it does not have the body of evidence that is available for other forms of interventions such as cognitive-behavioral therapy or mindfulness practices. It is also important to highlight that the process of designing, developing, and putting VRT to use is costly, and the necessary technology is often lacking in many locations, most especially in low income communities. Another limitation was that one or more of the users are likely to have some form of cyber sickness, that is motion sickness in other words, and this might affect the utilization of VRT [46]. Within the confines of this review, the findings enhance the understanding of VRT as a strategy in relation to university student stress, but the same cannot be said for its use in other settings. Most of the studies that satisfied the inclusion criteria for this review were too tailored to a specific kind of student. The other aspect was that since different types of VRTs and various study designs were used, it also means that the types of virtual environment in use, the level of stress in

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individuals, and the degree to which technologies are adopted will affect the efficacy of VRT. In the end, although VRT is, in some respect, an attempt to reduce the stress even when applied to people for academic research purposes, there are limits on the scope of any study due to principles of the functional design that define behavior in new environments with new audience. It would be of interest for subsequent research to assess the limitations of the VRT across a broader spectrum of people and in more diverse situations in order to define the potential use of the VRT. The application of VRT in stress management has various ethical challenges. There is also fear that rather than engaging in real life contextual plain interactions with fellow students, students may opt to interact within the confines of the virtual environments leading to increased isolation or dislocation. From an ethical perspective it was critical that stress management techniques and social interactions are not replaced by the Virtual Reality Therapy.

CONCLUSIONS

Throughout this review, the emerging field of VRT has been examined as a potential tool for stress reduction among university students. It seems likely that its mechanisms of action can be ascribed to several processes, such as relaxation, cognitive reframing, improved emotional management, and possibly the ensuing neurobiological effects of such practice. It also seems likely that students find it engaging and largely acceptable; meaning that it holds significant benefits likes personalization and immersion. However, the costs, availability, and the need for further research are some of the primary concerns associated with it. Future studies should focus on long-term effects, optimal programmatic choices, and possible disadvantages like cyber sickness. As the technology grows in sophistication and the body of research on it expands, this tool of stress reduction may prove revolutionary in how we conceptualize and approach how well students fare in their academic environment in the digital age.

Authors Contribution

Conceptualization: Z, SB, SK

Methodology: Z, SB, SK

Formal analysis: Z, SB, SK

Writing, review and editing: Z, SB, SK

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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Systematic Review

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Analyzing the Prevalence and Patterns of Antibiotic-Resistant Pathogens Causing Surgical Site Infections

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ABSTRACT

Surgical Site Infections (SSIs) remain a critical healthcare challenge, contributing to increased morbidity, mortality, and healthcare costs. SSIs represent the third most common nosocomial infection globally with an incidence of 19-20%, while their prevalence in Pakistan was significantly higher, ranging up to 33.6%. The emergence of Multidrug-Resistant (MDR) organisms has worsened this issue. **Objective:** To determine the prevalence of antibiotic-resistant pathogens responsible for SSIs and analyze their antibiotic susceptibility patterns over the past decade. **Methods:** A systematic review was conducted adhering to PRISMA guidelines. Studies published between 2006 and 2023 were included. Data on the prevalence of antibiotic-resistant organisms associated with SSIs were extracted and analyzed through several databases (PubMed, Google Scholar, Sci-hub and Science Direct) using Boolean logic "AND" and "OR", and Medical Subject Headings (MeSH Terms) and keywords. A total of 70 articles were retrieved from which 16 articles were considered eligible after applying detailed inclusion/exclusion criteria and removing the duplicates and irrelevant articles. **Results:** The study identified *Staphylococcus aureus, coagulase-negative staphylococci, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli,* and *Acinetobacter spp.* as predominant MDR pathogens. A significant increase in the prevalence of antibiotic-resistant strains was observed over the study period. Gram-negative bacteria exhibited a higher resistance rate (66.8%) compared to Gram-positive organisms (51.1%). **Conclusions:** The increasing prevalence of antibiotic-resistant pathogens underscores the urgent need for comprehensive infection prevention and control measures to address the burden of SSIs. Targeted interventions, antimicrobial stewardship, and continued surveillance were essential to combat this growing challenge.

