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# Global Cancer Burden and Its Projected Growth by 2050: Trends, Disparities, and Future Implications

OPEN ACCESS

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Cancer is a leading cause of disease and death globally, with millions of new diagnoses occurring annually [1]. In 2022, about 2 million new cancer cases and approximately 9.7 million cancer-related fatalities were documented worldwide, with respiratory malignancies being the most prevalent, followed by breast, colorectal, prostate, and gastric cancers [2]. In economically disadvantaged regions, infections from pathogens including Helicobacter pylori, human papillomavirus (HPV), and hepatitis B significantly contribute to the increasing cancer rates, underscoring the urgent necessity for extensive prevention and immunization initiatives [3]. These global disparities in cancer incidence and survival are further exacerbated by socioeconomic factors, with access to early diagnosis, treatments, and healthcare systems being unequally distributed across regions [4]. Significant inequalities in cancer incidence and mortality exist globally, predominantly affected by the Human Development Index. In countries with very high levels of development, the age-standardized cancer incidence rate in 2022 was 285.7 cases per 100,000 persons, while in countries with lower development indices, it was only 110.6 cases per 100,000 [5, 6]. This disparity is also reflected in survival rates, as the mortality-to-incidence ratio (which compares the number of cancer deaths to the number of cancer cases) is almost twice as high in countries with lower levels of development compared to those with higher levels. For example, in 2022, the global mortality-to-incidence ratio was 46.6%, while in Sub-Saharan Africa, it exceeded 67%. Furthermore, men generally have higher rates of cancer incidence and death than women, and low- and middle-income nations, notably in Africa and Asia, confront challenges in managing increasing cancer cases, owing to insufficient resources for prevention, diagnosis, and treatment [7]. The worldwide cancer burden is projected to rise significantly by 2050. The number of new cancer cases is projected to increase by 76.6%, reaching 35.3 million, while deaths related to cancer are expected to rise by 89.7%, to 18.5 million. However, this increase will not be uniform across regions. In countries with lower development, cancer cases are expected to rise by 142.1%, compared to a 41.7% increase in highly developed countries. Similarly, cancer deaths in less developed countries are expected to rise by 146.1%, whereas in more developed countries, the increase will be just 56.8%. This widening disparity highlights the urgent need for enhanced healthcare infrastructure, including prevention, early diagnosis, and treatment programs in low-resource settings. The number of new cancer cases is projected to rise by 76.6%, reaching 35.3 million, while deaths due to cancer are likely to increase by 89.7%, to 18.5 million [6, 8].

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**Original Article**

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# Early Detection of Cardiovascular Risk in Pediatric Populations: Are We Doing Enough Compared to Adult Protocols?

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## ABSTRACT

Cardiovascular diseases, once considered primarily adult health concerns, are increasingly being traced back to risk factors emerging during childhood. **Objectives:** To evaluate the early detection of cardiovascular risk factors in pediatric populations and compare current pediatric screening practices with established adult protocols in a low-resource setting. **Methods:** This was a cross-sectional analytical study conducted at the Department of Pediatric Cardiology, Quaid-e-Azam Medical College, Bahawalpur, from March 2024 to March 2025. A total of 341 children aged 5–12 years were enrolled using non-probability consecutive sampling. Data were collected through structured interviews, anthropometric measurements, blood pressure readings, and fasting laboratory investigations, including lipid profile, fasting blood glucose, HbA1c, and serum. Participants were stratified by BMI, lifestyle, and family history. **Results:** Obesity was observed in 8.2% of participants, and 27.3% had a waist-to-height ratio ≥0.5. Hypertension was identified in 27.0% of children and dyslipidemia in 38.7%. Low HDL (<45 mg/dL) was seen in 46.6%, and triglycerides ≥130 mg/dL in 38.7%. Vitamin D deficiency (<20 ng/mL) was found in 66.6%, with a significant inverse correlation with triglyceride levels ($r=-0.41$, $p<0.001$). Obesity (OR 3.67, 95% CI: 2.10–6.41, $p< 0.001$), sedentary lifestyle (OR 2.34, 95% CI: 1.33–4.12, $p=0.004$), and family history of CVD (OR 2.26, 95% CI: 1.30–3.95, $p=0.003$) were significant predictors. **Conclusions:** The high prevalence of early cardiovascular risk factors in Pakistani children highlights the urgent need for structured pediatric screening protocols.

## INTRODUCTION

Cardiovascular disease (CVD) continues to dominate global mortality charts, claiming nearly 17.9 million lives each year, according to the World Health Organization [1]. Alarmingly, evidence now indicates that atherosclerotic changes, the pathological hallmark of many CVDs, begin as early as childhood and adolescence [2]. While adult screening and prevention strategies are well-established and routinely practiced, the same cannot be said for pediatric populations, especially in low- and middle-income countries like Pakistan [3]. In a country where pediatric health services are already overburdened and under-resourced, early identification of cardiovascular risk factors in children remains a neglected priority, despite mounting evidence that early intervention can significantly reduce long-term morbidity and healthcare costs [4]. Cardiovascular risk in children is often silent but progressively damaging. Subclinical atherosclerosis, insulin resistance, obesity, dyslipidemia, and elevated blood pressure are now being identified in children as young as five years old, especially in urban and semi-urban communities adopting sedentary lifestyles and energy-dense diets [5]. This trend has been exacerbated by a rising

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prevalence of childhood obesity in Pakistan, which, according to a 2021 UNICEF report, affects over 9% of children under 12. These children often present with multiple risk factors, including central obesity, impaired glucose metabolism, and elevated serum lipid factors that are seldom screened for until the manifestation of overt disease in adulthood. The pathophysiology is complex and involves early endothelial dysfunction, lipid accumulation, and systemic inflammation all of which are detectable using simple, non-invasive tools if protocols are tailored and implemented effectively [6]. While it is well known that past studies in high-income nations reveal that elevated risk factors in children influence the development of CVD as adults, this data is mainly from different healthcare systems and groups of people. Instead, studies done in Pakistan are not common and often just involve hospitals or only analyze obesity by itself. However, the findings have not led to any new policies in screening for pediatric diseases or preventing heart problems in children. These works suggest that more organized guidelines are needed to tackle long-term heart problems in people at an early age [7, 8]. The lack of national screening guidelines for cardiovascular risk in children, especially in primary care and school-based health programs, has created a critical gap [9]. Unlike adult populations, where standardized assessments like the Framingham Risk Score are routinely used, no equivalent risk stratification exists for Pakistani children [10].

Although cardiovascular diseases originate from risk factors that begin in childhood, pediatric screening practices in Pakistan remain inconsistent and largely symptom-driven. Unlike adult populations, where structured risk assessment tools and preventive protocols are well established, there is no standardized framework for early cardiovascular risk stratification in children. Existing local studies are limited in scope and often focus on isolated factors such as obesity rather than comprehensive cardiometabolic profiling. This gap highlights the need for systematic evaluation of early cardiovascular risk detection in pediatric populations within low-resource settings. This study seeks to find out if testing for cardiovascular risks in young children in Pakistan is supported by the right structures and acknowledged as much as the methods and support for adults. Collecting information on children from various social groups and evaluating factors that can be altered or not, this study intends to fill the absence of reventive health methods. This study aimed to check the early detection of cardiovascular risk factors in pediatric populations and compare current pediatric screening practices with established adult protocols in a low-resource setting.

## METHODS

This cross-sectional analytical study was conducted from March 2024 to March 2025 at the Department of Pediatric Cardiology, Quaid-e-Azam Medical College, Bahawalpur. Ethical approval (Letter No: 2463/DME/QAMC Bahawalpur) was obtained from the Institutional Review Board of Quaid-e-Azam Medical College, Bahawalpur. Informed consent was secured from parents or guardians, and assent was obtained from children aged 7 years and above. Confidentiality of participant information was maintained throughout the study, adhering to the principles outlined in the Declaration of Helsinki. The purpose of the study was to check how many children between 5 and 12 years have cardiovascular risk factors and compare current pediatric screenings with guidelines used for adults. Children aged 5–12 years were included in the study when they attended the clinic for regular check-ups or simple treatment. Clinical and laboratory measurements were conducted using standardized protocols. Systolic blood pressure (SBP) was measured using a calibrated digital sphygmomanometer with an appropriate cuff size after the child had rested for five minutes in a seated position. Three readings were taken at one-minute intervals, and the average of the last two was recorded. Anthropometric data, including height, weight, and waist circumference, were recorded to calculate BMI, which was categorized using CDC age- and sex-specific percentiles. Fasting blood samples were collected after 8–12 hours of overnight fasting and analyzed in the hospital's central lab. The fasting blood samples were analyzed for lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides), fasting blood glucose, glycated hemoglobin (HbA1c), and serum 25-hydroxyvitamin D [25(OH)D] levels. The lipid profile, including total cholesterol, LDL-C, HDL-C, and triglycerides, was measured using enzymatic colorimetric assays on the Roche Cobas c311 analyzer (Roche Diagnostics, Germany), employing Roche Diagnostics commercial kits with internal and external quality controls maintained according to manufacturer protocols. Fasting blood glucose levels were determined using the glucose oxidase-peroxidase (GOD-POD) method on the same analyzer platform. Glycated hemoglobin (HbA1c) was measured via high-performance liquid chromatography (HPLC) using the Bio-Rad D-10 Hemoglobin Testing System, with results interpreted based on American Diabetes Association (ADA) pediatric guidelines. Serum 25-hydroxyvitamin D [25(OH)D] concentrations were quantified using a chemiluminescent immunoassay (CLIA) performed on the DiaSorin LIAISON® XL analyzer. Levels below 20 ng/mL were considered deficient. The vitamin D assay had a coefficient of variation below 10%, and calibrations were carried out using manufacturer-supplied

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standards. Data on physical activity, dietary habits, screen time, and family history of cardiovascular disease were collected through structured parental interviews using a validated questionnaire administered at enrollment. A non-probability consecutive sampling technique was employed. The sample size was calculated using the PS Power and Sample Size Calculator, considering a prevalence of dyslipidemia of 33.3% among Pakistani children as reported by Khan et al. [15]. With a confidence level of 95% and a margin of error of 5%, the required sample size was determined to be 341 participants. Data collection involved structured interviews with parents or guardians to gather demographic information, family history of cardiovascular disease, dietary habits, physical activity levels, and exposure to passive smoking. Anthropometric measurements, including height, weight, and waist circumference, were taken using standardized equipment. Body mass index (BMI) percentiles were calculated based on WHO growth charts. Cut-off values for abnormal lipid profiles were defined as follows: total cholesterol ≥170 mg/dL, LDL-C ≥110 mg/dL, HDL-C <45 mg/dL, and triglycerides ≥130 mg/dL. Fasting blood glucose levels ≥100 mg/dL were considered impaired. Blood pressure readings above the 90th percentile for age, sex, and height were classified as elevated. Statistical analysis was performed using SPSS version 26.0. The study's findings were compared with international data to contextualize the prevalence and patterns of cardiovascular risk factors among Pakistani children. This comparison aimed to identify gaps in current pediatric screening practices and to inform the development of targeted interventions for early detection and prevention of cardiovascular diseases in this population. Normality of continuous variables was assessed using the Shapiro-Wilk test. Variables such as BMI, SBP, DBP, total cholesterol, LDL, and triglycerides were found to be normally distributed ($p > 0.050$), while age, HDL, fasting blood sugar, HbA1c, and vitamin D were non-normally distributed. Normally distributed variables were expressed as mean ± SD, while non-normal variables were reported as median (IQR). Parametric tests (independent t-test, one-way ANOVA) were used for normally distributed data, while non-parametric tests (Mann-Whitney U test, Kruskal-Wallis) were used for non-normal distributions.

## RESULTS

A total of 341 children aged 5–12 years were included in the study, with a mean age of 8.4 ± 2.1 years. Of these, 53.1% were male and 46.9% were female. Based on BMI percentiles, 78.6% were of normal weight, 13.5% were overweight, and 8.2% were obese. Approximately 27.3% had a waist-to-height ratio ≥0.5. Regarding residence and activity levels, 14.4% lived in urban settings, and 41.9% reported a sedentary lifestyle. Vitamin D deficiency (<20 ng/mL) was highly prevalent (66.6%). These baseline characteristics provide essential context for interpreting the associations observed in later analyses. 14.4% of urban children were obese compared to only 5.1% in rural areas, with an unadjusted OR of 2.45 (95% CI: 1.34–4.47). The interpretation indicates that urban residence, obesity, and physical inactivity were significantly associated with increased cardiovascular risk. Adjusted odds ratios confirmed these associations even after accounting for confounders such as age and gender, Table 1

**Table 1:** Baseline Demographics of Pediatric Population Included in the Study (n=341)

| Variables | Mean ± SD / n (%) |
|---|---|
| Age (years) | 8.4 ± 2.1 |
| **Gender** | |
| Male | 181 (53.1%) |
| Female | 160 (46.9%) |
| **BMI Category** | |
| Normal weight | 268 (78.6%) |
| Overweight | 46 (13.5%) |
| Obese | 28 (8.2%) |
| Waist-to-Height Ratio ≥ 0.5 | 93 (27.3%) |
| Hypertension (Based on Age Percentiles) | 92 (27.0%) |
| Dyslipidemia | 132 (38.7%) |
| Low HDL (<45 mg/dL) | 159 (46.6%) |
| High Triglycerides (≥130 mg/dL) | 132 (38.7%) |
| Vitamin D Deficiency (<20 ng/mL) | 227 (66.6%) |
| Family History of CVD | 134 (39.3%) |
| **Lifestyle** | |
| Active | 198 (58.1%) |
| Sedentary | 143 (41.9%) |
| Urban Residence | 49 (14.4%) |

Obese children had a significantly higher mean SBP (126.4 ± 9.7 mmHg) than children with normal BMI (109.3 ± 8.3 mmHg; <0.001), Table 2.

**Table 2:** Association Between Categorical Risk Factors and Cardiovascular Outcomes in Pediatric Population (n=341)

| Variables | Category (Reference) | Prevalence (%) | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | p-Value |
|---|---|---|---|---|---|
| Obesity (Urban vs Rural) | Urban (Ref) | 14.4 vs 5.1 | 2.45 (1.34–4.47) | 2.12 (1.12–4.00) | 0.003 |
| Hypertension (Obese vs non-obese) | Non-obese (Ref) | 27.4 vs 8.3 | 3.91 (2.05–7.43) | 3.46 (1.89–6.32) | 0.001 |
| Dyslipidemia (Inactive vs Active) | Active (Ref) | 35.8 vs 16.4 | 2.17 (1.34–3.51) | 1.92 (1.12–3.27) | 0.002 |
| Low HDL (Male vs Female) | Female (Ref) | 48.8 vs 34.3 | 1.83 (1.07–3.12) | 1.65 (0.96–2.82) | 0.031 |

OR = Odds Ratio; CI = Confidence Interval

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Daily sugary beverage intake was present in 37.5% of children, among whom 42.7% exhibited dyslipidemia (p = 0.021). The interpretation highlights that sedentary behavior, screen time, and unhealthy diet are significant contributors to hypertension and dyslipidemia in this cohort, Table 3.

**Table 3:** Comparison of Continuous Variables Across High-Risk and Low-Risk Groups (n=341)

| Variables | High-Risk Group (n) | Mean ± SD | Low-Risk Group (n) | Mean ± SD | p-Value |
|---|---|---|---|---|---|
| SBP (mmHg) | Obese (n=28) | 126.4 ± 9.7 | Normal BMI (n=268) | 109.3 ± 8.3 | 0.001 |
| LDL (mg/dL) | Family History of CVD (n=134) | 122.3 ± 17.6 | No Family History (n=207) | 106.4 ± 15.3 | 0.004 |
| Triglycerides (mg/dL) | Vitamin D Deficient (n=227) | 139.8 ± 32.1 | Normal Vitamin D (n=114) | 120.6 ± 27.4 | 0.027 |
| BMI (kg/m$^2$) | Sedentary Lifestyle (n=143) | 24.8 ± 3.9 | Active Lifestyle (n=198) | 20.1 ± 2.8 | 0.009 |

SBP = Systolic Blood Pressure; LDL = Low-Density Lipoprotein; BMI = Body Mass Index

The prevalence of lifestyle behaviors correlates with rates of hypertension and dyslipidemia in the study cohort, Table 4.

**Table 4:** Prevalence of Lifestyle Behaviors and Associated Cardiovascular Risks (n=341)

| Factors | Prevalence (n, %) | Hypertension (n, %) | Dyslipidemia (n, %) | p-Value |
|---|---|---|---|---|
| Sugary Beverages (Daily) | 128 (37.5%) | 27 (21.4%) | 55 (42.7%) | 0.021 |
| Fast Food (>3x/week) | 92 (27.0%) | 17 (18.3%) | 35 (38.1%) | 0.035 |
| Screen Time > 4 hrs/day | 110 (32.3%) | 22 (20.2%) | 45 (41.2%) | 0.017 |
| No Physical Activity | 43 (12.6%) | 11 (25.6%) | 21 (49.1%) | 0.008 |

Behaviors assessed through structured questionnaires; p-values from Chi-square or Fisher's Exact Test

BMI ≥95th percentile was the strongest independent predictor (Adjusted OR: 3.67, 95% CI: 2.10–6.41; p<0.001). The interpretation reveals that even after adjusting for other variables, obesity, sedentary lifestyle, family CVD history, and vitamin D deficiency remained statistically significant, emphasizing the need for early screening and intervention in these subgroups, Table 5.

**Table 5:** Multivariate Logistic Regression Analysis for Independent Predictors of Cardiovascular Risk (n=341)

| Risk Factors | Adjusted OR (95% CI) | p-Value | Mean ± SD |
|---|---|---|---|
| BMI ≥95th percentile | 3.67 (2.10–6.41) | <0.001 | – |
| Sedentary lifestyle | 2.34 (1.33–4.12) | 0.004 | – |
| Family history of CVD | 2.26 (1.30–3.95) | 0.003 | – |
| Vitamin D <20 ng/mL | 1.89 (1.09–3.27) | 0.021 | 18.7 ± 6.2 ng/mL |

Adjusted for age, gender, urban/rural residence, and school type

## DISCUSSION

The results of this study underscore a critical gap in early cardiovascular risk screening among Pakistani children. More than one-third of participants displayed at least one modifiable cardiovascular risk factor, with a significant portion exhibiting multiple abnormalities. This prevalence aligns closely with international reports, such as a 2021 multicenter study from Turkey and a 2019 NHANES-based analysis from the U.S., both of which identified pediatric dyslipidemia rates between 20–30%. However, the figures from the present study reveal slightly higher rates in urban Pakistani settings, possibly reflecting increased urbanization, dietary transition, and reduced physical activity. This study revealed a high burden of modifiable cardiovascular risk factors in the pediatric population, particularly among urban children, those with elevated body mass index, vitamin D deficiency, sedentary lifestyles, and positive family history of cardiovascular disease. Elevated blood pressure, dyslipidemia, low HDL, and increased triglyceride levels were all found to be significantly associated with these predictors. Notably, obesity and sedentary behavior emerged as the strongest independent predictors of cardiovascular risk, with adjusted odds ratios of 3.67 and 2.34, respectively. A strong inverse correlation was observed between vitamin D levels and triglyceride concentrations. Additionally, children with acanthosis nigricans showed markedly higher fasting glucose and HbA1c values, suggesting early metabolic derangements. These findings were consistent with the results of logistic regression and stratified analyses across age and gender groups. The findings of the present study align closely with international data. In a study conducted in Italy, nearly 28% of children were found to have at least one major cardiovascular risk factor, with obesity being the most dominant predictor—an observation echoed in this study's high-risk cohort [10]. Similarly, the U.S.-based National Health and Nutrition Examination Survey (NHANES) 2018–2021 cycles identified dyslipidemia in 20–25% of adolescents, particularly those with elevated BMI and low physical activity levels, consistent with the 38.7% dyslipidemia rate observed here. A recent Turkish study also demonstrated a strong association between vitamin D deficiency and lipid profile abnormalities in children, supporting the inverse correlation seen between vitamin D and triglycerides in this study [11, 12]. In contrast, a study from Japan reported a relatively lower prevalence of elevated triglycerides and blood pressure in children, likely due to different dietary patterns and routine implementation of school-based screening programs—systems not widely established in Pakistan [13]. An Iranian school-based cohort study reported obesity rates of 10.8% and a metabolic syndrome prevalence of

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7.2% among children, rates somewhat lower than those observed in the current study, potentially due to demographic and cultural differences [14]. Meanwhile, a 2023 study in India showed similarly high prevalence of prehypertension and low HDL among urban children, affirming the influence of urbanization and lifestyle transition in South Asian populations [15]. The biological mechanisms behind these associations are multifaceted. Obesity in children is linked to insulin resistance, endothelial dysfunction, and systemic inflammation—all of which contribute to early vascular changes and lipid abnormalities [16]. Sedentary behavior decreases insulin sensitivity and promotes central adiposity, thereby exacerbating cardiometabolic risk. Vitamin D, beyond its skeletal role, has been shown to influence lipid metabolism and vascular tone through modulation of inflammatory pathways and parathyroid hormone regulation. Acanthosis nigricans, a visible skin marker of insulin resistance, further confirmed the presence of subclinical metabolic alterations [17]. Findings from this study may inform national policy by emphasizing the inclusion of non-communicable disease risk assessments in school health programs and pediatric outpatient care [18, 19]. Future research should include longitudinal designs to track risk progression and assess the impact of community-based interventions. Additionally, multicenter studies involving diverse socioeconomic and ethnic groups across Pakistan are needed to validate and expand upon these findings [20].