INTRODUCTION

Surgical Site Infections (SSIs) remain a significant challenge in surgical care, complicating the management of patients with surgical Site Infections (SSIs) by contributing to increased morbidity, mortality, and healthcare costs. They are characterized by inflammation of the surgical wound occurring within 30 days of surgery. These infections arise from microbial contamination of surgical wounds, often involving the patient's endogenous flora, such as Staphylococcus aureus and Escherichia coli, and can be exacerbated by the emergence of antibiotic-resistant pathogens [1, 2]. These infections are classified clinically based on the degree of contamination encountered during the operative procedure. Clean wounds are those without inflammation, while clean-contaminated wounds carry a minimal risk of infection. Contaminated wounds exhibit inflammation without purulent discharge but may involve contact with the gastrointestinal tract. Finally, dirty wounds are exposed to faecal matter, debris, or foreign bodies [3]. SSI prolong hospital stays, increases patient suffering, and imposes a substantial financial burden on healthcare systems. Globally, SSIs rank as the third most common nosocomial

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infection, with incidence rates varying from 19% to 20% based on patient demographics and surgical procedures [2]. Within Pakistan, the prevalence of SSIs is notably higher, ranging from 9.3% to 33.6% according to available literature [4]. Multiple factors contribute to the heightened risk of SSIs, including patient-related vulnerabilities such as immunosuppression and pre-existing infections. Surgical risk factors involve prolonged procedures, accidental contamination, inadequate sterilization, and improper instrument handling. Additionally, physiological conditions like multi-trauma, postoperative hyperglycemia, and hypoxia increase SSI susceptibility [5]. Other independent determinants of SSI risk include pathogen virulence, preoperative hospitalization, operative duration, surgical complexity, and the presence of wound debris, which collectively elevate the likelihood of severe infections caused by multidrug-resistant organisms [6]. The emergence of Multidrug-Resistant (MDR) organisms has further complicated the treatment of SSIs. Antimicrobial resistance was recognized as a global health threat at the 68th meeting of the United Nations General Assembly. The prevalence of such resistant bacteria associated with Surgical Site Infections (SSIs) has escalated dramatically in recent decades. These pathogens, including *Staphylococcus aureus* (methicillin-resistant), *Enterococcus spp.*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*, exhibit resistance to multiple antibiotic classes, necessitating a comprehensive understanding of their prevalence and antibiotic susceptibility patterns [7-9]. Predominant MDR pathogens isolated from hospital-acquired SSIs include Gram-positive bacteria such as *Staphylococcus aureus* (methicillin-resistant) and *Enterococcus spp.*, as well as Gram-negative bacteria like *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Escherichia coli*, which exhibit resistance to a broad spectrum of antibiotics, including tetracycline, cephalosporins, ampicillin, penicillin, and methicillin [10, 11]. The increasing prevalence of Surgical Site Infections (SSIs) coupled with the challenge of antibiotic resistance underscores an urgent need for comprehensive research. A comprehensive analysis of the evolving landscape of antibiotic-resistant pathogens responsible for these infections remains limited. This systematic review aims to address this critical gap by providing a comprehensive overview of the predominant antibiotic-resistant pathogens associated with SSIs and their historical trends. Understanding the dynamics of these pathogens is essential for developing effective prevention and control strategies, optimizing antibiotic use and ultimately improving patient outcomes. By identifying the prevalence and antibiotic susceptibility patterns of these organisms, this study contributes to the growing body of knowledge in this field and informs evidence-based practices in surgical care.

Therefore, based on this rationale, this systematic review was conducted to identify the predominant antibiotic-resistant pathogens responsible for SSIs and assess their prevalence rates over the past decade. By understanding the evolving landscape of these pathogens, surgeons can implement targeted infection prevention and control measures to improve patient outcomes and optimize antibiotic use.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed to perform this systematic review. The data for the last eighteen years (2006-2023) was collected using several databases (PubMed, Google Scholar, Sci-hub and Science Direct) using Boolean logic "AND" and "OR", Medical Subject Headings (MeSH Terms) and keywords. Different terminologies were used to explore the literature "Surgical site infections", "Antibiotic-resistant strains", and "Postoperative wound infections". A total of 70 articles were retrieved from the included databases. Out of all these articles 16 articles were considered eligible after applying inclusion/exclusion criteria and deleting the duplicates and irrelevant articles (Figure 1).