This study has several limitations, including its single-center design and non-probability sampling technique, which may limit generalizability to the broader pediatric population. The cross-sectional nature of the study precludes causal inference or assessment of long-term cardiovascular outcomes. Additionally, reliance on self-reported lifestyle behaviors may introduce reporting bias. Future multicenter longitudinal studies incorporating larger, more diverse populations and standardized pediatric risk scoring systems are recommended to better inform national screening guidelines and preventive strategies.

## CONCLUSIONS

This study highlights a high prevalence of modifiable cardiovascular risk factors among Pakistani children, including obesity, dyslipidemia, hypertension, and vitamin D deficiency. These findings underscore the urgent need for structured pediatric screening protocols comparable to those used in adult populations, particularly in low-resource settings.

## Authors' Contribution

Conceptualization: UM
Methodology: MN, FUR, AUH
Formal analysis: US, MAZ
Writing and Drafting: IA
Review and Editing: IA, US, MAZ, MN, FUR, AUH, UM

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Estimation of Stature from Index Finger and Ring Finger Length of Male Adults of Central Punjab

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## ABSTRACT

Forensic anthropology often relies on skeletal measurements for identifying unknown deceased individuals, with stature estimation being pivotal in cases involving dismembered remains. **Objectives:** To examine the correlation between stature and the lengths of the index and ring fingers in Central Punjabi adult male and to develop population-specific regression equations for height estimation. **Methods:** A descriptive cross-sectional study was conducted on 246 male adults aged 21-40 from Central Punjab at PGMI/Ameer-ud-Din Medical College Lahore. Height and finger lengths were measured using standardized methods, with a Vernier caliper for finger lengths. Data were analyzed using SPSS version 25.0. Pearson's correlation and regression analyses determined relationships and predictive models. **Results:** Statistically significant moderate positive correlations were observed between stature and both index and ring finger lengths. The right index finger length showed the highest correlation ($r=0.512$, $p<0.001$). Regression equations were derived, with Right Index Finger Length providing the best height prediction ($R^2 = 0.259$). **Conclusions:** Index and ring finger lengths can reliably estimate stature in Central Punjabi male, with right-hand measurements proving more predictive. Population-specific regression models enhance accuracy and provide important forensic tools for victim identification from mutilated remains. These findings bolster forensic research by enabling better biological profiling in this demographic.

## INTRODUCTION

Anthropometry is the measuring of people. Measurements of persons, both alive and deceased, can be studied using anthropometric methods and equipment. In terms of anthropometric measurements, humans differ greatly from one another. The oldest instance of anthropometrics is seen in the Stone Age. The Warring States period of ancient China (770–221 B.C.) is when physiological anatomy, a forerunner of anthropometry, first emerged [1]. Alphonse Bertillon, who was unsatisfied with the existing methods of identification in the nineteenth century, developed a scientific system of detection for the French police that utilized anthropometry in order to identify suspects with greater accuracy. He also developed a method to effectively store and retrieve such data. Identifying the individual is one of the primary goals of a medico-legal examination. This identification is established on the "big four" anthropological characteristics of age, sex, stature, and race [2]. The height of a person rises during adolescence but falls with old age. A human being's entire height is directly correlated with the dimension of a specific bone [3]. When the entire body has been discovered at the crime scene, it is very simple to identify

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the person by their stature [4]. However, in certain circumstances, such as killing, mass disasters, aeroplane crashes, terrorist assaults, unresolved natural deaths, conflict, corruption, and numerous others, when chopped-up figure portions or removed limbs of the figure are present at these kinds of events, it is very challenging to identify the person. The index and ring fingers are very important for determining stature due to their size. There is a considerable chance of finding little bones under the circumstances previously mentioned, which could be helpful to forensic experts as they carry out the investigation [5]. Numerous elements, including racial, ethnic, and dietary aspects, are crucial to the development and growth of humans; hence, distinct nomenclatures are required for various populations [6]. Stature (or bodily height) is typically calculated in forensic investigations utilizing 'anatomical' and mathematical methods. Researchers have discovered a connection between stature and other body component evaluations, which is frequently expressed by a linear regression equation generated from them [7, 8]. There are two ways to gauge someone's stature: a mathematical method and an anatomical method. Stature assessment using independent variables is a mathematical technique that can be applied to a given group or community, as opposed to anatomical methods that measure lower leg length, vertebral column length, and skull height. Numerous Long bones, comprising their component elements, the hip bone, scapula, skull, and small hand and foot bones, were used in studies to estimate stature [9, 10]. A forensic specialist's crucial job is to confirm identification. Only a very small amount of Pakistani DNA data is collected due to the country's poor economic conditions. Because of this, forensic experts rely on a person's biological description, which aids in determining their identity. One of the most crucial biological characteristics used to establish identity is stature [11]. Using the index and little fingers is one statistically significant way to estimate height. The length of a person's fingers is a reliable indicator of their stature. The average person may be reliably and accurately estimated using hand observations. The most accurate parameter to determine stature from basic linear regression models in both sexes is right-hand length [12]. In the right hand, the index finger is substantially more positively correlated with height than the other fingers [13]. There is a statistically significant association between the index finger and height, according to a study conducted in Pakistan [14, 15].

Accurate stature estimation is a fundamental component of forensic identification, particularly in cases involving fragmented or mutilated remains. Although various studies have explored the relationship between long bones and stature, limited research has focused on smaller skeletal elements such as finger lengths within specific Pakistani populations. Furthermore, anthropometric relationships vary across ethnic and regional groups, making the use of non-local regression models potentially inaccurate. There is a lack of population-specific data for Central Punjabi adult males, highlighting the need to develop localized regression equations for reliable stature estimation. This study aimed to examine the correlation between stature and the lengths of the index and ring fingers in Central Punjabi adult males and to develop population-specific regression equations for height estimation.

## METHODS

A descriptive cross-sectional study was conducted in the Department of Forensic Medicine and Toxicology in PGMI/Ameer-ud-Din Medical College, Lahore. The study population was Male adults of Central Punjab. The sample size was 246 individuals. The sample size was calculated by the following formula, keeping the confidence level equal to 95% and the margin of error equal to 5%. $n = (Z\sigma^2 p(1-p))/ W^2$. $Z\sigma^2 = 1.960$ Standard Normal Deviate for $\alpha$, $\alpha = 0.025(1\text{-}CL)/2)$ [16], P=0.5 (Expected Proportion), W = 0.1 (Total width of confidence interval) and CL = 95% (Confidence Level). Purposive sampling, one of the non-probability samplings, was the method used for sampling. Written informed consent was taken. Study variables were Stature (Dependent), Index Finger length (Independent), and Ring Finger Length (Independent). The study lasted for three month from April, 2025 to June, 2025. IRB was issued through letter no 2245. Inclusion criteria included apparently Normal Healthy Hands and asymptomatic male adults, between the ages of 18-40 years, residents of Central Punjab. Exclusion criteria were skeletal, spinal, and long bone abnormalities (acquired or congenital), dwarfism, gigantism, people who had a noticeable hand deformity or who had had surgery to repair damage to their index and ring fingers. Purposive sampling was selected over random sampling to ensure that the study targeted a specific population subgroup, male adults residing in Central Punjab, with relevant characteristics such as age (18-40 years) and ethnicity. This approach allowed for focusing on participants most likely to provide useful data pertinent to the study objectives. Purposive sampling was chosen because: Specific characteristics were needed (e.g., age group, ethnicity and region). The goal of the study was a particular subgroup relevant to the research. Resources or access were limited, and the study had to focus on participants who were most likely to provide useful data. In the context of stature estimation, the sample may have been limited to individuals of a particular population or ethnicity to develop population-specific

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regression models. Random sampling might have included too much variability, making it harder to build accurate models for that specific group. This study consists of 246 male Punjabi adults from Central Punjab. A thorough explanation of the study's objective was to include the subjects before obtaining their written permission. Only male adults travelling to Lahore General Hospital in Lahore were chosen for sampling using a non-probability purposive manner. The computerized national identity card issued by NADRA was used to verify the age. A single individual gathered the data to prevent measurement errors. The measurements were taken according to the following standards: The straight distance between the ring finger's tip and the border crease with the palm was measured. A Vernier caliper was used to measure it. Index Finger Length. It was measured as the straight distance from the tip of the index finger to the border crease with the palm. A Vernier caliper was used to measure it. In order to eliminate errors that could arise from individual variances, all measurements were taken by the same person. Standing straight-backed on the Frankfurt Plain was used to gauge an individual's height. The vertical distance between the vertex and the floor was employed for measuring it. Finger lengths were measured from the same anatomical landmarks on both hands, specifically from the tip of the finger to the border crease where the finger meets the palm. A Vernier caliper was used for measurement to ensure accuracy and consistency across all subjects. Analysis based on statistics. All statistical data were analyzed using version 25.0 of the Statistical Package of Social Sciences (SPSS). For height, index finger length, and ring finger length, we calculated descriptive statistics. The measurements listed above were totaled and statistically examined. The data's mean, standard deviation (SD), minimum, and maximum were shown. Pearson's correlation coefficient (r) was used to analyze the association between stature and both the length of the index finger and the ring finger. At p=0.050, the significance threshold was determined.

## RESULTS

246 male Punjabi adults from central Punjab participated in this study. Participants in the study ranged in age from 21 to 40 years old, with a mean age of 26.3 ± 4.97. People in the study had their height, index, and ring finger lengths measured. With a range of 162.5 to 189.3, the average body height length was 172.9 ± 5.64 cm. The right index finger's length ranged from 6.4 to 8.4 cm, with an average of 7.42 ± 0.41 cm. The left index finger's length ranged from 6.6 to 8.6 cm, with an average of 7.45 ± 0.39 cm. The right ring finger's length ranged from 6.4 to 8.5 cm, with an average of 7.48 ± 0.41 cm. The left ring finger's length ranged from 6.4 to 8.4 cm, with an average of 7.44 ± 0.41 cm (Table 1).

**Table 1:** Descriptive Statistics of Study Participants

| Variables | Minimum | Maximum | Mean ± SD |
|---|---|---|---|
| Age (years) | 21 | 40 | 26.3 ± 4.97 |
| Stature (cm) | 162.5 | 189.3 | 172.9 ± 5.64 |
| Right Index Finger (cm) | 6.4 | 8.4 | 7.42 ± 0.41 |
| Left Index Finger (cm) | 6.6 | 8.6 | 7.45 ± 0.39 |
| Right Ring Finger (cm) | 6.4 | 8.5 | 7.48 ± 0.41 |
| Left Ring Finger (cm) | 6.4 | 8.4 | 7.44 ± 0.41 |

The dependent variable (stature) and the independent variables (index and ring finger length) are correlated in the table below. Right index finger length (r=0.512) and left index finger length (r=0.491) show a moderately positive connection with stature. These correlations were statistically significant, as indicated by the p-value. In a similar vein, stature and the length of the right and left ring fingers showed a moderately positive link (r=0.467 and 0.444, respectively). Additionally, these associations were statistically significant (Table 2).

**Table 2:** Index and Ring Finger Length Pearson Correlation Coefficient (r) with Stature

| Variables (cm) | Stature | |
|---|---|---|
| | Correlation Coefficient (r) | p-value |
| Right Index Finger | 0.512 | <0.001* |
| Left Index Finger | 0.491 | <0.001* |
| Right Ring Finger | 0.467 | <0.001* |
| Left Ring Finger | 0.444 | <0.001* |

The right index finger length is more correlated with body height than all other finger lengths under study.

Using a regression equation, stature is estimated from the length of the index and ring fingers. The regression equation for determining stature from index and ring finger length separately was obtained using a straightforward regression analysis (Table 3).

**Table 3:** Univariate Regression Equation for Estimation of Stature from Index Finger and Ring Finger Length (n=246)

| Variables | Constant | β | SE | p-value | 95% CI | | Mean ± SD |
|---|---|---|---|---|---|---|---|
| | | | | | Lower | Upper | |
| Right Index Finger (RIF) | 120.23 | 7.097 | 0.762 | <0.001* | 5.596 | 8.597 | 120.23 + 7.097 |
| Left Index Finger (LIF) | 120.31 | 7.056 | 0.801 | <0.001* | 5.478 | 8.635 | 120.31 + 7.056 |
| Right Ring Finger (RRF) | 124.59 | 6.459 | 0.783 | <0.001* | 4.916 | 8.001 | 124.59 + 6.459 |
| Left Ring Finge (LRF) | 127.38 | 6.122 | 0.791 | <0.001* | 4.565 | 7.679 | 127.38 + 6.122 |

The regression formula for body height determination from the Right Index Finger (RIF) was analyzed, and Stature = 120.23 + 7.097(RIF) (Figure 1).

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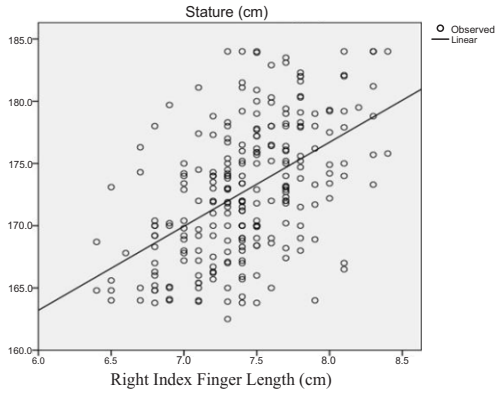


**Figure 1:** Regression Formula for Body Height Determination from Right Index Finger(RIF)

The regression formula for body height determination from the Light Index Finger (LIF) was analyzed, and Stature = 120.31 ± 7.056(LIF)(Figure 2).

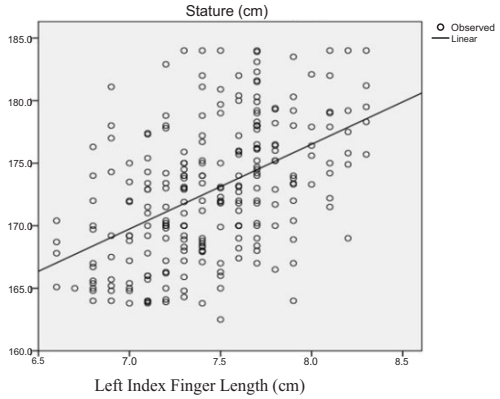


**Figure 2:** Regression Formula for Body Height Determination from Left Index Finger(LIF)

According to the Regression Formula, Stature = 124.59 + 6.459 for Right Ring Finger(RRF)(Figure 3).

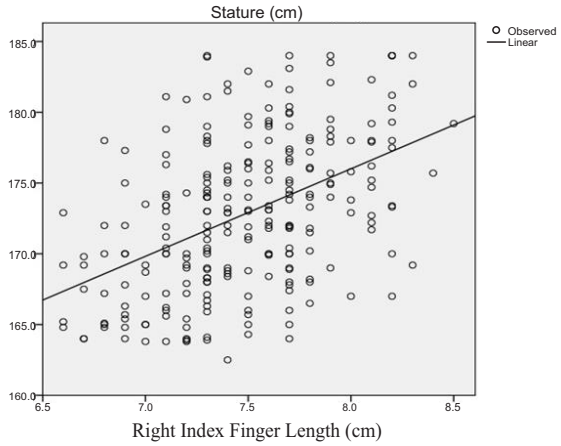


**Figure 3:** Regression Formula for Body Height Determination from Right Ring Finger(RRF)

According to the Regression Formula, Stature = 127.38 + 6.122 for Left Ring Finger(LRF)(Figure 4).

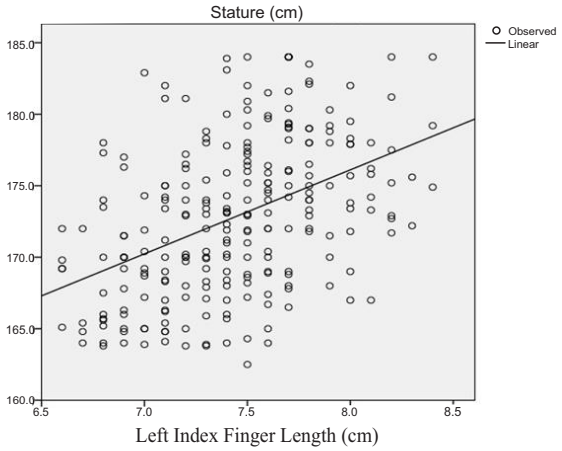


**Figure 4:** Regression Formula for Body Height Determination from Left Ring Finger(RRF)

Normality tests of data of stature, index and ring fingers length were analyzed(Table 4).

**Table 4:** Tests of Normality

| Variables | Kolmogorov-Smirnova | | | Shapiro-Wilk | | |
|---|---|---|---|---|---|---|
| | Statistic | df | Sig. | Statistic | df | Sig. |
| Stature (cm) | 0.068 | 246 | 0.200 | 0.975 | 246 | 0.129 |
| Right Index Finger Length (cm) | 0.078 | 246 | 0.104 | 0.988 | 246 | 0.098 |
| Left Index Finger Length (cm) | 0.079 | 246 | 0.074 | 0.983 | 246 | 0.059 |
| Right Ring Finger Length (cm) | 0.083 | 246 | 0.200 | 0.985 | 246 | 0.111 |
| Left Ring Finger Length (cm) | 0.062 | 246 | 0.200 | 0.985 | 246 | 0.129 |

a. Lilliefors Significance Correction

Mean, median, mode, skewness and standard error of skewness of stature, index and ring fingers length were calculated(Table 5). The correlation analysis demonstrated that the right index finger length is the strongest predictor of stature (r=0.512), with all correlations being statistically significant (p<0.001). The right index finger length had a higher coefficient of determination ($R^2$ = 0.259) compared to the left index finger ($R^2$ = 0.239). Right-hand measurements showed slightly better predictive capacity than left-hand measurements, supporting the use of right-hand finger lengths in regression models. The regression models were validated within the study population through multiple statistical approaches, including Pearson's correlation to confirm the strength and significance of associations, univariate regression to develop predictive equations, calculation of $R^2$ values to assess model fit, and normality tests to verify the assumptions of regression analysis. These steps collectively ensured the predictive accuracy and reliability of the regression equations for estimating stature from finger lengths in the Central Punjabi male population. The values of R2 were as follows: Right Index Finger Length = 0.259, Left Index Finger Length = 0.239, Right Ring Finger Length = 0.216 and Left Ring

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Finger Length = 0.197. The right index finger length is more predictive of height than all other lengths calculated. Fingers of the right hand are more predictive of body height.

**Table 5:** Statistics of All Variables

| Statistics | | Stature (cm) | Right Index Finger Length (cm) | Left Index Finger Length (cm) | Right Ring Finger Length (cm) | Left Ring Finger Length (cm) |
|---|---|---|---|---|---|---|
| N | Valid | 246 | 246 | 246 | 246 | 246 |
| | Missing | 0 | 0 | 0 | 0 | 0 |
| Mean | | 172.800 | 7.422 | 7.452 | 7.482 | 7.437 |
| Median | | 172.900 | 7.400 | 7.400 | 7.500 | 7.450 |
| Mode | | 170.0 | 7.4 | 7.7 | 7.3 | 7.5 |
| Skewness | | 0.191 | -0.022 | 0.058 | 0.049 | 0.074 |
| Std. Error of Skewness | | 0.155 | 0.155 | 0.155 | 0.155 | 0.155 |

## DISCUSSION

In the current study, stature in males aged 21 to 40 is determined by the link between stature and several other factors. Srinivasulu *et al.* investigated the relationship between a person's height and the length of their middle, ring, and index fingers in men [17]. An examination of the length of the index and ring fingers in the Kashmiri population revealed a higher association in boys than in girls, according to Gupta and Sehrawat [18]. Another study was conducted by Pournima *et al.* By measuring the length of ten fingers, they were able to estimate the stature of the intended population of South Indian students, and they concluded that there was a statistically significant association between the length of all fingers and height [19].The length of a man's ring and index fingers is positively and significantly correlated, and these findings are in line with those of earlier research [20]. Venkatesan *et al.* carried out a second investigation on both male and female. They discovered that whereas females' ring finger length had a higher Pearson correlation coefficient, men's left finger length had a higher value [21]. 200 students participated in a study conducted by Rai *et al.* According to the computed correlation coefficients, they discovered a moderately favourable relationship between stature and the length of the right and left index fingers. Based on the derived p-values, the statistical analysis showed that these relationships were considered statistically significant [22]. Similarly, a study conducted in Bihar found a very substantial positive association between stature and the length of the ring and index fingers [23]. In contrast, the study by Rhiu and Kim shows that the correlation between height and little finger length is +.485 for boys and +.293 for girls. Girls showed a low degree of connection, whereas boys showed a moderate amount [24]. Another study shows a correlation between finger lengths and height: + 0.58 to + 0.66 [25]. A study found a moderate correlation between stature and index finger length. The correlation between height and index finger length in men was 0.53 and 0.41, respectively [26].

This study has certain limitations, including the use of non-probability purposive sampling and recruitment from a single center, which may limit the generalizability of the findings to the broader population. The inclusion of only male participants restricts the applicability of the regression models to females. Additionally, environmental and nutritional factors influencing stature were not assessed. Future research should include larger, multicenter samples with both genders and diverse age groups to develop more comprehensive and widely applicable regression models for forensic use.

## CONCLUSIONS

The current study suggests that male stature can be determined by measuring the lengths of the index and ring fingers. In identification situations, estimating stature is crucial, as are anthropological findings in situations where body parts have been dissected. Population-specific regression equations derived from hand measurements, particularly of the right index finger, provide a valuable forensic tool for stature estimation and victim identification in Central Punjab. The use of purposive sampling targeting specific demographic characteristics allowed for the generation of relevant models. Consistency in anatomical landmarks and careful measurement methods ensured the validity of the data collected. The robust statistical validation further confirms the utility of these regression models in forensic anthropometry.