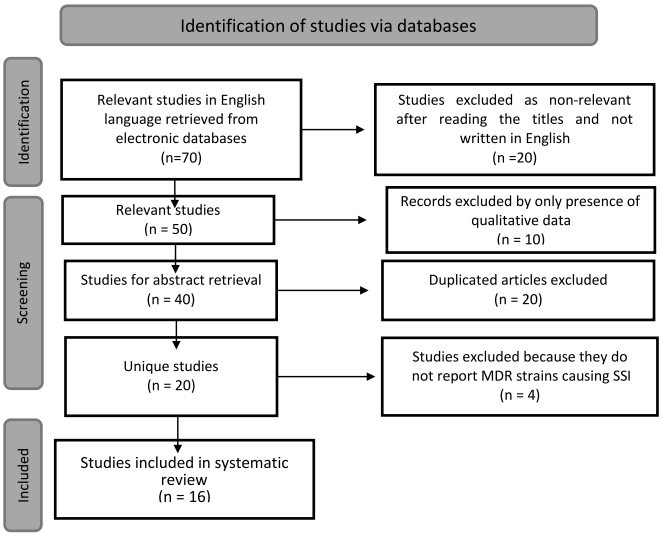

Figure 1: PRISMA Flowchart Depicting the Study Selection Process

All the required data were extracted from the eligible studies. Table 1 represented the epidemiological characteristics of studies included in the analysis of SSI.

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Table 1: Basic Attributes of the Studies Incorporated in this Review

S.No.	No of Isolates	Positive	Negative	Sample Source Post-Operative	Study type	References
1	147	95	NR	Pus Swab	Cross-Sectional	Palikhey *et al.*, 2023 [1]
2	147	147	NR	Wound Swabs	Cross-Sectional	Manyahi *et al.*, 2014 [2]
3	250	156	94	Wound Swabs	Prospective	Bhatt *et al.*, 2014 [3]
4	107	104	NR	Wound Swabs	Hospital-Based	Dessie *et al.*, 2016 [4]
5	177	177	NR	Wound Swabs	Cross-Sectional	Guta *et al.*, 2014 [5]
6	380	234	NR	Wound Swabs	Cross-Sectional	Hailu *et al* ., 2016 [6]
7	41	41	NR	Wound Swabs	Cohort Study	Abayneh *et al.*, 2022 [7]
8	168	168	NR	Wound Swabs	Cross-Sectional	Asres *et al.*, 2017 [8]
9	102	91	NR	Wound Swabs	Descriptive Cross-Sectional	Narula *et al.*, 2020 [9]
10	699	695	4	Wound Swabs	Cross-Sectional	Nobel *et al.*, 2022 [10]
11	150	145	NR	Wound Swabs	Cross-Sectional	Mama and Sewunet 2014 [11]
12	116	116	NR	Wound Secretion	Survey Study	Garoy *et al.*, 2021 [12]
13	128	123	NR	Wound Swabs	Prospective	Mengesha *et al.*, 2014 [13]
14	53	42	11	Wound Swabs	Cohort Study	Misha *et al.*, 2021 [14]
15	158	158	NR	Wound Swabs	Hospital-Based	Mwambete and Rugemalila 2015 [15]

NR=not reported

RESULTS

The following Factors Were Identified to Be Involved in Surgical Site Infection Showed in figure 2.

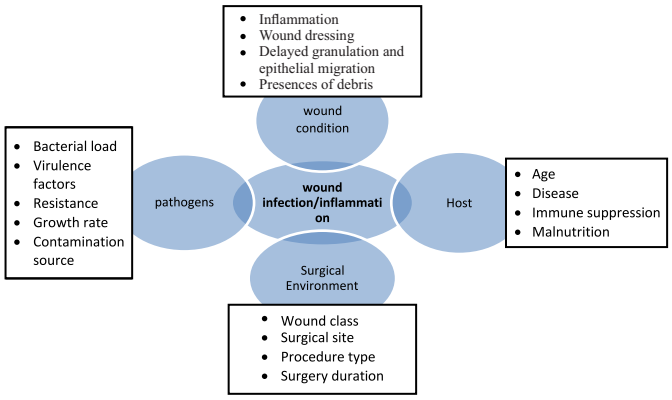

Figure 2: Factors Involved In Surgical Site Infection Evolution

To determine the antibiotic susceptibility profiles of bacteria associated with Surgical Site Infections (SSIs), numerous studies have employed the Kirby-Bauer disk diffusion method. A broad spectrum of antibiotics was tested, including tetracycline, cefoxitin, ciprofloxacin, gentamicin, penicillin and erythromycin for both Gram-positive and Gram-negative organisms. Additionally, ampicillin, ceftriaxone, and cefotaxime were utilized specifically for Gram-negative bacteria [12]. The frequency and percentage of isolated Gram-positive and Gram-negative resistant strains associated with SSIs were presented in tables 2. The percentage of antibiotic-resistant bacterial isolates was calculated using the following formula: Gram-positive bacteria represent a significant etiology of Surgical Site Infections (SSIs), with emerging antibiotic resistance posing a substantial clinical challenge. *Staphylococcus aureus* (S. aureus) and *Coagulase-Negative Staphylococci* (CoNS) have consistently emerged as predominant pathogens within this category. Studies have demonstrated a variable prevalence of S. aureus as a causative agent of SSIs. While Manyahi J *et al.*, reported a frequency of 21.3% in 2014, subsequent investigations have revealed a wider range. Guta M *et al.*, observed a prevalence of 25.5% in 2014, whereas Hailu D *et al.*, and Abayneh M *et al.*, reported slightly lower rates of 20.5% and 19.5%, respectively [2, 5, 6, 13-15]. Notably, Palikhey A *et al.*, identified the highest reported prevalence of S. aureus at 37.8% in 2023 [1, 7]. The World Health Organization (WHO) has further emphasized the significance of S. aureus as a leading cause of SSIs, with a global estimate of up to 30.4% incidence. CoNS have also been linked as a common pathogen in SSIs. Although generally considered less virulent than *S. aureus*, the development of antibiotic resistance has mitigated this distinction. Reported prevalence rates of CoNS in SSIs have ranged from 5.49% to 13.5% in various studies consistently lower than those observed for *S. aureus* [13, 15, 16-19].

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Table 2: Frequency and Percentage of Gram-Positive Antibiotic Strains

S.aureus N (%)	CoNS N (%)	*Enterococcus spp* N (%)	*Streptococcus spp* N (%)	Total Number of Isolates	MDR / Total Isolates N (%)
11 (7.05%)	1 (0.64%)	1 (0.64%)	0	156	102 (65.3%)
274 (21%)	36 (2.84%)	49 (3.87%)	4 (0.31%)	1266	850 (67.1%)
9 (1.29%)	70 (10.0%)	NR	NR	695	578 (83.1%)
36 (37.8%)	5 (5.26%)	NR	NR	147	95 (64.63%)
8 (5.44%)	8	4 (2.7%)	NR	147	75 (51%)
20 (17.2%)	NR	NR	NR	116	55.1 (64%)
48 (20.5%)	3 (1.2%)	NR	NR	234	127 (54.3%)
31 (21.3%)	17 (11.7%)	NR	NR	145	123 (8.4%)
NR	NR	NR	NR	123	102 (82.9%)
14 (15.3%)	5 (5.49%)	1 (1.0%)	NR	91	73 (80.2%)
25 (14.8%)	16 (9.5%)	1 (0.5%)	NR	168	110 (65.5%)
16 (10.1%)	NR	NR	NR	158	87 (55.5%)
45 (25.4%)	24 (13.5%)	NR	9 (5.0%)	177	164 (92%)
8 (19.5%)	2 (4.8%)	NR	NR	41	41 (100%)
5 (9.4%)	1 (1.88%)	NR	3 (5.6%)	53	42 (79.2%)
18 (17.3%)	4 (3.8%)	NR	NR	104	77 (74.0%)

MDR: Multi-drug-resistant; NR: Not reported; Spp: Species

The recorded percentage of *enterococcus spp* (0.64%, 2.7%, and 3.87%) and streptococcus spp (5.0%, 0, and 0.31%) were very low or was not reported in most of the studies carried out (figure 3).