## Authors' Contribution

Conceptualization: KM
Methodology: MA
Formal analysis: AF
Writing and Drafting: GM, AK, AH
Review and Editing: GM, AK, AH, AF, KM, MA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Knowledge and Opinions of Dental Practitioners for the Use of Artificial Intelligence (AI) in Dentistry

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## ABSTRACT

Recent technological developments have paved the way for the application of Artificial Intelligence (AI) in dental care, offering improvements in diagnosis, treatment planning, and overall service delivery. **Objective:** To assess the level of awareness and perceptions of dental practitioners in Pakistan regarding the utilization of AI in clinical dentistry. **Methods:** A cross-sectional survey was executed between January and June 2024, encompassing 126 dental professionals. A structured questionnaire was shared via email and social media, gathering data on demographics, familiarity, and perspectives on AI in dentistry. Perceptions were measured using a 5-point Likert scale. Statistical analysis was performed using SPSS version 21.0, employing both descriptive and inferential methods. A p-value of <0.05 was considered statistically significant. **Results:** The average participant age was 41.14±13.76 years, with a predominance of female respondents (66.7%). A considerable portion (74.6%) reported familiarity with AI, while 77.8% were informed about its uses in dentistry. Although practical engagement was limited, 48% acknowledged AI's potential to enhance the field, while the same proportion expressed concerns over AI possibly replacing dental professionals. Enthusiasm toward AI was notable, with 55% showing interest. Many participants recognized AI's benefits in diagnostics and prognosis. **Conclusions:** Despite strong awareness and interest, the practical implementation of AI in dental practice remains low. Educational updates and supportive policies are essential to promote the integration of AI tools in clinical workflows.

## INTRODUCTION

The progression of modern technology has enabled machines to replicate functions associated with human intelligence, such as decision-making, logical reasoning, and recognizing patterns [1]. Artificial Intelligence (AI), among the most impactful innovations, is transforming sectors including healthcare, finance, transport, and education [2]. Using advanced machine learning, AI processes vast datasets to generate accurate predictions and support decision-making [3]. AI has made a deep enrichment in medical sector as well and it is predicted that it will grow by decuple in coming years [4]. Its application in healthcare has expanded significantly, with projections suggesting substantial growth in coming years [5]. AI aims to make medical diagnostics and treatments safer, more efficient, and patient-specific due to its rapidly evolving capabilities [6]. Areas like radiology, ophthalmology, and pathology, which depend on data-heavy analysis, are seeing robust AI integration [6]. There are both optimistic and skeptical views regarding AI's impact on human life. While concerns exist, that AI could replace human roles in various sectors, others believe that its assistance could offer vast opportunities for progress and development [6, 7]. In dentistry, AI is being increasingly used, particularly in diagnostic imaging, to enhance accuracy and improve

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treatment outcomes [8, 9]. AI technologies have been employed in the early detection of oral cancers, management of orofacial conditions, and orthodontic treatment planning using models such as Artificial Neural Networks(ANN), Convolutional Neural Networks(CNN), and support vector machines [2, 10]. Hyperspectral imaging combined with CNNs has successfully identified cancerous from non-cancerous tissues, while predictive models help forecast oral cancer recurrence [11]. In Pakistan, AI adoption in dental settings holds potential for improving care quality and efficiency [12, 13]. However, the success of this transition depends on the readiness, knowledge, and attitudes of dental professionals. A survey in Karachi revealed that although 70.3% of dentists were aware of AI tools, practical usage was limited, with few employing systems like Cone Beam Computed Tomography (CBCT) or Computer-Aided Design and Computer-Aided Manufacturing(CAD-CAM)[13].

Although artificial intelligence (AI) is increasingly being integrated into various healthcare disciplines, evidence regarding its awareness, acceptance, and practical readiness among dental practitioners in Pakistan remains limited. Most available local studies have focused on students rather than practicing professionals, and few have examined the relationship between AI-specific knowledge and perception. Additionally, there is a lack of structured data exploring perceived barriers and educational needs related to AI adoption in clinical dentistry. This gap necessitates a focused assessment of dental practitioners' knowledge and opinions to guide curriculum reforms and policy development. This study aimed to assess the understanding, acceptance, and perceived barriers regarding AI use among dental professionals in Pakistan and inform future educational and policy initiatives.

## METHODS

This was a descriptive, cross-sectional study carried out over a six-month duration, spanning from January to June 2024.In addition to descriptive analysis, the study incorporated analytical elements and examined the associations between participants' knowledge levels and their perception scores.The target population comprised dental professionals, including general dentists, medical officers, postgraduate residents, and consultant dental surgeons. Eligible participants were those aged 18 years and above, of either gender, with active internet connectivity.However, including only participants with internet access may have introduced a selection bias favoring individuals more familiar or comfortable with technology, which could influence their awareness or perceptions of AI. Individuals who did not provide consent were excluded from the study.A non-probability convenience sampling technique was employed to enroll participants.To determine the appropriate sample size, the OpenEpi sample size calculator was used. Based on a presumed awareness rate of 70.3% regarding AI use in dentistry, with a margin of error set at 8% and a 95% confidence interval, a total of 126 participants were required [13].The study followed ethical standards applicable to human subjects' research, and informed consent was obtained from each respondent prior to data collection. A structured questionnaire was developed and circulated through online platforms including Google Forms, and shared via emails and social networking applications such as WhatsApp, Facebook, and LinkedIn. The questionnaire consisted of three parts.The first section of the questionnaire gathered demographic details such as age, gender, qualification, designation, and years of practice.The second section assessed participants' knowledge and awareness of AI applications in dentistry, including tools like CAD-CAM, CBCT, digital intraoral radiographs, and clinical decision support systems. The third section featured 15 statements adapted from a previous study by Akhtar *et al.*, designed to evaluate participants' perceptions [14]. These items were rated on a 5-point Likert scale, ranging from 1(Strongly Disagree) to 5 (Strongly Agree). A composite perception score was then derived by calculating the average of the individual item responses.The questionnaire was pretested on a small group of dental professionals (n=15) to ensure clarity, relevance, and consistency of the items. Necessary adjustments were made based on their feedback.This helped enhance the validity and reliability of the instrument.Cronbach's alpha value was estimated as 78%.All responses were stored securely in password-protected digital files to maintain data confidentiality. Statistical analysis was performed using SPSS software version 21.0. For categorical variables, frequencies and percentages were calculated, while continuous variables were analyzed using means and standard deviations. To evaluate the relationship between AI-related knowledge and perception scores, independent samples t-tests were conducted. Prior to performing the independent samples t-test, assumptions of normality and equality of variances were assessed. Normality was evaluated using the Shapiro-Wilk test, and Levene's test was used to check for homogeneity of variances. The assumptions were met, justifying the use of the t-test for group comparisons. A p-value of less than 0.050 was considered statistically significant.

## RESULTS

Out of 126 respondents, the average age was 41.14 ± 13.76 years, with 33.3% male and 66.7% female participants. The largest group had 1-5 years of professional experience (29.4%) and were primarily general dental practitioners (32.5%), (Table 1).

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**Table 1:** Baseline Characteristics of Study Participants(n=126)

| Variables | Mean ± SD / Frequency (%) |
|---|---|
| Age in Years | 41.14 ± 13.76 |
| **Gender** | |
| Male | 42 (33.3) |
| Female | 84 (66.7) |
| **Years of Experience** | |
| < 1 Year | 30 (23.8) |
| 1-5 Years | 37 (29.4) |
| 6-10 Years | 16 (12.7) |
| 11-15 years | 20 |
| > 15 years | 23 |
| **Current Designation** | |
| General Dental Practitioner | 41 (32.5) |
| Medical officer | 30 (23.8) |
| Resident | 25 (19.8) |
| Specialist Consultant Dental Surgeon | 30 (23.8) |

Approximately 74.6% reported basic knowledge of AI, and 77.8% knew of AI applications in dentistry. The most recognized AI tool was digital dental records, while decision support systems were less familiar.

Figure 1 shows some awareness of various AI tools among dental professionals; a significant portion remains uninformed about key technologies (22%). The highest awareness was for digital dental records (17%), whereas clinical decision support systems had the lowest awareness(14%).

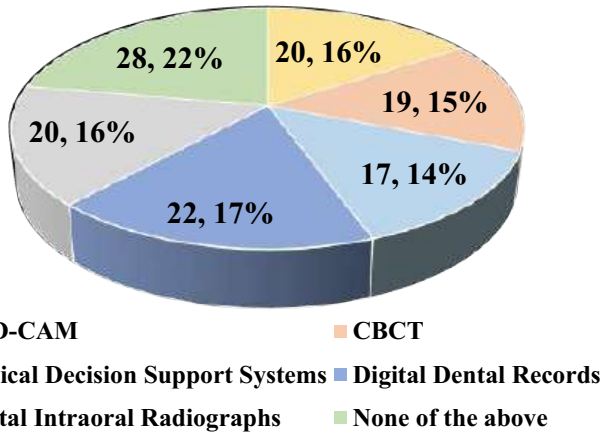


**Figure 1:** Awareness of Dental Professionals Regarding AI Tools in Dentistry

Table 2 shows the attitudes and perceptions of dental professionals towards AI in various aspects of dentistry. A significant proportion of dental professionals express positive attitudes towards the integration of AI in dentistry. A majority (strongly agree: 27% and agree: 21%) believe AI can lead to significant advancements. A considerable proportion (strongly agree: 26% and agree: 22%) think AI could replace dentists. A majority (strongly agree: 25% and agree: 30%) are excited about using AI in dentistry. Over half (strongly agree: 25% and agree: 28%) agree that AI can serve as a diagnostic tool. Half (strongly agree: 29% and agree: 21%) believe AI can be a prognostic tool. Nearly half (strongly agree: 18% and agree: 27%) see AI as useful for diagnosing tooth caries. A significant portion (strongly agree: 29% and agree: 26%) agree AI can diagnose periodontal diseases. A majority (strongly agree: 27% and agree: 30%) believe AI can diagnose soft tissue lesions. More than half (strongly agree: 23% and agree: 29%) support AI's use in 3D implant positioning. Over half (strongly agree: 25% and agree: 27%) agree AI can aid in treatment planning. Almost half (strongly agree: 21% and agree: 25%) think AI can be a quality control tool. More than half (Strongly Agree: 29% and Agree: 25%) believe AI can diagnose jaw pathologies. Nearly half (strongly agree: 20% and agree: 26%) support AI's use in forensic dentistry. A majority (strongly agree: 26% and agree: 27%) support integrating AI into undergraduate dental training. Almost half (strongly agree: 18% and agree: 22%) agree AI should be part of postgraduate dental curricula. Overall, dental professionals show strong support for the incorporation of AI into various aspects of dentistry, particularly in diagnostic, prognostic, and educational applications.

**Table 2:** Opinions of Dental Professionals Regarding AI in Dentistry

| Item | Strongly disagree Frequency (%) | Disagree Frequency (%) | Neutral Frequency (%) | Agree Frequency (%) | Strongly Agree Frequency (%) |
|---|---|---|---|---|---|
| AI Advancement in Dentistry | 11 (8.7) | 16 (12.7) | 26 (20.6) | 44 (34.9) | 29 (23.0) |
| AI Replace Dentists | 3 (2.4) | 9 (7.1) | 32 (25.4) | 39 (31.0) | 43 (34.1) |
| Excited for AI Use | 4 (3.2) | 9 (7.1) | 30 (23.8) | 36 (28.6) | 47 (37.3) |
| AI as Diagnostic Tool | 5 (4.0) | 8 (6.3) | 39 (31.0) | 32 (25.4) | 42 (33.3) |
| AI as Prognostic Tool | 4 (3.2) | 9 (7.1) | 38 (30.2) | 32 (25.4) | 43 (34.1) |
| AI in Radiographic Diagnosis of Caries | 2 (1.6) | 9 (7.1) | 40 (31.7) | 31 (24.6) | 44 (34.9) |
| AI in Radiographic Diagnosis of Periodontal Diseases | 4 (3.2) | 11 (8.7) | 38 (30.2) | 40 (31.7) | 33 (26.2) |
| AI in Diagnosis of Soft Tissue Lesions | 4 (3.2) | 9 (7.1) | 38 (30.2) | 39 (31.0) | 36 (28.6) |
| AI in 3D Implant Planning | 3 (2.4) | 11 (8.7) | 37 (29.4) | 41 (32.5) | 34 (27.0) |
| AI in Treatment Planning | 3 (2.4) | 9 (7.1) | 40 (31.7) | 40 (31.7) | 34 (27.0) |
| AI as Quality Control Tool | 10 (7.9) | 7 (5.6) | 38 (30.2) | 37 (29.4) | 34 (27.0) |
| AI in Radiographic Diagnosis of Jaw Pathologies | 10 (7.9) | 7 (5.6) | 37 (29.4) | 35 (27.8) | 37 (29.4) |

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| | | | | | |
|---|---|---|---|---|---|
| AI in Forensic Dentistry | 4 (3.2) | 9 (7.1) | 38 (30.2) | 38 (30.2) | 37 (29.4) |
| AI in Undergraduate Training | 5 (4.0) | 10 (7.9) | 36 (28.6) | 37 (29.4) | 38 (30.2) |
| AI in Postgraduate Training | 6 (4.8) | 8 (6.3) | 38 (30.2) | 33 (26.2) | 41 (32.5) |

Table 3 shows the comparison of the perception with knowledge of AI and AI usage in dentistry. Participants who had basic knowledge of AI had higher perception score compared to those who did not. Although no statistically significant difference was found between general AI knowledge and perception scores ($p = 0.461$). Moreover, Participants who were of aware of AI usage in dentistry had a significantly higher perception score compared to those who were not aware, showing a significant difference ($p=0.001$).

**Table 3:** Comparison of Knowledge of AI and AI Usage in Dentistry with Perception

| Variable | Perception Score Mean ± SD | p-Value |
|---|---|---|
| **Knew about AI** | | |
| Yes | 3.76 ± 0.52 | 0.461 |
| No | 3.69 ± 0.33 | |
| **Knew About AI Usage in Dentistry** | | |
| Yes | 3.87 ± 0.32 | 0.001* |
| No | 3.30 ± 0.65 | |

## DISCUSSION

The findings of this study align with previous research conducted globally.Similar studies, such as those by Akhtar *et al.*, and Yüzbaşıoğlu reported high levels of awareness and positive attitudes towards AI among dental students and professionals [6, 14]. However, like the current study, they also noted a gap between awareness and actual use. A study by Sajjad *et al.*, similarly observed strong awareness in Pakistan but found limited use of tools such as CAD-CAM or CBCT in routine practice [2]. Singh and colleagues observed a moderate understanding of AI among dental professionals, alongside recognition of its diagnostic capabilities [15]. A study conducted by Muller *et al.*, found that both patients and healthcare providers believed in potential benefits of AI in dental diagnostics, such as improved accuracy, reduced workload, and better patient care.However, concerns about reliance on AI, accountability, and transparency need to be addressed before widespread adoption [16].Another study by Parthasarathy *et al.*, revealed dental professionals had a positive attitude towards AI, but expressed concerns about technical barriers, costs, and ethical implications. Factors like perceived utility and ease of use significantly influenced AI adoption [17]. Aboalshamat found that dental professionals in Saudi Arabia were optimistic about AI's role in enhancing diagnostic accuracy but identified a significant need for structured training programs to improve AI literacy [18].In this study specific awareness of AI use in dentistry positively influences perception, whereas general knowledge of AI does not exhibit the same effect.This may indicate that practical or field-specific exposure to AI tools fosters more favorable opinions.The non-significant difference in perception among those with general AI knowledge ($p = 0.461$) may reflect limited relevance to clinical practice or could be due to insufficient statistical power.This underlines the importance of profession-specific AI education rather than generalized technological awareness.This study's primary strength lies in its use of a structured questionnaire to gather detailed insights into dental practitioners' knowledge and perceptions of AI. However, several limitations should be noted.The convenience sampling method may restrict the generalizability of the results, as the sample might not accurately represent the broader population of dental practitioners in Pakistan.Furthermore, the reliance on self-reported data could lead to response bias, with participants potentially overestimating their knowledge or downplaying challenges. Another limitation of this study is that it included only participants with internet access, which may have skewed the sample toward more technologically inclined professionals.This selection bias could affect the generalizability of findings, particularly regarding knowledge and attitudes toward digital tools like AI. While a composite perception score was calculated, the study did not define cut-off points for categorizing low, moderate, or high perception levels.Establishing such thresholds could enhance the interpretability of future findings.The findings highlight the need for targeted educational programs to address gaps between awareness and the practical use of AI in dentistry.Updating dental curricula to include comprehensive training on AI tools and their applications is essential.Policymakers should consider developing supportive frameworks to promote AI integration into dental practice, including financial incentives, subsidies for acquiring AI technologies, and guidelines for effective implementation.Future research should focus on identifying barriers to AI adoption, such as costs, usability, and trust in AI tools. Additionally, raising public awareness of the benefits of AI in dentistry could create greater demand for AI-driven dental services, encouraging wider adoption among practitioners.The integration of artificial intelligence (AI) into dental practice is gaining momentum, with growing interest in its potential to enhance diagnostic accuracy, treatment planning, and clinical efficiency. Hamd *et al.*, in 2023 reported that while dental professionals acknowledge the relevance of AI, there remains a gap in comprehensive knowledge and preparedness for its implementation [19]. Similarly, a study

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by Alzahrani in 2024 highlighted mixed perceptions among dental practitioners in Saudi Arabia, revealing both optimism about AI's benefits and concerns regarding its ethical, legal, and practical implications [20].

This study was limited by its cross-sectional design and use of non-probability convenience sampling, which may restrict generalizability and introduce selection bias. Inclusion of only internet-accessible participants may have favored technologically inclined practitioners, potentially inflating awareness levels. Furthermore, reliance on self-reported responses may be subject to response bias. Future multicenter longitudinal studies with larger, more diverse samples and qualitative assessments are recommended to better explore barriers to AI adoption and evaluate the impact of structured AI training on clinical implementation.

## CONCLUSIONS

The findings highlight significant awareness and generally positive attitudes toward AI among dental practitioners in Pakistan. However, the gap between recognition and routine usage calls for targeted interventions. Educational institutions must revise curricula to include practical AI training, while policymakers should establish frameworks that ease the adoption of emerging technologies in clinical settings. Addressing key barriers can lead to a more widespread and effective implementation of AI, improving both practitioner efficiency and patient outcomes.

## Authors' Contribution

Conceptualization: IM
Methodology: SAI, IM
Formal analysis: SAP
Writing and Drafting: SAI, SN, SA, IM, AFU
Review and Editing: SAI, SN, SA, IM, AFU, SAP, SAI, IM

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Prevalence and Impact of Vertigo and Dizziness in Adults: A Hospital-Based Evaluation

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## ABSTRACT

Vertigo and dizziness are common complaints in adults, often affecting daily functioning and potentially linked to conditions such as hypertension, anxiety, and migraine, highlighting the need for more local data. **Objectives:** To determine the prevalence of vertigo and dizziness among adults in the local population, assess their impact on daily functioning using the Dizziness Handicap Inventory, and identify associated clinical and demographic risk factors, including hypertension, anxiety, and migraine. **Methods:** This cross-sectional study was conducted from January 2025 to June 2025 at Bolan Medical College, Quetta and Jhalawan Medical College, Khuzdar, enrolled 371 adults (≥18 years, residing in Quetta or Khuzdar for at least one continuous year, experiencing vertigo/dizziness, and providing consent) via simple random sampling. Data from interviews, records, and DHI assessed demographics, comorbidities, and symptom characteristics. Exclusions included psychiatric/CNS disorders. Analysis (SPSS v25) used descriptive statistics, parameter estimation, chi-square, and logistic regression ($p<0.050$ significant). **Results:** The mean age of patients was 42.3 ± 12.7 years. Male were 170 (45.8%) and female 201 (54.2%). Hypertension was found in 123 (33.2%), diabetes mellitus in 77 (20.8%), migraine in 62 (16.7%), and anxiety/depression in 93 (25.1%). The overall mean Dizziness Handicap Inventory score was 48.6 ± 18.4; male had 44.7 ± 17.2 and female 51.8 ± 18.9. Based on the Dizziness Handicap Inventory score, 104 (28.0%) had mild, 193 (52.0%) moderate, and 74 (19.9%) severe symptoms. **Conclusions:** Dizziness and vertigo are common in adults, often linked to hypertension, anxiety, and migraines. Early diagnosis, screening, and multidisciplinary management help reduce the burden and improve outcomes.