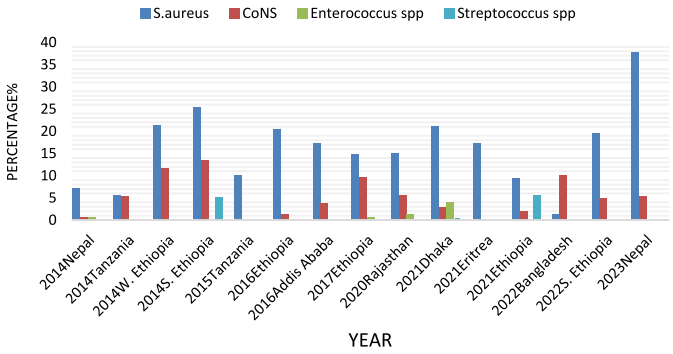

Figure 3: Isolation Frequency of Resistant Gram-Positive Strains from Post-Operative Wound Infections Gram-Negative Bacterial Strains: a Growing Threat in Surgical Site Infections

Gram-Negative Bacteria (GNB) pose a significant challenge in the prevention and management of Surgical Site Infections (SSIs). While Gram-positive organisms have traditionally been the primary focus of SSI research, the increasing prevalence of antibiotic-resistant GNB has underscored their critical role in postoperative morbidity [17]. *Pseudomonas aeruginosa*, *Escherichia coli*, and *Klebsiella pneumoniae* have emerged as the most prevalent GNB implicated in SSIs. Data from multiple studies reveal variability in the prevalence of these pathogens over time. *Pseudomonas aeruginosa* exhibited a wide range of reported prevalence, from 10.25% to 57.6% between 2014 and 2022 [6, 19-21]. *Escherichia coli* demonstrated a higher prevalence, with Mama M *et al.*, reporting a peak of 29.2%. *Klebsiella pneumoniae* prevalence ranged from 8.42% to 12.9% during the same period [1, 6, 11, 13, 15, 22]. Proteus mirabilis, although less frequently isolated, exhibited increasing trends, with reported percentages ranging from 0.64% to 14.6% [6, 13, 15] (Table 3). These data underscore the dynamic nature of the GNB landscape in the hospital setting. Effective prevention and control strategies should account for the evolving epidemiology of these pathogens to optimize patient outcomes.

Table 3: Frequency of Gram-Negative Antibiotic-Resistant Strain

Frequency and Percentage of Isolated Gram-Negative Antibiotic Strains							
Citrobacter N (%)	*Acinetobacter spp* N (%)	*P.aeruginosa* N (%)	*E.coli* N (%)	*Klebseilla* N (%)	*Enterobacter spp* N (%)	*Proteus mirabillus* N (%)	*A.batumanni* N (%)
NR	36 (23%)	16 (10.25%)	12 (7.6%)	16 (10.25%)	8 (5.1%)	1 (0.64%)	NR
23 (1.8%)	51 (4.0%)	145 (11.4%)	115 (9.0%)	65 (5.1%)	39 (3.0%)	44 (3.47%)	NR
NR	NR	401 (57.6%)	NR	54 (7.7%)	NR	44 (6.3%)	NR
NR	15 (15.79%)	11 (11.58%)	20 (21.05%)	8 (8.42%)	NR	NR	NR
NR	NR	1 (0.68%)	13 (8.84%)	14 (9.5%)	NR	12 (8.1%)	15 (10.2%)
15 (12.9%)	2 (1.7%)	8 (6.8%)	10 (8.6%)	10 (8.6%)	5 (4.3%)	8 (6.8%)	NR
3 (1.2%)	NR	15 (6.4%)	26 (11.1%)	12 (5.1%)	2 (0.8.5%)	18 (7.6%)	NR
NR	NR	11 (7.5%)	29 (20%)	13 (8.9%)	NR	22 (15.1%)	NR
NR	NR	NR	NR	NR	NR	NR	NR