## INTRODUCTION

Vertigo and dizziness are common health problems in adults, affecting daily activities and overall quality of life [1]. These symptoms are due to various causes, including vestibular disorders, cardiovascular diseases, and neurological conditions. Understanding their prevalence and associated risk factors is essential for improving prevention and management strategies [2]. Despite their frequent occurrence, data from the local population remain scarce. Most available studies focus on general causes rather than region-specific factors [3], creating challenges for healthcare planning and the development of targeted interventions [4]. An Italian population-based study involving 2,672 participants reported a lifetime prevalence of vertigo and dizziness of 40.3%, with the first episode occurring at a mean age of 39.2 years [5]. Women were 4.4 times more likely to report these symptoms than men, and individuals over 50 years had a 1.8-fold higher prevalence [6]. Among participants, 13.7% experienced spinning sensations, 26.3% had recurrent episodes, 12.9% reported positional exacerbation, and 4.8% exhibited cochlear symptoms. Headache history, present in 34.8% of cases, was linked to more frequent relapses, positional triggers, cochlear involvement, and earlier symptom onset, highlighting a strong association with migraine-like headaches [7]. Global studies estimate that 20–30% of adult's experience dizziness, though prevalence varies

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across populations. While these symptoms can occur at any age, they are more frequently reported in older adults. Known risk factors include advancing age, female sex, hypertension, and anxiety disorders. Vestibular migraine, Meniere's disease, and benign paroxysmal positional vertigo occur more commonly in women. Cardiovascular conditions such as orthostatic hypotension, arrhythmias, carotid artery disease, atherosclerosis, heart failure, myocardial infarction, and stroke also contribute by impairing brain perfusion. However, there is a lack of comprehensive local data despite strong evidence from other regions linking dizziness to these comorbidities [8]. It is expected that these symptoms will be significantly associated with the identified comorbidities and correlate with higher disability scores, providing evidence-based insights to support early detection, targeted interventions, and informed healthcare planning for improved clinical management and public health strategies [9, 10].

Vertigo and dizziness are frequent yet often under-recognized complaints in adult clinical practice, contributing substantially to functional impairment and reduced quality of life. Although international literature highlights strong associations with hypertension, migraine, and psychological disorders, region-specific epidemiological data from Balochistan remain scarce. Most local studies focus on isolated etiologies rather than assessing overall prevalence, severity, and comorbid risk factors using standardized tools such as the Dizziness Handicap Inventory (DHI). This gap limits evidence-based planning for early detection and multidisciplinary management in the local healthcare context. This study aims to determine the prevalence of vertigo and dizziness among adults in the local population, assess their impact on daily functioning using the Dizziness Handicap Inventory, and identify associated clinical and demographic risk factors, including hypertension, anxiety, and migraine.

## METHODS

This cross-sectional study was conducted at Bolan Medical College, Quetta and Jhalawan Medical College, Khuzdar Hospitals from January 2025 to May 2025. Data were collected from the medicine, ENT, Cardiology and Neurology Departments of the above-discussed hospital. Both indoor and outdoor patients were included in this study. The setting ensured a representative sample of the local community. The study was started after approval from the Institutional Review Board, approval no. 1056/BUMHS/IRB/24. The sample size was determined using the World Health Organization (WHO) sample size calculator, based on a 95% confidence level, a prevalence of vertigo or dizziness is 40.3, and an absolute precision of 0.05 [5]. A simple random sampling method was used to minimize selection bias. Daily registration logs from the medicine, ENT, Cardiology, and Neurology Departments were compiled into a master list of all patients meeting the inclusion criteria. This list was updated each day of recruitment. Each eligible patient was assigned a unique serial number, and random numbers were generated using the SPSS-25 "Random Sample of Cases" function to select participants. If a selected patient declined participation or met an exclusion criterion during screening, the next randomly generated number from the pre-determined list was used, ensuring the process remained unbiased. The randomization was conducted by a research assistant not involved in data collection, and the recruiting clinicians were blinded to the sequence [6-10]. Adults aged 18 years and above, experiencing vertigo and dizziness, and willing to provide informed consent were included in the study. Written informed consent was obtained from all participants before inclusion in the study. Participants were thoroughly informed about the study's objectives, procedures, potential risks, and benefits in their native language. it was then obtained and documented using a signed form approved by the Hospital Ethical Committee. Confidentiality of data was maintained throughout the study. Individuals with psychiatric disorders or known central nervous system pathologies were excluded. Data were collected through interviews conducted by trained healthcare professionals, covering demographics, medical history, and characteristics of vertigo and dizziness. Comorbidities were identified using standardized criteria and multiple data sources to ensure diagnostic accuracy. Hypertension was confirmed from patient medical records by a physician, if the patient was on antihypertensive medication, or if blood pressure measured during the visit was ≥140/90 mmHg on at least two occasions [3]. Migraine was recorded if previously diagnosed by a physician (based on International Classification of Headache Disorders criteria) and documented in medical records; in cases where records were unavailable, diagnosis was based on a consistent patient history of recurrent, unilateral, pulsating headaches associated with nausea, photophobia, or phonophobia [4]. Anxiety disorders were considered present if diagnosed by a mental health professional or documented in medical records, and in the absence of a formal diagnosis, patient self-report of persistent excessive worry or associated symptoms was corroborated with available clinical documentation [3, 4]. All comorbidity data were cross-checked against hospital records from Medicine, Neurology, and Psychiatry Departments to minimize misclassification bias. The Dizziness Handicap Inventory (DHI) serves as a valuable tool in diagnosing vestibular disorders, guiding treatment planning, and monitoring clinical progress. Its integration into the study's assessment proforma enhanced the depth

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and precision of the patient evaluation process. It is a standardized, 25-item self-assessment tool used to evaluate the impact of dizziness on an individual's daily life. In this study, the DHI was incorporated into the assessment proforma to ensure a comprehensive and structured evaluation. It was administered using standardized protocols to maintain consistency and reliability [11]. The inventory is divided into three domains: Functional (9 items) assessing limitations in performing daily activities, Emotional (9 items) evaluating psychological distress, and Physical (7 items) identifying dizziness-provoking triggers. Each item is scored as Yes (4 points), Sometimes (2 points), or No (0 points), with a total score ranging from 0 to 100. Higher scores indicate greater perceived disability, with severity classified as mild (0–30), moderate (31–60), and severe (61–100). Participant-reported symptoms were systematically categorized into vertigo and non-vertiginous dizziness, with particular attention to duration, frequency, and identifiable triggers such as head movements, postural changes, or emotional stress. Associated features, including hearing loss, tinnitus, aural fullness, nausea, vomiting, and focal neurological signs, were documented to aid in etiological differentiation. A comprehensive ontological and neurological examination was conducted, including otoscopy to exclude external or middle ear pathology. Vestibular assessments were conducted by trained clinicians using standardized protocols to evaluate peripheral and central vestibular function. The Dix-Hallpike maneuver was used to diagnose posterior canal BPPV, with a positive result defined as reproduction of vertigo and characteristic positional nystagmus [6]. The Head Impulse Test (HIT) assessed the vestibulo-ocular reflex, with corrective saccades after rapid, unpredictable head turns, indicating unilateral peripheral vestibular hypofunction [7]. The Romberg test evaluated postural stability, where marked sway or loss of balance with eyes closed suggested sensory ataxia from vestibular or proprioceptive deficits [8]. The Unterberger test assessed vestibulospinal reflexes, with rotation of ≥45° during stepping in place with eyes closed, indicating unilateral vestibular dysfunction [9]. Findings from these tests were integrated with history, otological/neurological examination, and symptom profile to distinguish peripheral from central causes and guide diagnostic impressions [10]. Data were analyzed using SPSS version 25 (IBM Corp., Armonk, NY, USA). Quantitative variables included age (years) and Dizziness Handicap Inventory (DHI) scores (range 0–100), which were summarized as mean ± standard deviation (SD) and compared between groups using the independent samples t-test. The DHI was treated primarily as a continuous variable; however, for severity distribution, it was also categorized into ordinal groups as mild (0–30), moderate (31–60), and severe (>60). Qualitative variables included gender, marital status, educational level, comorbidities (hypertension, diabetes, migraine, cardiovascular disease, anxiety/depression), and categorical DHI groups (mild, moderate, severe). These qualitative variables were expressed as frequencies and percentages, and associations were assessed using the chi-square test or Fisher's exact test where appropriate. Finally, multivariate binary logistic regression was applied to identify independent predictors of dizziness after adjusting for age and gender, and a p-value of <0.050 was considered statistically significant for all analyses.

## RESULTS

The total number of participants was 371. The mean age was 42.3 ± 12.7 years. Details of the demographic characteristics of participants are exhibited. Most participants were female: 201 (54.2%), while 170 (45.8%) were male (Table 1).

**Table 1:** Exhibits Demographic Characteristics of Participants (n=371)

| Variables | n (%) |
|---|---|
| **Educational Level** | |
| No Formal Education | 58 (15.6%) |
| Primary | 93 (25.1%) |
| Secondary | 108 (29.1%) |
| Higher Secondary | 66 (17.8%) |
| Graduate and Above | 46 (12.4%) |
| **Marital Status** | |
| Married | 247 (66.6%) |
| Single | 81 (21.8%) |
| Divorced/Widowed | 43 (11.6%) |

The details of medical comorbidities and their association with dizziness are reported in detail. Vestibular Disorders were found in 8.3% of cases, but no statistical assessment was performed (Table 2).

**Table 2:** Reports Medical Comorbidities and Their Association with Dizziness

| Comorbidity | Present, n (%) | Absent, n (%) | Chi-square ($\chi^2$) | p-value | Significant? |
|---|---|---|---|---|---|
| Hypertension | 123 (33.2%) | 248 (66.8%) | 5.87 | 0.015 | ✔ Yes |
| Diabetes Mellitus | 77 (20.8%) | 294 (79.2%) | 1.18 | 0.277 | ✖ No |
| Migraine | 62 (16.7%) | 309 (83.3%) | 3.65 | 0.056 | ~ Borderline |
| Cardiovascular Disease | 46 (12.4%) | 325 (87.6%) | 0.94 | 0.331 | ✖ No |
| Anxiety/ Depression | 93 (25.1%) | 278 (74.9%) | 6.42 | 0.011 | ✔ Yes |

The mean DHI score for all participants was 48.6 ± 18.4, with males scoring 44.7 ± 17.2 and females 51.8 ± 18.9, showing a statistically significant gender difference (p=0.009). The details of Dizziness Handicap Inventory (DHI) scores and gender comparison are demonstrated. To further assess the relationship between vestibular function and perceived disability, DHI scores were compared between patients

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with positive and negative vestibular test results. Independent samples t-test analysis showed significantly higher mean DHI scores among patients with positive vestibular test findings compared to those with negative results (t=3.21, p=0.001) (Table 3).

**Table 3:** Demonstrates Dizziness Handicap Inventory (DHI) Scores and Gender Comparison

| Parameters | Males (n=170) | Females (n=201) | Total (n=371) |
|---|---|---|---|
| Mild (<30) | 56 (32.9%) | 48 (23.9%) | 104 (28.0%) |
| Moderate (31-60) | 92 (54.1%) | 101 (50.2%) | 193 (52.0%) |
| Severe (>60) | 22 (12.9%) | 52 (25.9%) | 74 (19.9%) |

Multivariate logistic regression identified hypertension and anxiety/depression as significant independent predictors of dizziness after adjusting for age and gender. The multivariate logistic regression analysis of factors associated with dizziness is reported. Migraine showed a borderline association, while diabetes mellitus and cardiovascular disease were not significant predictors (Table 4).

**Table 4:** Multivariate Logistic Regression Analysis of Factors Associated with Dizziness

| Variables | Adjusted OR | 95% CI | p-value |
|---|---|---|---|
| Age (Per Year) | 1.01 | 0.99–1.03 | 0.278 |
| Female Gender | 1.32 | 0.89–1.97 | 0.164 |
| Hypertension | 1.88 | 1.18–3.00 | 0.008 ✔ |
| Migraine | 1.54 | 0.97–2.45 | 0.065 ~ |
| Anxiety/Depression | 2.21 | 1.37–3.57 | 0.001 ✔ |
| Diabetes Mellitus | 1.09 | 0.68–1.74 | 0.720 |
| Cardiovascular Disease | 1.15 | 0.64–2.09 | 0.634 |

## DISCUSSION

This study found dizziness to be highly prevalent among adults, affecting more than half of the participants, with notable variations in severity and impact on daily functioning. Significant associations were identified for hypertension and anxiety/depression, while migraine showed a borderline relationship that warrants further investigation [11]. Females not only reported symptoms more frequently but also demonstrated higher DHI scores, indicating a greater perceived handicap. An unexpectedly high prevalence among middle-aged adults challenges the conventional assumption that dizziness is primarily a condition of older age. These findings emphasize that vestibular disorders are a substantial health burden in the community and highlight the importance of addressing both the physical limitations and psychological consequences of dizziness [12]. Multivariate logistic regression confirmed hypertension and anxiety/depression as independent predictors, even after adjusting for age and gender, suggesting robust associations. Migraine, although not reaching statistical significance, may still play a contributory role, and its clinical relevance should not be dismissed, particularly given its established association with vestibular symptoms in other studies. Diabetes mellitus and cardiovascular disease did not show significant associations in this study, indicating that the relationship between chronic comorbidities and dizziness is selective rather than universal [13]. Recognizing which comorbidities carry the strongest influence can help direct resources toward high-yield screening and management. This study's findings are consistent with a large body of international literature identifying cardiovascular risk factors, migraine, and psychological disorders as important contributors to dizziness and vertigo. Similar patterns have been observed in Europe, North America, and Asia, where population-based studies have confirmed the impact of these conditions on vestibular health. For example, research from the United States has demonstrated that psychological stress and cardiovascular risk factors significantly increase the likelihood of developing dizziness, while German studies have specifically linked hypertension with vestibular dysfunction. In contrast, studies from several Asian countries, particularly Korea, have reported higher prevalence rates among older adults, reflecting possible demographic, cultural, or lifestyle differences [14]. The relatively high burden among middle-aged adults in this study contrasts with such reports and may be explained by factors including occupational stress, sedentary work environments, and differences in healthcare-seeking behaviour. Additionally, regional disparities in access to specialized care could influence both the detection and management of vestibular disorders [15]. These contextual differences underscore the importance of region-specific epidemiological data to guide public health strategies and ensure interventions are culturally and logistically appropriate. From a clinical perspective, these findings support incorporating routine dizziness screening into primary care assessments, especially for patients with a history of hypertension, migraine, or anxiety symptoms. Such screening could be achieved using validated tools such as the DHI, which not only helps identify affected individuals but also quantifies the severity of functional impairment. Early recognition may allow for timely referral to specialist services, thereby preventing progression to chronic disability [16]. A multidisciplinary model of care that brings together primary care physicians, ENT specialists, neurologists, physiotherapists, and mental health professionals would offer a more holistic approach. This model could improve diagnostic accuracy, tailor interventions to individual patient needs, and ensure psychological factors are addressed alongside physical rehabilitation. Community-level strategies, such as educational campaigns on

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hydration, posture correction, and stress management, could further reduce preventable triggers. Evidence from community programs in the United Kingdom shows that such initiatives can improve both symptom control and quality of life [17]. At the policy level, integrating vestibular health into broader non-communicable disease frameworks could leverage existing healthcare infrastructure to address dizziness as part of routine chronic disease management. Given the association between dizziness and work-related disability, workplace health programs could also play a role in reducing the socioeconomic impact [18]. Key strengths of this study include the use of the DHI as a standardized, validated measure of functional impairment, the inclusion of both inpatient and outpatient populations, and the use of multivariate analysis to identify independent predictors while minimizing confounding effects. The multicenter design, incorporating two distinct geographic locations, also enhances the generalizability of the findings within the regional context [19].

This study was limited by its cross-sectional design, which precludes causal inference between identified risk factors and dizziness. Although multicenter, it was hospital-based and may not fully represent the general community population, potentially overestimating symptom severity. Additionally, reliance on clinical history and record-based comorbidity assessment may introduce information bias. Future research should adopt longitudinal designs to better establish causal relationships between identified risk factors and dizziness. Incorporating advanced diagnostic modalities, including vestibular function testing and neuroimaging, could improve etiological classification. Investigating the psychosocial impact of chronic dizziness, including its effects on employment and social participation, would provide a more comprehensive understanding of its burden [20]. Furthermore, exploring the role of digital health tools, such as mobile symptom tracking applications and telemedicine platforms, may offer innovative solutions for monitoring and managing dizziness, particularly in resource-limited settings.

## CONCLUSIONS

Vertigo and dizziness are common in adults, often linked to hypertension, anxiety, and migraines, particularly in women. Routine primary care screening, use of standardized tools like the DHI, and timely specialist referral are recommended. Community education, stress management initiatives, and workplace balance safety programs can reduce burden, while multidisciplinary clinics improve coordinated long-term care.

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## Authors' Contribution

Conceptualization: I
Methodology: I, AH, MA, AB
Formal analysis: AW
Writing and Drafting: AB
Review and Editing: AB, I, AH, MA, AW

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Prescribing Patterns and Utilization Trends of Anti-Asthmatic Drugs in Children: An Observational Study in a Pediatric Population

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## ABSTRACT

Pediatric asthma occurs as a common chronic respiratory illness. **Objectives:** To evaluate the prescribing patterns and utilization trends of anti-asthmatic medications in pediatric patients, assessing adherence, appropriateness, and factors influencing drug selection. **Methods:** This observational study investigated pediatric asthma patients over six months, collecting data from 160 children aged 4–10 years. The data was obtained from pediatric asthma patients about their demographic information, alongside their asthma severity status and medication choices, and delivery methods. Data were analyzed by SPSS version 21.0. Chi-square test evaluated all associations between variables. **Results:** The study included 160 patients, with 31.3% of them within the age range of 8–9 years, and males represented 56.3% of the group. Urban residents (62.5%) were more affected. The bronchodilator medicine Salbutamol received the highest prescription rate (56.3%), and Budesonide held the position as the most commonly chosen corticosteroid (31.3%). The usage rate of Montelukast reached 45.0% while Theophylline's prescription was limited to just 11.3% of patients. The primary choice of medication delivery involved nebulization for 53.1% of patients, whereas 31.3% received inhalers and 15.6% had oral administration. The standard treatment for mild asthma patients involved Montelukast at a rate of 37.5% and Budesonide treated 34.4% of moderate cases, while severe asthma patients received Salbutamol + Ipratropium in 28.1% of cases. **Conclusions:** Prescribing patterns in pediatric asthma were closely linked to disease severity, with increased use of nebulizers and combination therapies in severe cases. Tailored, severity-based management can enhance treatment outcomes and promote rational drug use in children.

## INTRODUCTION

Children with asthma deal with one of the most widely occurring chronic respiratory conditions, which causes significant hurdles for their life quality as well as their attendance in school and their general health status [1]. Cutting-edge research defines asthma as a disease that creates airway inflammation that combines with bronchial tube over reactivity and temporary respiratory blockage, which results in breathing problems and wheezing, along with tightness in the chest and frequent coughing episodes [2]. The growing global occurrence of pediatric asthma requires complete research on medical treatments for asthma control and management. Anti-asthmatic medication serves as a fundamental treatment approach for asthma because it helps achieve symptom control while stopping attacks in pediatric patients [3]. Pediatric asthma treatment includes two basic medicinal groups, which are reliever medications for immediate use combined with controller medications for sustained effect. The main quick-relief medication for treating acute bronchospasms consists of albuterol/salbutamol as short-acting beta-

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agonists (SABAs) [4]. People with severe asthma need inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), long-acting beta-agonists (LABAs), as well as biologic agents to gain proper control of symptoms. Various factors determine the selection process of appropriate anti-asthmatic medication since they include disease severity and how the patient responds, as well as their adherence and availability, together with healthcare provider preferences [5]. Widespread implementation of recognized treatment guidelines by GINA and NAEPP has not yet occurred, yet pediatricians and general practitioners, and pulmonologists show different behavioral patterns in prescribing treatments [6]. Clinical practice faces major issues in asthma management because medical professionals overutilize bronchodilators while underutilizing inhaled corticosteroids and repeatedly write incorrect antibiotic scripts. The results of medication adherence and appropriate drug utilization depend significantly on the awareness of physicians, while parental understanding, together with socioeconomic conditions also contribute to these outcomes [7]. Children with asthma face difficulties when following their prescribed medications. Various research shows that a major number of children with asthma display inconsistent behavior in following their prescribed controller medications, which produces both inadequate symptom management and multiple hospital visits. The young patients fail to adhere to their medications because of fearful corticosteroid side effects in addition to difficulty with inhalation techniques and poor recognition of symptoms, and economic limitations [8]. The patients did not follow their medications correctly, needed more hospital stays and Emergency Room visits, which increases healthcare organization costs. Knowledge about how children utilize healthcare services and how doctors write prescriptions remains essential for enhancing asthma control and lowering childhood asthma-related outbreaks [9]. The utilization of combination treatments for pediatric asthma treatment has become increasingly important in current medical practice. Doctors suggest the use of budesonide-formoterol and fluticasone-salmeterol ICS-LABA combinations to treat moderate to severe asthma for enhancing symptom control. Steadfast evaluations for determining the safety profile of LABA usage in children result from existing doubts about their safe practices. Widely adopted use of biologic treatments such as monoclonal antibodies that target IgE (omalizumab) and IL-5 (mepolizumab) remains limited because of their high costs in treating severe pediatric asthma [10]. Asthma treatment requires regular evaluation of prescribing patterns because anti-asthmatic drug utilization patterns change constantly.

Although asthma is one of the most prevalent chronic respiratory diseases in children, evidence regarding real-world prescribing patterns of anti-asthmatic drugs in Pakistani pediatric populations remains limited. Variations in adherence to international guidelines such as GINA and differences in drug selection based on physician preference, availability, and socioeconomic factors may influence treatment outcomes. Furthermore, local data examining the association between asthma severity and medication utilization trends are scarce. This gap necessitates systematic evaluation of prescribing practices to promote rational, severity-based asthma management in children. This study aimed to evaluate the prescribing patterns and utilization trends of anti-asthmatic medications in pediatric patients, assessing adherence, appropriateness, and factors influencing drug selection.

## METHODS

This observational study was conducted over six months, from October 2024 to March 2025, in the Pediatric Department at Khairpur Medical College, Khairpur Mir's. Ethical approval was obtained from the Institutional Review Board (IRB No. KMC/RERC/120) before data collection, and parents or guardians provided written informed consent for participant inclusion. The research evaluated prescription methods and treatment strategies used for pediatric asthma patients. The study focused on children aged 4–10 years who were diagnosed with asthma based on clinical reports, physical evaluations, and spirometry tests conducted according to the Global Initiative for Asthma (GINA) criteria [11]. The sample size was calculated using the standard formula for estimating a single population proportion: $n = Z^2 \times P \times (1 - P) / e^2$, where Z is the Z-score corresponding to a 95% confidence level (1.96), P is the estimated prevalence of pediatric asthma, and e is the desired margin of error. Based on prior regional data, the prevalence of pediatric asthma was estimated at 10.6% (0.106). Using a margin of error of 5% (0.05), the calculated sample size was n=162 [12]. The study included only children with asthma diagnoses made by pediatric pulmonologists who received care at the study facility during the defined study period. Exclusion criteria included cystic fibrosis, bronchopulmonary dysplasia, incomplete medical records, or hypersensitivity to asthma medication. Data were collected using structured proformas to document demographic information, clinical history, asthma severity ratings, and medication prescriptions. Patient details included age, gender, type of residential area, symptom frequency, asthma test results (mild, moderate, or severe), exposure to allergens and environmental pollutants, family history of asthma, and prescribed treatment protocols. Drug delivery methods

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were also recorded, including nebulizers, metered-dose inhalers (MDIs), dry powder inhalers (DPIs), and oral medications. Data collection was carried out by trained researchers under the direct supervision of pediatric pulmonologists. Statistical analysis was performed using SPSS version 21.0. Descriptive statistics were used to summarize demographic and clinical characteristics. The Chi-square test was applied to examine the association between medication prescriptions and asthma severity categories (mild, moderate, severe). A p-value <0.05 was considered statistically significant.

## RESULTS

The study of 160 pediatric asthma patients showed 31.3% were between 8 and 9 years old, with 28.1% in the 6–7 years age bracket, while 18.7% were 10 years old. Childhood asthma mostly affects young children because their immune systems have not fully developed, and they experience more exposure to allergens. Male pediatric asthma patients surpassed females by 56.3% to 43.7% in this sample group, potentially because of structural as well as hormonal reasons that affect breathing responsiveness. Environmental pollution seems to raise asthma risk because patients from urban areas (62.5%) outnumber those from rural areas (37.5%). The study results demonstrate why early intervention programs must target vulnerable children because they help enhance asthma management practices and reduction methods. Most pediatric asthma patients in the study had mild to moderate asthma, accounting for 71.9% of cases, while severe asthma was present in 28.1%. A majority of children (68.8%) reported contact with allergens, and an even larger proportion (75%) were exposed to environmental pollutants, both of which are known to contribute to asthma exacerbations. Additionally, 43.7% of patients had a family history of asthma, indicating a significant genetic or familial predisposition within this population. These findings highlight the combined influence of environmental and hereditary factors in the prevalence and severity of pediatric asthma (Table 1).

**Table 1:** Demographic Characteristics of the Study Population (N=160)

| Characteristics | Categories | Frequency (n %) |
|---|---|---|
| Age Group (Years) | 4–5 | 35 (21.9%) |
| | 6–7 | 45 (28.1%) |
| | 8–9 | 50 (31.3%) |
| | 10 | 30 (18.7%) |
| Gender | Male | 90 (56.3%) |
| | Female | 70 (43.7%) |
| Residence | Urban | 100 (62.5%) |
| | Rural | 60 (37.5%) |
| Asthma Severity | Mild | 60 (37.5%) |
| | Moderate | 55 (34.4%) |
| | Severe | 45 (28.1%) |
| Contact with Allergens | Yes | 110 (68.8%) |
| | No | 50 (31.3%) |
| Exposure to Environmental Pollutants | Yes | 120 (75.0%) |
| | No | 40 (25.0%) |
| Family History of Asthma | Yes | 70 (43.7%) |
| | No | 90 (56.3%) |

Acute asthma management requires bronchodilators, which physicians prescribed to 160 pediatric asthma patients and preferred the use of Salbutamol (56.3%) over Ipratropium Bromide (21.9%). The prescription data showed inhaled steroids had a higher preference among corticosteroid treatments, with Budesonide being preferred over Fluticasone by 31.3% versus 17.5%. Healthcare professionals prescribed Montelukast to 45.0% of patients for asthma control, yet Theophylline received only 11.3% of usage because of its associated side effects. The combination therapy Salbutamol + Ipratropium (25.0%) and Budesonide + Formoterol (18.8%) were frequently used since they provided dual-action therapeutic benefits (Table 2).

**Table 2:** Prescribing Patterns of Anti-Asthmatic Drugs (N=160)

| Drug Class | Medication | Frequency (n %) |
|---|---|---|
| Bronchodilators | Salbutamol | 90 (56.3%) |
| | Ipratropium Bromide | 35 (21.9%) |
| Corticosteroids | Budesonide | 50 (31.3%) |
| | Fluticasone | 28 (17.5%) |
| Leukotriene Antagonists | Montelukast | 72 (45.0%) |
| Methylxanthines | Theophylline | 18 (11.3%) |
| Combination Therapy | Salbutamol + Ipratropium | 40 (25.0%) |
| | Budesonide + Formoterol | 30 (18.8%) |

A significant association was found between asthma severity and mode of drug administration (p=0.004). Nebulizer use increased notably with severity, from 16.7% in mild cases to 44.4% in severe cases. In contrast, metered-dose inhaler (MDI) use was highest in mild asthma (50.0%) and declined in severe cases (33.3%). Dry powder inhaler (DPI) prescriptions were more common in mild and moderate asthma (25.0% and 27.3%, respectively) but dropped to 11.1% in severe asthma. Oral medication use remained low and relatively consistent across all severity categories. These findings suggest a shift toward nebulizer therapy in more severe cases and greater use of inhalers in milder disease (Table 3).

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**Table 3:** Association Between Asthma Severity and Mode of Drug Administration (N=160)

| Mode of Administration | Mild (N=60) | Moderate (N=55) | Severe (N=45) | Total N (%) | $\chi^2$ Value | P-Value |
|---|---|---|---|---|---|---|
| Nebulizer | 10 (16.7%) | 15 (27.3%) | 20 (44.4%) | 45 (28.1%) | - | - |
| Metered-Dose Inhaler (MDI) | 30 (50.0%) | 20 (36.4%) | 15 (33.3%) | 65 (40.6%) | - | - |
| Dry Powder Inhaler (DPI) | 15 (25.0%) | 15 (27.3%) | 5 (11.1%) | 35 (21.9%) | 18.74 | 0.004* |
| Oral Medication | 5 (8.3%) | 5 (9.1%) | 5 (11.1%) | 15 (9.4%) | - | - |

The analysis revealed a significant association between asthma severity and the prescribing trends of several anti-asthmatic medications. Use of Salbutamol was notably higher among patients with moderate (63.6%) and severe asthma (66.7%) compared to those with mild disease (41.7%) (p=0.015). A similar pattern was observed for Ipratropium Bromide, with prescription rates increasing from 13.3% in mild asthma to 33.3% in severe asthma (p=0.028). Budesonide was prescribed more frequently in moderate (36.4%) and severe (40.0%) cases compared to mild asthma (20.0%) (p=0.037), whereas Fluticasone showed no statistically significant variation across severity categories (p=0.478). Prescription of Montelukast also increased with disease severity, being used in 33.3% of mild, 50.9% of moderate, and 53.3% of severe cases (p=0.047). Theophylline use, although higher in severe asthma (20.0%) than in mild (6.7%), did not reach statistical significance (p=0.053). Combination therapy with Budesonide + Formoterol was significantly more common in severe asthma (33.3%) than in moderate (18.2%) or mild (8.3%) cases (p=0.004), while Salbutamol + Ipratropium combinations showed a non-significant upward trend with increasing severity (p = 0.089) (Table 4).

**Table 4:** Association Between Asthma Severity and Prescribing Trends of Anti-Asthmatic Drugs (N = 160)

| Medication | Mild (N=60) | Moderate (N=55) | Severe (N=45) | Total N (%) | $\chi^2$ Value | P-Value |
|---|---|---|---|---|---|---|
| Salbutamol | 25 (41.7%) | 35 (63.6%) | 30 (66.7%) | 90 (56.3%) | 8.45 | 0.015* |
| Ipratropium Bromide | 8 (13.3%) | 12 (21.8%) | 15 (33.3%) | 35 (21.9%) | 7.12 | 0.028* |
| Budesonide | 12 (20.0%) | 20 (36.4%) | 18 (40.0%) | 50 .(31.3%) | 6.59 | 0.037* |
| Fluticasone | 8 (13.3%) | 10 (18.2%) | 10 (22.2%) | 28 (17.5%) | 1.47 | 0.478 |
| Montelukast | 20 (33.3%) | 28 (50.9%) | 24 (53.3%) | 72 (45.0%) | 6.13 | 0.047* |
| Theophylline | 4 (6.7%) | 5 (9.1%) | 9 (20.0%) | 18 (11.3%) | 5.89 | 0.053 |
| Salbutamol + Ipratropium | 10 (16.7%) | 15 (27.3%) | 15 (33.3%) | 40 (25.0%) | 4.84 | 0.089 |
| Budesonide + Formoterol | 5 (8.3%) | 10 (18.2%) | 15 (33.3%) | 30 (18.8%) | 10.92 | 0.004* |

The treatment regimen of dual therapy was adopted most often by clinicians to treat 40.6% of pediatric asthma patients for combined symptom relief and inflammation control. Single drug therapy was used in 31.3% of cases, whereas 28.1% of patients received multiple drug classes as part of their triple therapy or higher prescription (Table 5).

**Table 5:** Polypharmacy and Single-Drug Therapy Distribution (N=160)

| Prescription Type | Frequency (n %) |
|---|---|
| Monotherapy | 50 (31.3%) |
| Dual Therapy | 65 (40.6%) |
| Triple Therapy or More | 45 (28.1%) |

## DISCUSSION

The study reveals that pediatric asthma affects children mostly during their 6 to 9 years of age, with the 8–9-year group showing the maximum prevalence of 31.3% patients. Studies confirm that asthma symptoms peak during early childhood because both the immune and respiratory systems remain undeveloped. Research confirms that the male child population (56.3%) shown in this study aligns with established asthma studies due to their anatomy and hormone regulation. The airway resistance increases and asthma exacerbations occur more frequently in boys since their airways remain smaller relative to their lung volume compared to girls [13]. Testosterone and estrogen hormones, along with their influence on immune responses, affect asthma intensity differently between male and female patients. Asthma prevalence shows significant links to environmental factors since urban populations having 62.5% asthma make up exceeds the 37.5% rural patient population with asthma. The development of asthma is associated with the urbanization process due to air pollutant hazards, along with allergens and lifestyle pattern shifts. The air pollutants like $NO_2$ and PM2.5 act as inflammation agents, which produce more asthma cases in urban residents. The discovered data shows that urban areas require public health actions to control pollution while simultaneously improving air quality monitoring systems [14, 15]. The medication choice for asthmatic patients showed Bronchodilators as the leading type due to their role in acute symptom relief, as described in standard guidelines, through Salbutamol prescription at 56.3%. Medical guidelines explain Ipratropium Bromide use at 21.9% because this medicine serves as a supporting treatment for severe to moderate asthma attacks. The selection of inhaled corticosteroids (ICS) shows Budesonide (31.3%) being used more often than Fluticasone (17.5%) by physicians whose practice aligns with worldwide recommendations that recommend ICS as the primary controller therapy for persistent asthma. The

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data reveal that medical practitioners choose Budesonide over other available medications presumably because of its desirable pharmacokinetics together with reduced systemic adverse effects [16]. The prescription rate of Montelukast as a leukotriene receptor antagonist reached 45.0% in patients, thus demonstrating its importance for long-term asthma control in mild persistent asthmatic conditions. Thephanine prescription below other drugs (11.3%) may result from its limited therapeutic window as well as potential adverse effects that affect physician prescribing practices within pediatric asthma management. Results showed Salbutamol + Ipratropium saw wide prescription rates at 25.0% while Budesonide + Formoterol was prescribed to 18.8% of patients. These therapy pairs support asthma stepwise guidelines because they treat patients with moderate to severe asthma through a combination of instant bronchodilator benefits with extended anti-inflammatory effects. The treatment approach of combining different therapies demonstrates an increase in asthma symptom control and exacerbation reduction in pediatric care [17, 18]. Patients tend to select nebulizers as their preferred asthma delivery device because they are simpler to use while also showing better effectiveness for treating acute asthma attacks compared to MDIs and DPIs. Small children experience difficulties with correct inhaler use, and this could be a reason behind their reduced preference for using inhalers. Pediatric patients without spacer devices face difficulties when using inhalers because they must simultaneously activate the device and then inhale the medication [19]. The present study demonstrates a clear association between asthma severity and both the mode of drug administration and the prescribing trends of anti-asthmatic medications. In terms of delivery methods, nebulizer use increased with disease severity, being most prevalent in severe asthma (44.4%), whereas MDIs and DPIs were more common in mild and moderate asthma. This trend is in agreement with previous studies, which suggest that nebulizers are often preferred in severe exacerbations due to their ability to deliver higher drug doses over a sustained period, particularly in patients with compromised inspiratory capacity. In contrast, MDIs and DPIs are generally recommended for stable patients with good inhalation technique, which may explain their higher usage in mild cases [20]. The prescribing pattern analysis further reinforces the adaptation of therapy to disease severity. Short-acting $\beta_2$-agonists, particularly salbutamol, showed a stepwise increase in use from mild to severe asthma, consistent with their role as first-line rescue medication during acute symptoms. Similarly, the use of Ipratropium Bromide, either alone or in combination with Salbutamol, increased in moderate and severe cases, aligning with guideline recommendations for adding anticholinergics during severe exacerbations. Budesonide use also rose with increasing severity, reflecting the escalating need for inhaled corticosteroids (ICS) to achieve anti-inflammatory control in poorly controlled asthma. The significant increase in the prescription of Budesonide + Formoterol in severe asthma underscores the role of ICS/LABA combination therapy in achieving optimal symptom control when monotherapy proves insufficient. Montelukast, a leukotriene receptor antagonist, also demonstrated increased prescription rates with severity, possibly reflecting its utility as an adjunct therapy in patients with persistent symptoms or concomitant allergic rhinitis. Interestingly, Fluticasone and Theophylline did not exhibit statistically significant differences in prescribing trends across severity levels. This could be due to physician preference for Budesonide over Fluticasone in this population, and a more conservative use of Theophylline given its narrow therapeutic index and side effect profile [21]. During the study period, 40.6% of pediatric asthma patients received dual therapy and 31.3% needed monotherapy, and 28.1% received triple therapy or exceeded triple therapy. Research indicates that dual and triple therapy treatments exist frequently among asthmatic patients because many patients need extra medication beyond single drugs to effectively control their asthma symptoms. Use of combination therapy for asthma treatment remains necessary, but implementation of polypharmacy treatment increases treatment complications, specifically among children, due to possible drug interactions as well as adverse effects, which may decrease patient adherence [22]. Multiple practice implications and practical suggestions stem from the study results. Health professionals need to focus on diagnosing asthma at an early stage because city dwellers need prevention measures for their exposure to pollution and allergens. Healthcare providers should prioritize treatment selection by using inhaled corticosteroids as base therapy, but save Theophylline and oral medications for subjects not able to use inhaled therapies. Inhaler technique improvement through caregiver education programs alongside child education results in better adherence and treatment results. Each needs unique asthma care strategies where treatment plans advance according to their observed symptoms to achieve better results with minimal medication requirements.

This study was limited by its single-center design and relatively small sample size, which may restrict the generalizability of the findings. The short study duration also limited the assessment of long-term treatment adherence, clinical outcomes, and adverse effects. Additionally, guideline adherence was inferred from

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prescribing trends rather than directly measured. Future multicenter, longitudinal studies incorporating larger cohorts and outcome-based evaluations are recommended to better assess the impact of prescribing patterns on asthma control and to strengthen evidence for optimized pediatric asthma management.

## CONCLUSIONS

This study highlights important prescribing patterns in pediatric asthma management, showing that drug choice and mode of administration are strongly influenced by disease severity. Nebulizers were preferred in severe cases, while MDIs and DPIs were more common in mild asthma. Salbutamol, Budesonide, Montelukast, and combination therapies such as Budesonide + Formoterol were significantly more frequently prescribed as severity increased. These findings underscore the need for tailored treatment strategies that align with asthma severity, while promoting early intervention and rational drug use to optimize symptom control and reduce exacerbations in children.

## Authors' Contribution

Conceptualization: UB
Methodology: IHS, AAK, PK
Formal analysis: HIS, MZ
Writing and Drafting: AAK, MAB, MZ
Review and Editing: AAK, MAB, MZ, UB, IHS, MZ

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Association of Serum Creatinine and Cortical Thickness with Renal Echogenicity on Ultrasound in Chronic Kidney Disease

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## ABSTRACT

The Incidence of chronic kidney disease (CKD) is increasing day by day all over the globe. In assessing the progression of CKD, both the function and structure of the kidney need to be evaluated. **Objectives:** To determine the association between serum creatinine and cortical thickness with renal echogenicity on ultrasound in patients with CKD. **Methods:** This cross-sectional analytical research was carried out at the Department of Radiology and Biochemistry, Shahida Islam Medical and Dental College, Lodhran, for six months (June 2024 to November 2024). All patients who were referred for ultrasonography of the kidneys, with serum creatinine and serum urea checked on the same day on which U/S was carried out, were included. Patients who were k/c of acute renal injury, on hemodialysis, peritoneal dialysis, renal transplant, chronic liver disease, fatty liver, or those having a solitary kidney were all excluded. SPSS version 23.0 was used for data analysis. A one-way ANOVA test was applied to test for association, keeping $p<0.050$ statistically significant. **Results:** Mean age of participants was 52.26 ± 12.50 years (95% CI: 39.76–64.76). The study found that higher serum creatinine and urea levels were significantly associated with increased cortical echogenicity and reduced cortical thickness on ultrasound. The mean serum creatinine was 2.11 ± 1.2 mg/dL, and cortical thickness progressively declined from 1.11 cm to 0.71 ± 0.10 cm across echogenicity grades. **Conclusions:** The study found a significant association between elevated serum creatinine and cortical thickness levels with renal echogenicity on ultrasound in CKD patients.

## INTRODUCTION

Chronic kidney disease (CKD) is affecting people increasingly all over the world, and its incidence is increasing. A characteristic feature of CKD is a steady decline in the function of the kidney [1]. Chronic kidney disease (CKD) is characterized by a decrease in the glomerular filtration rate (GFR) and/or an elevation in urine albumin excretion [2]. Among CKD patients, impaired structure and function of the kidney are interrelated. Therefore, in assessing the progression of CKD, both the function and structure of the kidney need to be evaluated. Previously, information regarding kidney function was provided by laboratory testing, while structural information was provided through imaging techniques [3]. At present, various imaging techniques such as ultrasound (U/S), CT-scan (Computed Tomography), and MRI (Magnetic Resonance Imaging) tend to provide information about the

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kidney's structural alterations; however, little input is provided with regard to functional impairments in CKD [4]. Ideally, diagnosing CKD must provide both functional and structural information in detail [5]. A deranged level of serum creatinine for months to years is indicative of CKD. Based on kidney damage, the extent of CKD is termed by the decrease in GFR (i.e., <60 ml/min per 1.7 m2 for over three months [6]. With regard to the structural function of the kidney, the most commonly used modality is ultrasonography. It is a non-invasive and inexpensive technique that shows sufficient anatomy of the kidneys that is required for diagnosing kidney diseases without any exposure of the patient to contrast or radiation [7]. Therefore, U/S has become the standard radiological procedure of choice worldwide. Such factors tend to promote detecting CKD early and predict derangement of kidney function tests necessary for making a clinical diagnosis [8]. U/S helps to identify the length of the kidney, its thickness, and the echogenicity of the renal parenchyma in addition to details of the dilated collecting system [9]. The details help in assisting in identifying the extent of damage to renal parenchyma and reversibility. The decision to perform a renal biopsy depends on the extent of damage. Literature states U/S reports abnormal renal findings in as high as 67 % of cases with CKD [10]. The morphology of the kidney can be assessed by various means, such as by measurement of renal length, volume, and cortical thickness [11]. The function of the kidneys can be estimated via renal length and cortical thickness. Through assessment of these functions, clinical decisions can easily be made [12]. Serial ultrasonography findings can help in assessing the progression of renal diseases or their normality [13]. Even though the volume of renal parenchyma is relatively accurate, especially in end-stage kidney diseases, measuring the kidney's longitudinal length is enough for patients with normal or abnormal kidney function [14]. Some studies have reported that the calculation of renal volume via ultrasound provides a more exact measurement of functioning kidney compared to renal length. Recently, a study reported length of the kidney and volume substantially correlated with the estimated GFR [15]. In CKD patients, cortical echogenicity tends to increase at U/S. Additionally, the renal cortex seldom becomes thinned [16]. To date, the relationship in-between the function of the kidneys and cortical thickness has not been well established in terms of U/S for structural integrity of kidneys and serum creatinine for functional evaluation of the kidneys [17].

Chronic kidney disease (CKD) requires integrated evaluation of both functional and structural renal parameters; however, the relationship between biochemical markers such as serum creatinine and sonographic parameters like cortical thickness and renal echogenicity remains inadequately defined. Most existing studies have assessed these variables independently, with limited data examining their combined association in a single analytical framework. Furthermore, region-specific evidence from Southern Punjab is scarce. Therefore, there is a need to clarify the correlation between serum creatinine, cortical thickness, and renal echogenicity to enhance diagnostic and prognostic assessment in CKD patients. The present study aimed to determine the association between serum creatinine and cortical thickness with renal echogenicity on ultrasound in patients with CKD.