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NR	NR	15 (16.4%)	11 (12.0%)	21 (23.0%)	NR	6 (6.5%)	NR
0	7 (4.1%)	2 (1.1%)	21 (12.5%)	14 (8.3%)	4 (2.3%)	0	NR
NR	NR	16 (10.1%)	6 (3.79%)	6 (3.79%)	16 (10.1%)	15 (9.4%)	NR
4 (2.2%)	NR	16 (2.2%)	NR	23 (12.9%)	3 (1.69%)	12 (6.77%)	NR
3 (7.31%)	NR	5 (12.1%)	12 (29.2%)	4 (9.7%)	NR	6 (14.6%)	NR
4 (7.5%)	NR	8 (15.0%)	9 (16.9%)	5 (9.4%)	NR	6 (11.3%)	NR
2 (1.9%)	22 (21.1%)	4 (3.8%)	20 (19.2%)	6 (5.7%)	0	1 (0.96%)	NR

NR: Not reported; Spp: Species

Graphical representation of recorded data demonstrates that K. pneumonia, *Acinetobacter spp, P. aeruginosa* and *E.coli* along, with proteus mirabillus were the most commonly observed resistant strains in cases of postoperative wound infections (figure 4). The isolation rates of *Enterobacter spp* and *Citrobacter* were low and not reported in a few studies. In another study carried out by Ali KM *et al.*, the reported percentages of *P. aeruginosa*, *Enterobacter spp* and *Citrobacter* were 14.58% 6.25% and 2.08% [23].

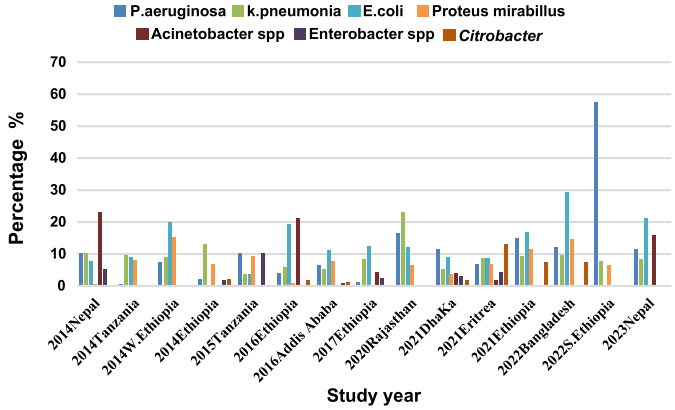

Figure 4: Isolation Frequency of Resistant Gram-Negative Strains from Postoperative Wound Infections

Prevalence of Antibiotic-Resistant Strains: Surgical Site Infections (SSIs) pose a significant challenge in the present healthcare system, ranking as a leading cause of healthcare-associated infections. A global multicenter study spanning 66 countries, comprising both developed and developing nations, reported a concerning overall SSI prevalence of 12.3% [24]. A meta-analysis of diverse geographical regions revealed a substantial increase in antibiotic-resistant strains associated with SSIs. While studies conducted in 2014 documented a prevalence ranging from 51% to 92% [2, 6, 13, 22], subsequent investigations in 2020 and 2022 reported even higher rates, with peaks of 80.2%, 83.1%, and an alarming 100% in certain regions [15, 19, 21] (table 3). Mukagendaneza MJ *et al.*, highlighted the substantial contribution of GNB to SSIs, constituting over 25% of cases [25]. This finding underscores the need for heightened surveillance and targeted interventions to address this emerging threat. This increasing trend of antibiotic resistance underscores the critical need for effective prevention and management strategies to mitigate the harmful effects of SSIs [25].

Table 4: Prevalence of Gram-Positive and Gram-Negative Resistant Strains of Post-Surgical Wounds

Prevalence	Country	References
64.4	Nepal	Palikhey *et al.*, 2023 [1]
51	Tanzania	Manyahi *et al.*, 2014 [2]
65.3	Nepal	Bhatt *et al.*, 2014 [3]
74	Addis Ababa	Dessie *et al.*, 2016 [4]
92	Southern Ethiopia	Guta *et al.*, 2014 [5]
54.3	Ethiopia	Hailu *et al.*, 2016 [6]
100	Southwest Ethiopia	Abayneh *et al.*, 2022 [7]
65.5	Ethiopia	Asres *et al.*, 2017 [8]
80.2	Rajasthan	Narula *et al.*, 2020 [9]
83.1	Bangladesh	Nobel *et al.*, 2022 [10]
84	West Ethiopia	Mama *et al.*, 2014 [11]
67.1	Dhaka	Garoy *et al.*, 2021 [12]
82.9	Ethiopia	Mengesha *et al.*, 2014 [13]
79.2	Ethiopia	Misha *et al.*, 2021 [14]
55.5	Tanzania	Mwambete and Rugemalila *et al.*, 2015 [15]