## METHODS

This cross-sectional analytical study was conducted in the Departments of Radiology and Biochemistry, Shahida Islam Medical & Dental College, Lodhran, over six months (June–November 2024), after obtaining ethical approval from the Institutional Review Board of Shahida Islam Medical Complex (IRB No. SIMC/ET.C./00030/24). All patients referred for renal ultrasonography with serum creatinine and serum urea tested on the same day were eligible. Non-probability consecutive sampling was used. Informed consent was obtained from all participants. Inclusion criteria were male and female patients aged >18 years presenting for chronic kidney disease (CKD) workup or known CKD with GFR <60 ml/min/1.73m$^2$, calculated using the Modification of Diet in Renal Disease (MDRD) equation. Exclusion criteria were patients with acute kidney injury, on hemodialysis or peritoneal dialysis, renal transplant recipients, those with chronic liver disease, fatty liver, or solitary kidney. Sample size was calculated using OpenEpi, based on a local prevalence of CKD (21.2%), 95% confidence interval, and 5% margin of error, resulting in 257 subjects [18]. Serum creatinine and urea were measured using an automated chemistry analyzer (Roche Cobas c311 or equivalent) via an enzymatic colorimetric method. Renal ultrasound was performed using a GE LOGIQ P5 system with a 3.5–5.5 MHz curved array transducer, utilizing low tissue harmonic and speckle reduction imaging. Manual gain and time-gain compensation were optimized. Kidney length, width, and cortical thickness were measured in the largest longitudinal and transverse sections. Renal echogenicity was compared with adjacent liver and spleen and graded as follows: Grade 0 (Normal): Cortex hypoechoic or isoechoic vs. liver/spleen, preserved corticomedullary differentiation (CMD). Grade 1: Cortex isoechoic to liver/spleen, CMD preserved. Grade 2: Cortex mildly hyperechoic, partial CMD loss. Grade 3: Cortex markedly hyperechoic, poor/absent CMD. Grade 4: Cortex markedly hyperechoic with complete CMD loss, indistinct renal architecture [9]. Data were analyzed using SPSS

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version 23.0. Quantitative variables (age, kidney size, cortical thickness) were presented as mean ± SD, while categorical variables (echogenicity grades) were expressed as frequency and percentage. One-way ANOVA was applied to assess associations between serum creatinine, cortical thickness, and renal echogenicity. Normality of data was confirmed using the Shapiro-Wilk test (p=0.51). A p-value <0.050 was considered statistically significant.

## RESULTS

From the total of 257 patients, the baseline demographics and laboratory values of patients included in the study are presented in Table 1. The mean age of participants was 52.26 ± 12.50 years (95% CI: 39.76–64.76). The mean serum creatinine was 2.11 ± 1.2 mg/dL (95% CI: 0.58–3.31), while the mean serum urea was 64.25 ± 15.75 mg/dL (95% CI: 48.5–80), both elevated beyond normal ranges, consistent with chronic kidney disease. The mean longitudinal kidney length was 9.25 ± 1.1 cm (95% CI: 8.15–10.35), parenchymal thickness was 4.88 ± 0.92 cm (95% CI: 3.96–5.80), and cortical thickness was 0.82 ± 0.24 cm (95% CI: 0.61–1.11) (Table 1).

**Table 1:** Baseline Demographics of Patients Included in the Study (N=257)

| Variables | Mean ± SD | 95 % Confidence Interval | |
|---|---|---|---|
| | | Lower Limit | Upper Limit |
| Age (years) | 52.26 ± 12.50 | 39.76 | 64.76 |
| Serum Creatinine (mg/dL) | 2.11 ± 1.2 | 0.58 | 3.31 |
| Serum Urea (mg/dL) | 64.25 ± 15.75 | 48.5 | 80 |
| Longitudinal Length (cm) | 9.25 ± 1.1 | 8.15 | 10.35 |
| Parenchymal Thickness (cm) | 4.88 ± 0.92 | 3.96 | 5.80 |
| Cortical Thickness (cm) | 0.82 ± .24 | 0.61 | 1.11 |

A progressive increase in serum creatinine was noted with higher echogenicity grades. Patients with Grade 0 echogenicity had a mean serum creatinine of 0.91 ± 0.77 mg/dL (95% CI: 0.58–1.22), while those with Grade 4 had the highest mean of 2.81 ± 0.99 mg/dL (95% CI: 1.56–3.31). The association was statistically significant ($p < 0.001$), indicating a strong correlation between worsening echogenicity and elevated serum creatinine (Table 2).

**Table 2:** Association of Serum Creatinine with Cortical Echogenicity of Kidneys (N=257)

| Grading of Echogenicity (Based on U/S) | Serum Creatinine (mg/dL) | | | p-Value |
|---|---|---|---|---|
| | Mean ± SD | 95 % Confidence Interval | | |
| | | Lower Bound | Upper Bound | |
| Grade 0 (n=74) | 0.91 ± 0.77 | 0.58 | 1.22 | <0.001 |
| Grade 1 (n=61) | 1.88 ± 0.87 | 0.82 | 2.1 | |
| Grade 2 (n=58) | 2.26 ± 0.95 | 1.2 | 2.56 | |
| Grade 3 (n=44) | 2.54 ± 0.96 | 1.33 | 2.64 | |
| Grade 4 (n=20) | 2.81 ± 0.99 | 1.56 | 3.31 | |

Patients with Grade 0 echogenicity had the highest cortical thickness of 1.11 cm, while those with Grade 4 showed the lowest, at 0.71 ± 0.10 cm (95% CI: 0.66–0.72). A steady decrease in mean cortical thickness was observed from Grade 1 (1.02 ± 0.067 cm) to Grade 3 (0.81 ± 0.14 cm), with a significant trend ($p<0.001$), suggesting cortical thinning correlates with more advanced renal parenchymal changes (Table 3).

**Table 3:** Association of Cortical Thickness with Cortical Echogenicity of Kidneys (n=257)

| Grading of Echogenicity (Based on U/S) | Cortical Thickness (cm) | | | p-Value |
|---|---|---|---|---|
| | Mean ± SD | 95 % Confidence Interval | | |
| | | Lower Bound | Upper Bound | |
| Grade 0 (n=74) | 1.11 | 1.11 | 1.11 | <0.001 |
| Grade 1 (n=61) | 1.02 ± 0.067 | 0.98 | 1.06 | |
| Grade 2 (n=58) | 0.92 ± 0.13 | 0.83 | 0.99 | |
| Grade 3 (n=44) | 0.81 ± 0.14 | 0.77 | 0.95 | |
| Grade 4 (n=20) | 0.71 ± 0.1 | 0.66 | 0.72 | |

## DISCUSSION

The results of this study showed that of 257 patients with chronic kidney disease, the mean serum creatinine and urea levels were elevated at 2.11 ± 1.2 mg/dL and 64.25 ± 15.75 mg/dL, respectively. Kidney ultrasound findings showed a mean cortical thickness of 0.82 ± 0.24 cm and a mean longitudinal length of 9.25 ± 1.1 cm. A statistically significant increase in serum creatinine and a decrease in cortical thickness were observed with higher grades of cortical echogenicity ($p<0.001$), indicating a strong association between biochemical deterioration and structural kidney damage. The ultrasound findings reported in this research, for instance, echogenicity, longitudinal length, cortical and parenchymal thickness, all parameters tend to be affected by CKD. In addition, GFR and grading of disease (stage) can be determined by assessing endogenous levels of serum creatinine [19]. According to Kovesdy, the normal upper limit of the length of the kidney was recorded at 12 cm, while in our research, the mean longitudinal length was 9.25 ± 1.1 cm [20]. In another research by Roy and Pal, the length of the kidney below 8 cm was defined as reduced length and was attributed to CKD [21]. As the length of the kidney decreased, renal function was also observed to decline along with renal length. This is traditionally attributed to CKD [22]. A similar finding was reported in our study as well, where both cortical thickness and serum creatinine were significantly associated with renal echogenicity in CKD patients. Therefore, in determining the progression of CKD, estimating renal length must be preferred to renal volume. In addition, assessing levels of serum creatinine can also aid in the assessment of disease progression [22]. The mean serum creatinine levels observed in our research, according to the grade of renal echogenicity on U/S, were found to be in line with other studies. Wang *et al.* study found a substantial association ($p<0.050$) between the parameters [23].

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Ammirati *et al.* observed values ($p<0.050$) similar to those in our study [24]. Serum creatinine levels have long been used to assess kidney function, not only in CKD but also in other kidney-related disorders. In our study, the mean cortical thickness was 8.2 ± 2.4 mm and showed a significant association with renal echogenicity grades ($p<0.001$). Similar to our findings, other researchers have also reported increased renal echogenicity with decreased cortical thickness [25]. Although our study included CKD patients with varying grades of renal echogenicity, it was not without limitations. Being single-centered with a limited sample size, the findings may not be generalizable, and observer bias could not be fully excluded. Nonetheless, the study highlights important ultrasound parameters associated with both structural (cortical thickness) and functional (serum creatinine) aspects of kidney function.

This study was limited by its single-center design and cross-sectional nature, which restrict causal inference and generalizability. Interobserver variability in ultrasound measurements could not be completely excluded. Additionally, long-term renal outcomes and progression to end-stage renal disease were not assessed. Future multicenter longitudinal studies incorporating serial ultrasound evaluation and extended follow-up are recommended to better establish the prognostic value of cortical thickness and echogenicity in CKD progression.

## CONCLUSIONS

This study demonstrated a significant association between elevated serum creatinine and cortical thickness with renal echogenicity on ultrasound in CKD patients. Ultrasonographic parameters can serve as reliable indicators of renal function and disease progression.

## Authors' Contribution

Conceptualization: MI
Methodology: MFA, NM
Formal analysis: NM, SA
Writing and Drafting: MFA, SA, SSS, KA
Review and Editing: MFA, SA, SSS, KA, NM, MI

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Safety and Efficacy of Spinal Anaesthesia for Ureteroscopy and in Situ Lithotripsy in Proximal Solitary Pelvic Stones

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## ABSTRACT

Ureteroscopy and in situ lithotripsy provide an alternative treatment for patients with proximal solitary pelvic stones, but their safety and efficacy using spinal anesthesia are poorly studied. **Objectives:** To evaluate the safety, efficacy and patient satisfaction with spinal anesthesia during these procedures. **Methods:** A single-arm, prospective observational study was conducted at Islam Medical College, Sialkot, from May to October 2024, involving a total of 81 patients aged 20 to 60 years, ASA class I to III, who underwent elective ureteroscopy or lithotripsy. 15 mg of 0.75% bupivacaine was used to perform spinal anesthesia at the L3-L4 interspace. The main endpoints were success, complications, recovery times, and patient satisfaction. Other secondary outcomes were intraoperative hypotension, bradycardia, pain as measured by visual analogue scale (VAS) and post-dural puncture headache (PDPH). SPSS version 26.0 was used for statistical analysis. **Results:** A total of 97.5% patients completed the procedure under spinal anesthesia. The mean procedure time was 37.4 ± 6.2 min. In 53.1% of patients, the maximum sensory blockade level was T6. Hypotension (14.8%), bradycardia (6.2%), and PDPH (2.5%) were the complications. Next, postoperative pain significantly decreased over the 24 hours. In 55.6% of patients, excellent satisfaction was observed. Mean recovery time was 165.3 ± 22.4 minutes. **Conclusions:** Overall, spinal anesthesia for ureteroscopy and in situ lithotripsy in patients with proximal solitary pelvic stones is safe, effective, and has a high patient satisfaction rate.

## INTRODUCTION

Endoscopic management of ureteral stones is a commonly encountered urological problem worldwide, and the proximal ureter is a difficult site [1, 2]. Proximal solitary pelvic stones are now routinely treated with an intact URS with in situ lithotripsy using a minimally invasive procedure [3, 4]. There have traditionally been preferred anaesthetic techniques for these procedures, general anesthesia (GA), because it can provide controlled airway, muscle relaxation, and patient immobility [5, 6]. Although regional anesthesia (RA) for ureteroscopy has been largely abandoned due to the risks associated with hypotension and the general enthusiasm for general anesthesia, recent advances in anaesthetic techniques and growing experience with spinal anesthesia have encouraged rethinking the use of RA as a safe and effective alternative [7, 8]. Several advantages of spinal anesthesia are reduced anesthesia-related complications, early postoperative recovery, and shorter hospital stays as well as cost

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effective [9]. However, while spinal anesthesia in urological procedures such as transurethral resection of the prostate (TURP) and percutaneous nephrolithotomy (PCNL) has been extensively utilized, the efficacy in proximal ureteroscopy regarding patient safety, intraoperative events and postoperative outcomes has not been fully explored [10, 11]. Several studies have evaluated the use of spinal anesthesia for distal ureteric stones and other lower urinary tract procedures. Still, there is no clinical evidence regarding the use of spinal anesthesia for proximal solitary pelvic stones treated with ureteroscopy and in situ lithotripsy. Few published studies address the question of the comparison of general anesthesia and spinal anesthesia with respect to perioperative characteristics of patients and patient satisfaction with this anesthesia method used in this setting. This study evaluated spinal anesthesia as an alternative single anesthetic technique for ureteroscopy and in situ lithotripsy in proximal solitary pelvic stones, focusing on intraoperative events and postoperative outcomes.

Although general anesthesia remains the preferred technique for ureteroscopy and in situ lithotripsy in proximal solitary pelvic stones, concerns regarding anesthesia-related complications, delayed recovery, and cost burden persist. While spinal anesthesia has demonstrated favorable outcomes in other urological procedures, its safety, efficacy, and patient satisfaction profile specifically for proximal ureteric and solitary pelvic stones remain insufficiently explored. Existing literature largely focuses on distal ureteric stones or compares anesthesia techniques without dedicated evaluation of spinal anesthesia as a sole approach in this subset. Therefore, evidence addressing perioperative safety, recovery characteristics, and patient-centered outcomes in this setting is limited. This study aims to evaluate the safety, efficacy and patient satisfaction with spinal anesthesia during these procedures.

## METHODS

This single-arm, prospective observational study was conducted at Islam Medical College, Sialkot, from May 2024 to October 2024. A total of 81 participants were included in the study. The study followed ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board of Islam Medical College, Sialkot (900/IMC/ERC/000103). All the participants provided written informed consent after a briefing of the nature, objectives, procedures and possible risks of the study. Throughout the research, patient confidentiality and data protection were at great attention. The sample size for this study was calculated based on the primary outcome of successful completion of ureteroscopy under spinal anaesthesia. Previous studies have reported success rates of spinal anaesthesia in ureteroscopy ranging from 90% [12]. Assuming an expected success rate of 90%, a 95% confidence level (Z = 1.96), and a margin of error of 4%, the minimum required sample size was calculated using the formula for estimating a single proportion: n=Z2·p·(1-p)d2 = 81 [12]. The study used a non-probability purposive sampling technique. Patients aged between 20 and 60 years, with ASA (American Society of Anesthesiologists) class I, II, or III, and scheduled for elective ureterorenoscopy or lithotripsy for upper ureteric or solitary pelvic stones, were included in the criteria. Obesity, spinal deformity, mental disturbance, neurological disorder, and patients with multiple renal calculi or whose calculi involved the pelvic ureteric junction were the exclusion criteria. The night before surgery, each patient received oral diazepam 5 mg and continued on any ongoing medical treatment. One liter of intravenous fluids was preloaded in the patients before the procedure. Blood pressure, pulse rate, oxygen saturation, and ECG were used with a 5-minute recording interval. The patient was sat up and spinal anesthesia was administered at L3-L4 interspace with 25G Whitacre needle. After confirmation of clear cerebrospinal fluid flow, 15 mg of 0.75% bupivacaine was injected intrathecally for all patients, regardless of their individual body weight. Stone size and side: These were obtained from preoperative imaging (ultrasound and non-contrast CT, where available. Ultrasound examinations were performed using a GE Healthcare LOGIQ P9 system with a 3.5–5 MHz convex transducer, while non-contrast CT scans were acquired on a Siemens SOMATOM Definition AS 64-slice scanner. All anaesthetic procedures were undertaken by a single experienced anesthetist. Intraoperative hypotension was defined as SBP less than 90 mmHg or a fall of 50 mmHg from baseline and was managed by IV fluids and plasma expanders. Bradycardia was documented as HR <50 bpm or 20 % drop from baseline, and treated with 0.5mg intravenous atropine. The other adverse events, such as vomiting, were also addressed accordingly. The sensory block level was assessed using the pinprick method on the midclavicular line at 5, 10, 20, and 30 minutes after the anaesthetic injection, at the end of the operation, and 2 hours after the operation. Hip flexion (L2) and knee extension (L3) were used to evaluate motor block. The Visual Analogue Scale (VAS) was used for pain measurement. Postoperative pain was assessed using the Visual Analogue Scale (VAS, 0–10; 0 = no pain, 10 = worst imaginable pain) [13]. The highest sensory block level (ranging from T10 to T4) was determined. The same urologist performed all surgical procedures with an average surgical duration of 30 to 45 minutes. Postoperatively, pain was managed with intravenous nalbuphine 0.1 mg/kilogram at the conclusion

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of the procedure and intramuscularly every eight hours with ketorolac 100 mg intramuscularly. Safety was evaluated through intraoperative hemodynamic stability (hypotension, bradycardia), intra- and postoperative complications (nausea/vomiting, PDPH, bleeding, urinary retention), and the ability to manage these events conservatively. Efficacy was assessed by procedural success rate (completion of ureteroscopy and lithotripsy under spinal anesthesia without conversion to GA), adequacy of sensory and motor block, procedure time, postoperative analgesia (VAS), and time to recovery and discharge. The statistical analysis was carried out using SPSS version 26.0. Age, stone size, procedure time, time to recovery, and discharge were measured as mean ± standard deviation (SD) of quantitative variables. Gender, ASA class, sensory block level, complications and procedural success rate were presented in quantities and percentages of categorical variables. Pearson's correlation test was used to assess the relationship between motor recovery time and time to discharge, with a significant statistical significance of p≤0.050. The demographic data, in addition to intraoperative efficacy, safety outcomes, postoperative pain scores, recovery times and patient satisfaction, were summarized in tabular form.

## RESULTS

This study enrolled a total of 81 patients with a mean age of 42.3 ± 9.5 years. The sample was predominantly of male patients (69.1%), while female patients (30.9%) constituted the rest. Classes I, II, and III, in regard to ASA classification, were 37%, 43.2%, and 19.8%, respectively. The average stone size was 9.2 ± 3.4 mm and was nearly even between the right (53.1%) and left (46.9%) sides (Table 1).

**Table 1:** Demographics and Baseline Characteristics

| Parameters | Value |
|---|---|
| **Age (Years)** | |
| Mean ± SD | 42.3 ± 9.5 |
| **Gender** | |
| Male | 56 (69.1%) |
| Female | 25 (30.9%) |
| **ASA Class** | |
| Class I | 30 (37%) |
| Class II | 35 (43.2%) |
| Class III | 16 (19.8%) |
| **Stone Size (mm)** | |
| Mean ± SD | 9.2 ± 3.4 |
| **Stone Side** | |
| Right | 43 (53.1%) |
| Left | 38 (46.9%) |

Out of the cases, 97.5 % were completed under spinal anesthesia. The mean procedure time was 37.4 (6.2) minutes. In 53.1% of the patients, the maximum sensory block was achieved at the T6 level, 24.7% at the T8, 14.8% at the T4, and 7.4% at the T10 level. The respective mean time to motor block recovery was 165.3 ± 22.4 minutes; the mean time to discharge from the recovery area was 198.6 ± 30.5 minutes (Table 2).

**Table 2:** Efficacy Outcomes (n=81)

| Outcomes | Value |
|---|---|
| Procedure Completed Under Spinal, n (%) | 79 (97.5%) |
| Procedure Time (min), Mean ± SD | 37.4 ± 6.2 |
| **Maximum Sensory Block Level** | |
| T4 | 12 (14.8%) |
| T6 | 43 (53.1%) |
| T8 | 20 (24.7%) |
| T10 | 6 (7.4%) |
| Time to Motor Block Recovery (min), Mean ± SD | 165.3 ± 22.4 |
| Time to Discharge from Recovery (min), Mean ± SD | 198.6 ± 30.5 |

The Visual Analogue Scale (VAS) postoperative pain did not exceed low levels throughout the first 24 hours. In 2 hours, the mean VAS score was 2.4 ± 1.1, rose slightly to 3.6 ± 1.2 in 8 hours, and dropped to 2.2 ± 1.0 by 24 hours. There was this apparent trend, which was statistically significant (p<0.001) (Table 3).

**Table 3:** Postoperative VAS Pain Scores

| Time Point (Hours) | Mean VAS ± SD |
|---|---|
| 2 | 2.4 ± 1.1 |
| 4 | 2.9 ± 1.3 |
| 8 | 3.6 ± 1.2 |
| 12 | 3.1 ± 1.5 |
| 24 | 2.2 ± 1.0 |
| p-value | <0.001* |

It was found that there was a strong positive correlation between motor recovery time and discharge timing (r=0.72, p=0.011). Quick motor recovery leads to earlier discharge (Table 4).

**Table 4:** Time to Recovery and Discharge (Reformatted)

| Parameters | Value | p-Value |
|---|---|---|
| Mean Time to Motor Recovery (minutes) | 85.4 ± 10.3 | — |
| Mean Time to Discharge (minutes) | 135.2 ± 22.1 | — |
| Correlation between Recovery and Discharge | r=0.72 | 0.011 |

Complications intraoperative and postoperative were minimal and managed. 14.8% of patients had hypotension, 6.2% had bradycardia, and 9.9% nausea or vomiting. Out of these, only 2.5% suffered post-dural puncture headache (PDPH); urinary retention was not seen amongst any; and only one (1.2%) sustained bleeding (Figure 1).

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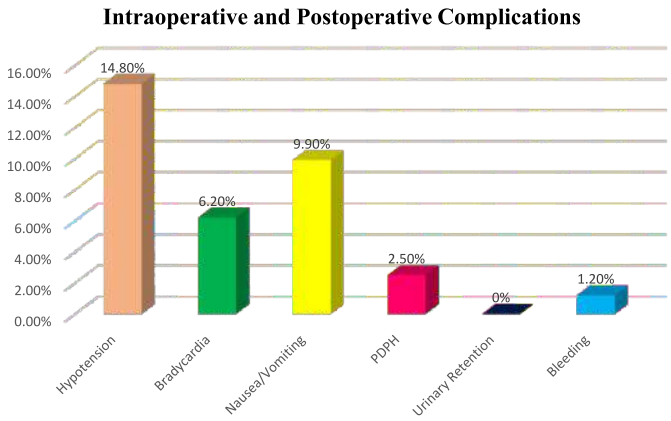


**Figure 1:** Intraoperative and Postoperative Complications

The high rate of patient satisfaction was reflected in rating results: 55.6% gave the experience excellent, 34.6% good, and 9.9% were fair. Although individuals in this setting did not have a poor experience with spinal anesthesia for ureteroscopy and in situ lithotripsy, the overall safety, effectiveness, and patient acceptability of spinal anesthesia in this setting are evident (Figure 2).

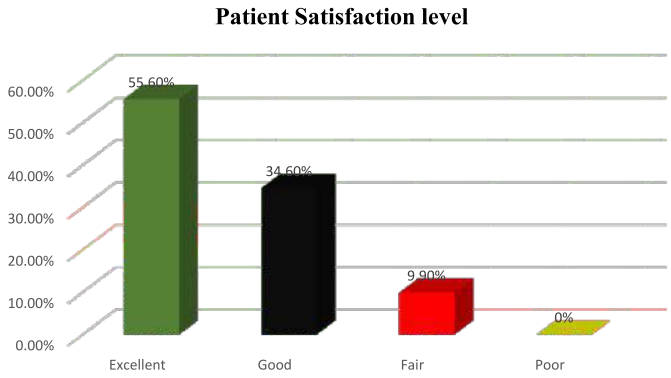


**Figure 2:** Patient Satisfaction

## DISCUSSION

This study confirms that spinal anesthesia is a safe and effective means of rendering patients anaesthetized for ureteroscopy and in situ lithotripsy for proximal solitary pelvic stones. In 97.5% of cases, the procedure was performed under spinal anesthesia and was associated with few intraoperative and postoperative complications. These results are consistent with previous studies, which have reported that spinal anesthesia is safe and efficacious for urological surgeries [14]. The procedure time was found to be 37.4 ± 6.2 minutes, consistent with previous reports. For instance, other studies investigating the use of spinal anesthesia in patients undergoing similar urological procedures, Iqbal *et al.* provided an average procedure time of about 40 minutes [15]. The relatively short duration of the procedure decreases the risk of complications and further enhances potential patient outcomes [16]. In our study, the maximum sensory block level was at T6, being 53.1%, with some sensory blocks reaching up to T4. The levels are similar to those reported by Varghese *et al.* who showed most patients received T6 to T8 sensory block during a similar urological intervention [17]. Spinal anesthesia is effective in achieving an adequate sensory block to allow a successful procedure to be completed by means of patient comfort and adequate surgical conditions [18, 19]. Our study demonstrates intraoperative complications of hypotension (14.8%) and bradycardia (6.2%). The rates were relatively low in comparison to the 22% incidence of hypotension reported by Hernandez *et al.* in patients undergoing spinal anesthesia for urological procedures [20]. This lower rate could, however, be explained by closely monitoring the patients' vital signs and being ready to treat patients with hypotension promptly with intravenous fluids and plasma expanders. Moreover, unlike other studies on spinal anesthesia, spinal anesthesia by us did not cause any cases of urinary retention, a complication commonly observed in spinal anesthesia (specifically, in the immediate postoperative period), where other studies, e.g. Mormol *et al.* report urinary retention in patients 5% [21]. Current study showed similar postoperative recovery as in previous studies. Overall, the mean time to motor block recovery was 165.3 ± 22.4 minutes, which is not different from what is typical, reported by Prabhakar *et al.* to be approximately 160 minutes after spinal anesthesia for urological procedures [22]. The mean time to discharge from the recovery area was 198.6 ± 30.5 minutes, which is also in line with Chitnis *et al.* for patients having comparable procedures conducted under spinal anesthesia [23]. Our study showed that the postoperative VAS pain scores in regard to pain management were low, and a significant decline in the pain intensity was observed in the first 24 hours. There was very little difference from Zhou *et al.* who noted moderate pain at the 8-hour mark and then decreasing pain intensity over time. In our study, the intravenous nalbuphine and intramuscular ketorolac allowed for adequate pain control, and are supportive of previous studies in which multimodal analgesia has been deemed the most effective method for relief of post-surgical pain [24]. Regarding patient satisfaction, 55.6% of our participants graded the procedure excellent compared to Neuman *et al.* who reported that 52% of patients graded their experience with spinal anesthesia for urological procedures as excellent [25]. In current study, a high level of satisfaction was found, showing that spinal anesthesia is a safe and effective means of providing anesthesia that patients tolerated well. Given this finding, spinal anesthesia for ureteroscopy and lithotripsy should be a reasonable alternative to general anesthesia because the patients reported better comfort and satisfaction [26].

This study has certain limitations, including its single-center design, relatively small sample size, and absence of

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a comparative general anesthesia control group, which may limit the generalizability of findings. Additionally, long-term outcomes such as stone recurrence, delayed complications, and extended patient-reported satisfaction were not assessed. Future multicenter randomized controlled trials with larger populations and direct comparisons between spinal and general anesthesia are recommended to strengthen the evidence base and establish standardized anesthesia protocols for proximal ureteroscopic procedures.

## CONCLUSIONS

Spinal anesthesia for ureteroscopy and in situ lithotripsy in patients with proximal solitary pelvic stones was concluded to be a safe, effective and well-tolerable procedure. The outcomes of this experiment are consistent with prior studies; therefore, spinal anesthesia could still be utilized for these procedures. Considering the good results, further investigation into optimization strategies and large-scale studies would be useful in proving spinal anesthesia as the preferred technique for anesthesia in this setting.

## Authors' Contribution

Conceptualization: SA
Methodology: SS, RHKN, AAC
Formal analysis: SS, HFA
Writing and Drafting: RHKN, AAC, IHK
Review and Editing: RHKN, AAC, IHK, SS, HFA, SA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Comparing the Efficacy of Microscopic Tympanoplasty (MT) and Endoscopic Tympanoplasty (ET) For Tympanic Membrane and Middle Ear Surgery

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## ABSTRACT

Endoscopic tympanoplasty and microscopic tympanoplasty is performed to restore hearing. But ET superior to MT as it less invasive. **Objective:** To evaluate the comparative efficacy of endoscopic tympanoplasty vs microscopic tympanoplasty for middle ear and tympanic membrane surgery. **Methods:** A prospective, quasi-experimental study was conducted in the ENT and Surgical Department of Bakhtawar Amin Memorial Trust Hospital, Multan from 15th October 2024 to 15th May 2025. A total of 100 adult patients undergoing type 1 endoscopic tympanoplasty or microscopic tympanoplasty were selected for the study by convenience sampling. Preoperative and postoperative air conduction, air bone gap and bone conduction were measured by pure tone. Picture archiving and communication system was used to perform preoperative speech audiometry to measure the perforation size. **Results:** The average surgery duration in endoscopic group was 79.23 ± 11.97 minutes and in microscopic group was 93.05 ± 19.81, which was significantly longer than the former ($p<0.001$). The length of hospital stay was also significantly short in endoscopic group (4.44 ± 1.11 min) due to less postoperative pain and minimally invasive procedure than microscopic group (8.09 ± 1.27 min) ($p<0.001$). On follow up, 5 (10%) patients in endoscopic group and 6 (12%) patients had a re-perforation ($p=1.0$). There was no significant difference between incidence of otorrhea (6% vs 12%, $p=0.360$) and pain (4% vs 2%, $p>0.050$). **Conclusions:** The audiological outcomes between type 1 endoscopic tympanoplasty and microscopic tympanoplasty were similar. However, surgical duration and length of hospital stay was better in endoscopic group.

## INTRODUCTION

Tympanoplasty is common procedure performed to repair the tympanic membrane and middle ear for prevention of infection and hearing restoration. It is performed with the help of microscopes or endoscope to reconstruct the damages the hearing mechanism. Although endoscopes were previously employed for diagnosis and visualization only, at present, they are a major part of middle ear procedures performed for cochlear implants, otitis media and otosclerosis [1, 2]. When comparing both procedures, endoscopic tympanoplasty is superior to microscopic tympanoplasty as it less invasive, achieves favorable cosmetic outcomes and patients have reduces pain after the procedure [3, 4]. Although a relatively incision is made, it allows for a wider viewing plane for operating. It also provides an advantage to explore the direct view of the regions inaccessible by microscope such as sinus tympani, epi-tympanic space and fascial recess. However, endoscopic procedure has several limitations [5]. It does not provide a three-dimensional view unlike microscopic technique that determines the depth of structures. Secondly, only one hand of surgeons is actively involved in surgery while the other hand holds the endoscope which

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make the finer movements difficult. Lastly, the success of this procedure depends on ample practice and experience of surgeon to master it [6]. Previous studies conducted to compare the outcomes of these techniques involved performance of surgery by multiple surgeons which yielded variable results [7]. Additionally, most of these studies only focuses on hearing outcomes. In this study it was included that surgeries performed by three surgeons, experienced in both techniques, to limit the variability, excluded learning curve as confounding factor and evaluate a more controlled comparison. Additional surgical parameters were included such as frequency of complications, graft success rates, operative time and duration of hospital stay.

Despite increasing adoption of endoscopic tympanoplasty due to its minimally invasive nature, limited local evidence exists comparing its efficacy with microscopic tympanoplasty in the Pakistani population under standardized surgical expertise. Previous studies often involved multiple surgeons with varying skill levels, focused mainly on hearing outcomes, and inadequately assessed operative efficiency, complication rates, and hospital stay. This study aimed to provide a controlled comparison of endoscopic versus microscopic tympanoplasty by evaluating audiological improvement, graft success, surgical duration, postoperative complications, and recovery outcomes to determine the overall comparative effectiveness of both techniques. This study was conducted to evaluate the comparative efficacy of endoscopic tympanoplasty vs microscopic tympanoplasty for middle ear and tympanic membrane surgery.

## METHODS

A prospective-quasi-experimental study was conducted in the ENT and Surgical Department of Bakhtawar Amin Memorial Trust Hospital, Multan from 15th October 2024 to 15th May 2025. A total of 100 adult patients undergoing type 1 endoscopic tympanoplasty or microscopic tympanoplasty without ossicular reconstruction were selected for the study by convenience sampling. The sample size was calculated by G power software for detecting a difference in postoperative air-bone gap reduction between groups keeping 0.8 power of test, 95% confidence interval, 0.05 statistical significance and a minimum effect size of 5 decibels as in Saini *et al* [8]. Patients with a previous history of otitis media surgery or mastoidectomy and those who could not attend follow-up for a minimum of 3 months were excluded.The study was approved by The Ethical Review Board was approved the study by Ref No.3437/BAMTH dated 10th Oct 2024. Patients were divided into two groups based on the surgical technique performed; endoscopic group and microscopic group. Preoperative and postoperative air conduction was measured by pure tone audiometry at frequencies 125, 250, 500, 1000, 2000, 3000, 4000 and 8000 Hz along with air bone gap at 500, 1000, 2000 and 4000 Hz and bone conduction at 250, 500, 1000, 2000, 3000 and 4000 Hz. Preoperative speech audiometry was performed and tympanic membrane perforation size was estimated from endoscopic or microscopic images retrieved from the PACS system. The relative perforation size was quantified as a of the total tympanic membrane area using image-based analysis. To limit selection bias, all surgeries were percentage conducted by three surgeons with over 5 years' experience in both techniques to standardize technical performance [9]. The endoscopic procedure was performed by making endomeatal incisions to elevate the tympanomeatal flap and the microscopic procedure was performed through traditional postauricular route. All patients were administered local infiltration anesthesia using 0.01 mg/mL epinephrine in 2% lidocaine to minimize bleeding. Grafts in endoscopic group were taken from tragal perichondrium and in microscopic group from temporalis fascia. Before making incisions, perforation margins were scarified. A 10 mm tympanomeatal flap elevation was done lateral to tympanic annulus. Keeping the chorda tympani nerve intact, annulus was detached from the tympanic sulcus to reach the middle ear and assess mobility and integrity of ossicles. Grafts were placed in the middle ear space by underlay technique between manubrium mallei and fibrous annulus supported by Wet Cutanplast to prevent medial migration. Dry Cutanplast in external ear canal was used to support healing and aid fixation. Tragal incisions were closed by unabsorbable sutures which were removed 1 week postoperatively. Cutanplast was removed 14 days after the surgery. The surgical site was covered with non-compressive dressing in endoscopic group and with postauricular compressive dressing in microscopic group. In the endoscopic group, the procedure was performed with the help of 3 mm rigid endoscope with 0- and 30-degree lenses connected to a 24-inch full monitor. Illumination was provided by Xenon light source and instrumentation was done using endoscope instrument for middle ear procedures. In microscopic group, surgical microscope was used to perform the procedures. All included patients completed a uniform minimum follow-up of 3 months. Follow-up visits were scheduled at 1 months, 3 months and 6 months postoperatively. The primary outcome variable was audiological improvement, measured by change in air-bone gap at 3 months postoperatively. Secondary outcomes included surgery duration, graft uptake, complication rates (re-perforation, otorrhea, otalgia), and hospital stay duration. Anatomical success was defined as intact graft on otoscopic examination. Functional success (air conduction, air bone gap) was defined as ≥10 dB improvement in ABG [10]. Data

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analysis was done by SPSS version 20.0. Categorical data (graft success, postoperative complications) was compared by chi-squared test while parametric data (surgery duration, hearing threshold) was evaluated by t-tests. Variables were calculated as mean ±SD. Baseline clinical variables were statistically compared to confirm intergroup comparability. The statistical significance was set at p<0.050.

## RESULTS

A total of 100 patients divided into endoscopic and microscopic group were included for analysis. The mean age in endoscopic group was 50.82 ± 13.02 years with 74% women while the mean age in microscopic group was 44.11 ± 16.58 with 50% women. The difference in gender was significant (p=0.050). The laterality, perforation location and size, anesthesia and revision rate were statistically similar between both groups, table 1.

**Table 1:** Patients' Baseline Characteristics(n=100)

| Variables | Endoscopic Group Mean ± SD / Frequency (%) | Microscopic Group Mean ± SD / Frequency (%) | p-Value |
|---|---|---|---|
| Mean age | 50.82 ± 13.02 | 44.11 ± 16.58 | 0.050 |
| **Gender** | | | |
| Male | 13 (26) | 25 (50) | 0.020 |
| Female | 37 (74) | 25 (50) | |
| **Laterality** | | | |
| Right | 23 (46) | 28 (56) | 0.530 |
| Left | 27 (54) | 22 (44) | |
| **Perforation Location** | | | |
| Anterior inferior quadrant | 40 (80) | 35 (70) | 0.320 |
| Posterior inferior quadrant | 10 (20) | 15 (30) | |
| **Anesthetic** | | | |
| General | 45 (90) | 49 (98) | 0.190 |
| Local | 5 (10) | 1 (2) | |
| Relative Perforation size | 14.15 ± 10.38 | 14.18 ± 10.77 | 0.880 |
| Revisions | 1 (2) | 2 (4) | 1.000 |

There was no significant difference between preoperative and postoperative audiological parameters among groups but there was significant improvement them postoperatively, table 2.

**Table 2:** Preoperative Audiological Parameters(n=100)

| Variables | Endoscopic Group Mean ± SD | Microscopic Group Mean ± SD | p-Value |
|---|---|---|---|
| **Operative Side** | | | |
| Mean air conduction | 39.31 ± 16.86 | 39.47 ± 20.43 | 0.840 |
| Mean bone conduction | 20.22 ± 14.37 | 19.88 ± 15.39 | 0.700 |
| Mean air bone gap | 20.09 ± 8.68 | 21.55 ± 10.33 | 0.480 |
| Speech discrimination score | 95.80 ± 10.41 | 94.54 ± 17.11 | 0.660 |
| Mean low tone | 48.64 ± 20.85 | 45.10 ± 15.06 | 0.330 |
| Mean high tone | 49.49 ± 22.29 | 50.86 ± 23.47 | 0.900 |
| **Contralateral Side** | | | |
| Mean air conduction | 24.60 ± 15.90 | 18.29 ± 13.58 | 0.060 |
| Mean bone conduction | 24.42 ± 12.02 | 25.08 ± 15.53 | 0.760 |
| Speech discrimination score | 99.09 ± 4.89 | 99.24 ± 5.86 | 0.060 |

Both endoscopic and microscopic tympanoplasty significantly improved air conduction and air-bone gap postoperatively (p<0.001 for both). Bone conduction changes were not statistically significant in either group. Low-tone hearing improved significantly, while high-tone changes were non-significant. There were no significant differences between the two groups in any audiological outcomes, indicating comparable hearing restoration efficacy, table 3.

**Table 3:** Comparison of Preoperative and Postoperative Hearing Thresholds

| Variables | Endoscopic Group | | | Microscopic Group | | | p-Value |
|---|---|---|---|---|---|---|---|
| | Preoperative Mean ± SD | Postoperative Mean ± SD | P | Preoperative Mean ± SD | Preoperative Mean ± SD | P | |
| Air conduction | 39.31 ± 16.86 | 30.41 ± 18.28 | <0.001 | 39.47 ± 20.43 | 30.31 ± 18.56 | <0.001 | 0.750 |
| Bone conduction | 20.22 ± 14.37 | 17.87 ± 12.73 | 0.42 | 19.88 ± 15.39 | 18.87 ± 12.34 | 0.83 | 0.530 |
| Air bone gap | 20.09 ± 8.68 | 10.36 ± 6.97 | <0.001 | 21.55 ± 10.33 | 11.83 ± 7.89 | <0.001 | 0.540 |
| Low tone | 48.64 ± 20.85 | 26.28 ± 20.86 | <0.001 | 45.10 ± 15.06 | 27.32 ± 15.94 | <0.001 | 0.270 |
| High tone | 49.49 ± 22.29 | 45.89 ± 19.43 | 0.25 | 50.86 ± 23.47 | 47.30 ± 26.85 | 0.24 | 0.810 |

Functional success was achieved in 44 (88%) patients in the endoscopic group and 43 (86%) in the microscopic group (p=0.780). The average surgery duration in endoscopic group was 79.23 ± 11.97 minutes and in microscopic group was 93.05 ± 19.81, which was significantly longer than the former (p<0.001). The length of hospital stay was also significantly short in endoscopic group (4.44 ± 1.11 min) due to less postoperative pain and minimally invasive procedure than microscopic group (8.09 ± 1.27 min) (p<0.001). On follow up, 5(10%) patients in endoscopic group and 6 (12%) patients had a re-perforation (p=1.000). There was no significant difference between incidence of otorrhea (6% vs 12%, p=0.36) and pain (4% vs 2%, p>0.050), Table 4.