The predominant antibiotic-resistant strains identified as causative agents of surgical site infections in the present study were *Staphylococcus aureus* (16.2%) and coagulase-negative staphylococci (CoNS) among Gram-positive bacteria, while *Pseudomonas aeruginosa* (11.5%), *Klebsiella pneumoniae* (9.09%), *Escherichia coli* (13.8%), and *Acinetobacter spp.* (11.6%) were the most prevalent Gram-negative isolates (figure 5).

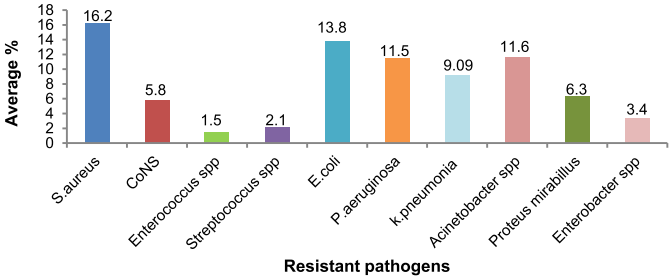

Figure 5: Frequency of Bacterial Strains Isolated from Surgical Site Infection

Overall prevalence of Gram-Positive and Negative resistant strains of Post-Surgical wounds is shown in figure 6

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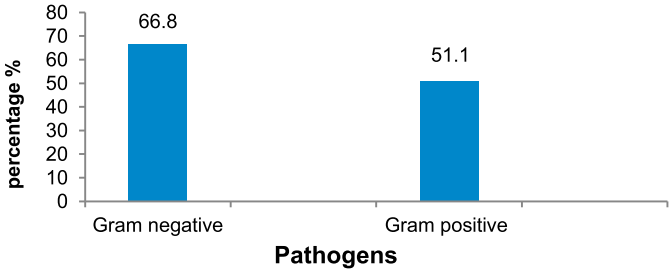

Figure 6: Prevalence of Gram-Positive and Negative Resistant Strains of Post-Surgical Wounds

DISCUSSION

The current study underscores the worsening burden of antibiotic-resistant pathogens contributing to Surgical Site Infections (SSIs). Our findings align with the global trend of increasing SSI rates, particularly those caused by multidrug-resistant organisms. The predominance of *Staphylococcus aureus, coagulase-negative staphylococci, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli,* and *Acinetobacter spp.* as causative agents highlights the urgent need for comprehensive infection prevention and control measures. The complex relationship between patient-related factors, surgical procedures, and the emergence of resistant strains necessitates a multidisciplinary approach to address this critical challenge. Effective strategies must include antimicrobial stewardship, adherence to surgical best practices, and robust surveillance systems to monitor the evolving landscape of SSI pathogens. The predominant antibiotic-resistant strains identified as causative agents of surgical site infections in the present study were Staphylococcus aureus (16.2%) and coagulase-negative staphylococci (CoNS) among Gram-positive bacteria, while *Pseudomonas aeruginosa (11.5%), Klebsiella pneumoniae (9.09%), Escherichia coli (13.8%),* and *Acinetobacter spp.* (11.6%) were the most prevalent Gram-negative isolates. These findings align with previous research conducted by Mshana *et al.*, and Mulu A *et al* [2, 26]. The elevated prvalence of *S. aureus* can be attributed to its status as a common skin commensal, facilitating its colonization of surgical wounds. Other potential sources include the hospital environment and contaminated surgical instruments. Our results were consistent with those reported by Shahane V *et al.*, and Kakati B *et al.*, in different geographic regions [27, 28]. In a study by Ali A *et al.*, *S. aureus* (66.7%) and CoNS (19.05%) were the predominant Gram-positive pathogens, while *E. coli* (33.3%) and *K. pneumoniae* (25%) were the most frequent Gram-negative isolates, demonstrating a similar pattern of antibiotic resistance [24]. The predominant etiological agent of Surgical Site Infections (SSIs) has been the subject of extensive investigation. Multiple studies have consistently identified Gram-negative bacteria as the primary causes. *Staphylococcus aureus* (31%), *Escherichia coli* (20.7%), and Klebsiella pneumoniae (8.9%) were frequently associated in these studies. A geographic expansion of this analysis revealed similar trends. Singh PP *et al.*, reported a predominance of Gram-negative organisms (56.25%) over Gram-positive bacteria (43.75%) in postoperative wound infections [29, 30]. Our systematic review supports these findings, demonstrating a higher prevalence of Gram-negative (66.8%) compared to Gram-positive (51.1%) strains associated with SSIs . These results align with the observations of Raza MS *et al.*, and Biadglegne F *et al.*, who also documented a higher incidence of resistant Gram-negative pathogens [31-36]. Maoulainine FM *et al.*, and Alkaaki A *et al.*, reported *Escherichia coli* as the most prevalent organism in their respective cohort studies [37, 38]. The prevalent nature, antimicrobial resistance, and potential faecal contamination during surgery have contributed to the emergence of *Klebsiella pneumoniae* as a significant pathogen, as highlighted by Hope D *et al.*, Worku S *et al.*, Kalayu AA *et al.*, and Bitew Kifilie A *et al.*, further emphasized the association between specific bacterial isolates and SSIs [39-42]. Dessie W *et al.*, highlighted the dominance of Gram-negative organisms in postoperative wound infections, underscoring the evolving landscape of Surgical Site Infection (SSI) pathogens [4, 12]. To effectively combat this challenge, identifying the precise origins of resistant pathogens was necessary for the effective selection of antimicrobial therapy and the prevention of antimicrobial resistance. Antimicrobial resistance poses a significant threat to global health and modern surgical practices. Characterizing the spectrum of resistant pathogens associated with SSIs was crucial for healthcare providers to develop and implement tailored antibiotic stewardship strategies. This systematic review offers valuable insights into the prevalence of drug-resistant organisms in postoperative wounds, enabling surgeons to make informed treatment decisions, reinforcing targeted infection control measures, and stimulating research into novel antimicrobial agents and alternative therapeutic approaches. Ultimately, these efforts contribute to improved patient outcomes and the preservation of effective antimicrobial therapies. This systematic review provides a comprehensive overview of the prevalence of antibiotic-resistant strains associated with Surgical Site Infections (SSIs). By systematically reviewing a range of studies, this has contributed to the growing body of knowledge on this critical issue. The inclusion of both Gram-positive and Gram-negative bacteria expands the scope of this study and enhances its clinical relevance. The discussion effectively highlights the implications of the study's findings for clinical practice and future research, emphasizing the need for targeted infection prevention and control strategies. The present study is subject to certain limitations. The heterogeneity of study designs, patient populations, and geographical

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settings may have influenced the overall findings. Additionally, the published literature might have excluded studies with negative or inconclusive results. Furthermore, the absence of data on greater patient comorbidities limits the ability to draw definitive conclusions about the impact of these factors on SSI rates and antibiotic resistance. While the study provides valuable insights into the prevalence of antibiotic-resistant pathogens, further research was needed to develop a deeper understanding of the underlying mechanisms of resistance and to develop novel strategies for optimal surgical care.

CONCLUSIONS

The emergence of antibiotic-resistant pathogens has significantly complicated the management of Surgical Site Infections (SSIs), necessitating a comprehensive understanding of their prevalence and antibiotic resistance patterns. This systematic review underscores the increasing burden of antibiotic-resistant organisms associated with SSIs, particularly Gram-negative bacteria. The predominance of *Staphylococcus aureus, coagulase-negative staphylococci, Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli*, and *Acinetobacter spp.* highlights the urgent need for targeted infection prevention and control measures. To effectively combat this challenge, multidisciplinary collaboration, antimicrobial stewardship, and robust surveillance systems were imperative. By implementing evidence-based strategies, surgeons can mitigate the impact of antibiotic resistance and improve post-operative patient outcomes. Further research was needed to explore the underlying mechanisms of resistance and to develop innovative interventions for the surgical management of SSI caused by multidrug-resistant pathogens.

Authors Contribution

Conceptualization: SM

Methodology: ZA, HA, AS

Formal analysis: KR

Writing, review and editing: AS, SA

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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