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**Table 4:** Operative Parameters and Postoperative Complications

| Variable | Endoscopic Group Frequency (%) / Mean ± SD | Microscopic Group Frequency (%) / Mean ± SD | p-Value |
|---|---|---|---|
| Graft success rate | 45 (90) | 44 (88) | 1.000 |
| **Complications** | | | |
| Re-perforation | 5 (10) | 6 (12) | 1.000 |
| Otorrhea | 3 (6) | 6 (12) | 0.360 |
| Otalgia | 1 (2) | 2 (4) | 1.000 |
| Wound infection | - | - | 1.000 |
| Surgery duration (minutes) | 79.23 ± 11.97 | 93.05 ± 19.81 | <0.001 |
| Length of hospital stay (days) | 4.44 ± 1.11 | 8.09 ± 1.27 | <0.001 |

## DISCUSSION

Endoscopic approach for middle ear surgery is a more advantageous as it is less invasive and more visibility, however, it was not preferred by surgeons due to low resolution and poor imaging. These limitations were solved by new technology and updates in resolution systems but its longer learning curve and use of one hand during procedure are still major drawbacks. A study by Gkrinia *et al.*, favors the use of endoscope in events of limited visibility and when there is a suspected lesion in the tympanic canal [11]. It is also preferred to explore inaccessible structures of middle ear when there is risk of recurrence of lesions. However, hemorrhage or extensive bone removal, can obstruct the view of endoscope so it cannot fully replace the microscopic approach. This present study shows that there the audiological outcomes between endoscopic and microscopic procedure were similar but surgical duration and length of hospital stay was better in endoscopic group. Other studies also showed similar results [12, 13]. Yang *et al.*, also reported that type 1 endoscopic tympanoplasty has a shorter operative time, improved health outcomes and less discomfort [14]. But it yields similar graft success, hearing outcomes and improvement in air bone gap compared to microscopic tympanoplasty. The graft success rate was 45 (90%) in endoscopic group and 44 (88%) in microscopic group but the difference was not significant. Similarly, in Elnahal *et al.*, the difference between endoscopic group and microscopic group was insignificant (85% vs 86.4%) [15]. Zakir *et al.*, also showed no significant difference for graft success with a odds ratio of 0.70 (95% CI: 0.39-1.30, p=0.252), but the rate of recurrence was significantly higher microscopic surgery with odds ratio of 0.61 (95% CI: 0.42-0.88, p=0.005) [16]. In Ulkumen *et al.*, there were comparable results between both procedures for surgery duration (weighted mean difference: -20.08, 95% CI: -41.55-0.41), graft uptake rate (OR: 1.18, 95% CI: 0.79-1.83) and hearing outcomes (WMD: -1.22, 95% CI: -2.66-0.51) [17]. Gulsen *et al.*, reported different results as endoscopic tympanoplasty had a better pooled canaloplasty rate (OR: 8.02, 95% CI: 4.27-13.83, p=1) and cosmetic outcomes (OR: 20.35, 95% CI: 12.42-31.67, p=0.740) than microscopic tympanoplasty [18]. Hence, this literature indicates that endoscopic surgery is superior such as in terms of surgical duration and complications. As graft type was consistent within but not between groups, it was considered during interpretation of outcomes and may represent a potential confounding factor; however, both materials are widely used with comparable success in the literature. Similarly, since three surgeons had over five years of experience with both endoscopic and microscopic tympanoplasty and only patients who underwent type 1 tympanoplasty with no ossicular chain reconstruction were included, the surgeon skill and case complexity were not considered as confounding factors. It is integral to reduce the surgical duration to reduce the time under anesthetic which can consequently reduce complications. The surgical duration was significantly shorter in endoscopic group (79.23 ± 11.97 minutes vs 93.05 ± 19.81, p<0.001). This is similar to previous studies [19, 20].

This study has some limitations. The number of patients included was limited as only the cases handled by the authors were selected. Secondly, the follow-up was shorter and it was not possible to test the hearing simultaneously in all patients. Large studies preferably randomized studies are recommended to achieve specific results with a longer follow-up. Future research should involve larger multicenter randomized controlled trials with longer follow-up periods, standardized graft materials, and broader patient populations to better assess long-term hearing outcomes, recurrence rates, and procedural superiority.

## CONCLUSIONS

The audiological outcomes between type 1 endoscopic tympanoplasty and microscopic tympanoplasty were similar. However, surgical duration and length of hospital stay was better in endoscopic group.

## Authors' Contribution

Conceptualization: SB
Methodology: MMB, SJ
Formal analysis: IA, HS, SJ
Writing and Drafting: SB, AI
Review and Editing: SB, AI, HS, SJ, MMB

All authors approved the final manuscript and take responsibility for the integrity of the work

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## Conflicts of Interest

All the authors declare no conflict of interest.

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# Prevalence of Intradialytic Hypertension in Patients with End-Stage Renal Disease on Maintenance Hemodialysis

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## ABSTRACT

Intradialytic hypertension (IDH) is emerging as a relevant and recurrent problem in end-stage renal disease patients. This can result in escalated morbidity and even fatality in the event of this not being diagnosed promptly. **Objectives:** To determine the prevalence of intradialytic hypertension in end-stage renal disease (ESRD) patients on maintenance hemodialysis. **Methods:** This descriptive cross-sectional study included adult patients with end-stage renal disease (ESRD) on maintenance hemodialysis. Data on demographic and co-morbid conditions were noted. Six dialysis sessions were observed for each patient. Presence of >10 mmHg increases in systolic blood pressure between before and after the start of four out of six dialysis sessions was used to label IDH. Descriptive analysis was run, and the factors associated with IDH were compared through a chi-square test at 5% significance level. **Results:** The participants had a mean age of 48.03 ± 13.2 years, with females comprising 52.8% (n=76) of the total 144 patients. Hypertension emerged as the most frequent comorbidity, affecting 77.8% (n=112), while intradialytic hypertension (IDH) was identified in 19.4% (n=28) of cases. IDH showed a significant association with diabetes (30.9% vs. 12.4%, p=0.006) and was exclusively present in hypertensive patients (p=0.001). **Conclusion:** IDH is a relatively common occurrence and warrants careful monitoring, particularly among individuals with hypertension and diabetes mellitus.

## INTRODUCTION

Among the various comorbidities, hypertension (HTN) is commonly observed in patients undergoing continuous hemodialysis (HD) for end-stage kidney disease (ESKD). One contributing factor to this condition is the expansion of extracellular fluid volume in these patients [1]. For ESKD patients, this necessitates the use of pharmaceutical treatment and hydration management to control blood pressure (BP) [2]. Intradialytic hypertension (IDH) and hypotension are two of the blood pressure abnormalities that occur during dialysis treatment [3]. Improving Global Outcomes (KDIGO) guidelines define intradialytic hypertension (IDH) as a rise in systolic blood pressure exceeding 10 mm Hg within the hypertensive range from pre- to post-dialysis in at least four out of six consecutive dialysis sessions [4]. Peripheral vasoconstriction and excess extracellular volume are implicated in the pathogenesis of IDH [5]. In addition to these reasons, dialysate temperature, sodium profiling, dialysate calcium, sodium salinity, and ultrafiltration rate are some other risk factors that influence blood pressure during dialysis [6]. Because several risk factors are involved, the prevalence of IDH has fluctuated with the passage of time and across different regions of the world. Recent studies show a frequency of 81.8% in India [7] and 17% in Pakistan [8]. From Karachi, Pakistan, Mujtaba *et al.* studied 263 patients (aged 18 years and older) with ESKD on maintenance hemodialysis. They found that around 16% of patients were found to have IDH [9]. In another study, Diakite *et al.*

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reported that out of 131 patients with ESKD on hemodialysis, 53 had intradialytic hypertension (a frequency of 40.5%) [10]. As far as we know, no study has been reported from this part of Punjab, Pakistan, to assess the magnitude of IDH, where the burden of chronic kidney disease (CKD) is large. Therefore, this study has been planned to determine the magnitude of IDH in our local setting. The study results will help in devising strategies to overcome this intradialytic complication so that its associated risks of morbidity and mortality may be reduced. Identifying the prevalence of IDH will encourage routine monitoring during hemodialysis sessions, enabling early detection and intervention. It will provide baseline data for future studies exploring the pathophysiology, risk factors, and long-term outcomes associated with IDH.

Although intradialytic hypertension (IDH) is increasingly recognized as a clinically significant complication of maintenance hemodialysis, reported prevalence rates vary widely due to inconsistent diagnostic criteria and heterogeneous patient populations. In Pakistan, available data are limited and largely derived from major metropolitan centers, with scarce evidence from Punjab, particularly from public-sector tertiary care hospitals. Moreover, region-specific evaluation using standardized KDIGO criteria remains insufficient. This gap underscores the need to determine the local burden of IDH to inform monitoring strategies and optimize patient management. The present study aims to determine the prevalence of intradialytic hypertension in end-stage renal disease (ESRD) patients on maintenance hemodialysis

## METHODS

This descriptive cross-sectional study was conducted at the Nephrology department of Sir Ganga Ram Hospital over the duration of six months from 20th July 2024 to 19th January 2025, following approval from the institutional ethics review committee (ERC No. 187-Synopsis /FCPS/FJ/ERC). Adults aged 20–65 years, both male and female, diagnosed with end-stage renal disease (ESRD) and receiving maintenance hemodialysis (HD) were included in the study after obtaining informed consent, using non-probability consecutive sampling. Patients with acute infections such as diarrhea or pneumonia, as well as those with acute-on-chronic kidney injury, were excluded. We recorded demographic data like age, gender, duration of ESRD (in months), and duration of maintenance hemodialysis (in months). We also noted the co-morbidity data for smoking, diabetes mellitus, and hypertension from history and medical records. All the patients were observed for six dialysis sessions for assessment of intradialytic hypertension. Pre-dialysis blood pressure was monitored using an automated monitor, then every thirty minutes during the dialysis session, and after the end of the session. Patients were labeled to have intradialytic hypertension if a systolic blood pressure increase of more than 10 mmHg was observed between the start and end of the dialysis session in four out of six sessions [4]. A sample size of 144 patients was calculated using OpenEpi software with the single proportion formula, considering a 16% prevalence of intradialytic hypertension [9], a 95% confidence level, and a precision of 6%. The sample size formula used was: n = deff×Np^q^/(d$^2$/1.96$^2$) (N–1) +p^q^. All statistics were done with SPSS version 23.0. Shapiro-Wilk was used to evaluate normality of numerical data. Summarizing the quantitative data, the results of variably distributed, which are normally distributed ones, are presented as mean (standard deviation), and the results of non-normally distributed ones are reflected as median (inter quartile range). Qualitative data comparison across patients with and without intradialytic hypertension was through chi-square test, whereas Fisher exact test was applied when the cells contained less than 5. Statistical significances were discussed as values of p<0.050.

## RESULTS

The study enrolled 144 patients with an average age of 48.03 ± 13.2 years, and more than half were females (52.8%, n=76). The prevalence of comorbid conditions was 12.5% for smoking, 38.2% for diabetes mellitus and 77.8% for hypertension. The median (IQR) duration of end-stage renal disease was 36 (66) months, and the duration of hemodialysis was 24 (70) months. All the patients were on thrice-weekly maintenance hemodialysis. Of all the study participants, 28 (19.4%) developed intradialytic hypertension (Table 1).

**Table 1:** Characteristics of End Stage Renal Disease Patients on Maintenance Hemodialysis (N=144)

| Characteristics | Values |
|---|---|
| Age (years) | 48.03 ± 13.2 |
| Male | 68 (47.2%) |
| Female | 76 (52.8%) |
| Smoking – Yes | 18 (12.5%) |
| Diabetes Mellitus – Yes | 55 (38.2%) |
| Hypertension – Yes | 112 (77.8%) |
| Duration of End-Stage Renal Disease (Months)* | 36 (66%) |
| Duration of Hemodialysis (months)* | 24 (70%) |
| **Intradialytic Hypertension** | |
| Yes | 28 (19.4%) |
| No | 116 (80.6%) |

*Median (IQR)

Prevalence of intradialytic hypertension was significantly high in diabetic cases in contrast to non-diabetic cases (30.9% vs. 12.4%, p-value=0.006). All cases of intradialytic hypertension occurred in hypertensive patients in contrast to non-hypertensive patients (100% vs. 0%, p-value=0.001) (Table 2).

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**Table 2:** Clinical and Demographic Factors Associated with Intradialytic Hypertension(N=144)

| Factors | | Intradialytic Hypertension | | p-Value* |
|---|---|---|---|---|
| | | Yes (28) | No (116) | |
| Age | < 50-years | 10 (13.7%) | 63 (86.3%) | 0.077 |
| | ≥ 50-years | 18 (25.4%) | 53 (74.6%) | |
| Gender | Male | 14 (20.6%) | 54 (79.4%) | 0.743 |
| | Female | 14 (18.4%) | 62 (81.6%) | |
| Smoking | Yes | 5 (27.8%) | 13 (72.2%) | 0.340 |
| | No | 23 (18.3%) | 103 (81.7%) | |
| Diabetes Mellitus | Yes | 17 (30.9%) | 38 (69.1%) | 0.006€ |
| | No | 11 (12.4%) | 78 (87.6%) | |
| Hypertension ¥ | Yes | 28 (25%) | 84 (75%) | 0.001€ |
| | No | 0 (0.0%) | 32 (100%) | |
| Duration of ESRD | ≤ 5-years | 18 (18.8%) | 78 (81.3%) | 0.766 |
| | > 5-years | 10 (20.8%) | 38 (79.2%) | |
| Duration of hemodialysis | ≤ 3-years | 18 (20.9%) | 68 (79.1%) | 0.583 |
| | > 3-years | 10 (17.2%) | 48 (82.8%) | |

*chi-square test, ¥ Fischer's exact test where cell count < 5, €Statistically significant

## DISCUSSION

One-fifth of the subjects in our study had intra-dialytic hypertension (IDH). In contrast to previous reports, which have estimated IDH frequencies ranging from 22.3% to 44.5% based on varying definitions, our findings reflect a relatively low prevalence [11-13]. Mujtaba *et al.* reported a 16% prevalence of IDH in patients undergoing hemodialysis , which is lower than our observation [9]. Such differences may arise from variations in ultrafiltration rates, blood pressure monitoring practices, and the criteria used to define IDH across different centers. Our study employed a strict operational definition, requiring a >10 mmHg rise in systolic BP during at least four out of six dialysis sessions. By contrast, earlier studies often considered fewer dialysis sessions or smaller BP changes, which may have inflated reported prevalence rates. These definitional discrepancies are a well-recognized contributor to the variability in IDH estimates across the literature. Prabhu *et al.* conducted a study on 136 patients and reported IDH prevalence of 57%, 24%, and 11% when defined by an increase in systolic blood pressure, mean arterial pressure (MAP), and symptomatic increases, respectively [14]. Similarly, Kakai, who conducted a study on 86 chronic kidney disease patients over 512 hemodialysis sessions, found a frequency of 51.2% [15]. Current study results align more closely with those of Gathmyr *et al.*, who reported a 17.7% prevalence in a cross-sectional study of 130 patients on chronic hemodialysis [16]. The development of IDH has also been linked to dialysis frequency. All our patients underwent thrice-weekly sessions. Patients on less frequent regimens are more likely to be volume overloaded, which, combined with higher ultrafiltration demands, may increase the risk of IDH. Since IDH patients tend to remain, volume overloaded compared to other hemodialysis patients, their hypertension management typically depends on pre- and post-dialysis blood pressure measurements [17]. Standardization of IDH testing and consensus on diagnostic criteria are therefore essential to guide management approaches [18]. IDH has been associated with higher mortality risk, yet its pathophysiology, particularly its link with increased vascular resistance during dialysis and persistent volume overload, remains incompletely understood. This highlights the importance of vigilant fluid management as a first-line strategy [19]. Despite growing evidence, therapeutic options remain limited, largely due to uncertainty regarding underlying mechanisms and a lack of a universally accepted diagnostic definition. In our study, IDH appeared more common in patients aged ≥50 years, though this association did not reach statistical significance. The link between IDH, advancing age, and multiple comorbidities has, however, been demonstrated in earlier studies [20]. Hypertension and diabetes mellitus were the major comorbidities significantly associated with IDH in our cohort, consistent with findings reported by Mujtaba *et al.* [9]. Previous studies have also documented clinical consequences of IDH, including metabolic disturbances, all-cause mortality, cardiac failure, and cardiovascular-related hospitalizations [21]. Prabhu *et al.* reported that both diabetes mellitus and malnutrition (P=0.03) were significantly associated with IDH [14]. Kakai, identified high pulse pressure and elevated systolic BP as significant predictors [15]. While IDH has been linked to shorter dialysis duration in earlier work [19], we did not observe such an association in our study. Effective management of IDH requires a multifaceted approach, including dialysate adjustments, careful assessment of dry weight, improved techniques for blood pressure monitoring, vigilance for signs of chronic fluid overload, and optimization of antihypertensive therapy. Given the elevated mortality risk among IDH patients, collaboration among nephrologists, dialysis nurses, dietitians, and cardiologists are vital to develop individualized care plans [20]. The etiology of IDH is likely multifactorial, involving overlapping contributions from fluid overload, autonomic dysregulation, and hormonal imbalances, though their relative significance remains unclear [21, 22]. Present study adds valuable data to the growing body of literature, but has limitations. It was a single-center study, which may limit generalizability. In addition, its cross-sectional design precluded exploration of temporal or causal associations.

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single-center design and cross-sectional nature, which limit generalizability and preclude causal inference. The absence of longitudinal follow-up restricts assessment of long-term cardiovascular outcomes and mortality associated with IDH. Additionally, dialysis-related parameters such as ultrafiltration rate and dialysate composition were not analyzed in detail. Future multicenter, prospective studies incorporating standardized diagnostic criteria, comprehensive dialysis variables, and long-term outcome assessment are recommended to better understand the pathophysiology and prognostic implications of IDH.

## CONCLUSIONS

The study concluded that intradialytic hypertension (IDH) is a frequent occurrence in chronic kidney disease patients on maintenance hemodialysis. Diabetes and pre-existing hypertension are major risk factors. Clinicians should ensure standardized blood pressure monitoring before, during, and after dialysis, with closer surveillance of high-risk patients. Multi-center longitudinal studies and regular quality audits of dialysis facilities are needed to evaluate IDH prevalence and management effectiveness.

## Authors' Contribution

Conceptualization: MT,
Methodology: MT, SY, SA
Formal analysis: MT, SY
Writing and Drafting: MT, HTU, SA
Review and Editing: MT, HTU, SA, SY

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Comparative Analysis of Pain Relief and Adverse Effects of Ibuprofen versus Naproxen in Elderly Knee Osteoarthritis

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## ABSTRACT

Osteoarthritis (OA) has no definitive cure, and to improve the quality of life, analgesic medications are used. **Objectives:** To evaluate ibuprofen and naproxen in elderly patients with knee osteoarthritis in terms of pain relief (primary outcome) and adverse effects (secondary outcome). **Methods:** This comparative analytical study was conducted at the Rheumatology Clinic of Shahida Islam Medical College and Hospital from June to November 2024. Following ethical approval, patients aged over 50 years with stage I-III knee OA willing to participate were included. Exclusion criteria were stage IV OA, systemic or rheumatologic co-morbidities (e.g., hypertension, diabetes), prior use of naproxen or ibuprofen within one month, and history of surgery within the past year. **Results:** A total of 310 participants were enrolled, equally divided between two groups: Naproxen Sodium (440/660 mg, n=155) and Ibuprofen (1200 mg, n=155). Both drugs significantly reduced pain from baseline to day 7 post-medication, including pain at rest, on weight-bearing, during passive movements, morning stiffness, and pain throughout the day and night ($p<0.010$, assessed via Visual Analogue Scale). **Conclusions:** Minimal side effects were observed in both groups. Naproxen and ibuprofen were both effective and well-tolerated options for pain relief in elderly patients with knee OA.

## INTRODUCTION

Osteoarthritis (OA) is a chronic musculoskeletal disease which affects synovial joints and manifests in terms of degeneration of cartilage and bony hypertrophy. In developed countries, OA ranks among the top ten most common conditions with significant health impact [1]. Osteoarthritis primarily affects the elderly, with the knee and hip joints most commonly affected. That is why OA is ranked first in the most common factor for musculoskeletal disability in the elderly [2]. Pain in OA is thought to arise from capsular distention, periosteal elevation, synovial inflammation and/or trabecular micro-fractures. OA is becoming an increasingly significant healthcare challenge due to the growing proportion of the elderly population [3]. The pattern of affected joints tends to vary by gender, with male more prone to hip OA while female is more likely to experience a more severe and poly-articular form of disease. The specific area of the body involved in OA plays an important role in terms of pain and degree of disability [4]. For instance, if a person suffers OA of weight-bearing joints such as the knee and hip, the

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person may be immobilized, potentially reducing the quality of life. In comparison, OA of the inter-phalangeal joints of the hand might lead to less altered activities of daily living (ADL) [5]. The most common reason patients with OA seek medical help is to obtain analgesia during the night. Since there is no definitive cure for OA, current management primarily relies on analgesic medications, educating patients, pain relief, preservation and optimization of joint function [6]. Weight loss encouragement is also advised to such patients in order to decrease stress on weight-bearing joints, which will help to reduce pain while increasing mobility [7]. Nonetheless, evidence supporting the efficacy of various treatment strategies, both individual and in combination, is variable [8]. The first line of treatment in any pain condition is acetaminophen (paracetamol). A maximum of 4000 mg/day is given to patients suffering from OA for pain relief. However, usually, pain relief is limited to paracetamol [9]. After failure or pain relief by paracetamol, the next line of drug is a non-selective non-steroidal anti-inflammatory drug (NSAID), either naproxen 500 mg/day or ibuprofen 1200 mg/day or in combination with acetaminophen [10]. The usual use of NSAIDs is as required rather than as a fixed daily dose. According to the American College of Rheumatology's Subcommittee on Osteoarthritis Guidelines, treatment for patients diagnosed with OA should begin with a low drug dose, which should only be increased if adequate symptomatic relief is not achieved [11, 12]. Even though published data in terms of the contribution of NSAIDs to inflammation of joint pain and cartilage breakdown remains uncertain, there is rising evidence in terms of the role of OA-associated low-grade inflammation for which NSAIDs might be an ideal choice for effective analgesia [13]. The efficacy of NSAIDs in managing knee OA has been studied; however, their effects have been counterbalanced by the broader side effects of NSAIDs on the gastrointestinal tract [14]. Naproxen sodium, a non-selective NSAID, contains smaller naproxen particles compared to standard naproxen, resulting in a faster absorption rate. Naproxen is available over-the-counter (OTC) at doses of 275 mg and 550 mg. Recommended OTC dose for naproxen sodium is 220 mg every 8 to 12 hours with a maximum daily dosage of 660 mg up to 7 days. In elderly individuals greater than 65 years old, the recommended naproxen dose is one 220 mg tablet 12 hourly, with a total daily dose of 440 mg [15]. The maximum dosage of over-the-counter ibuprofen is 1200 mg/day. The efficacy of both naproxen sodium and ibuprofen is reported and recommended in rheumatologic conditions, including OA, in addition to dysmenorrhea and dental pain as well [16]. In developing countries such as Pakistan, where the rate of OA is ever-increasing, coupled with enormous use of OTC drugs such as naproxen and ibuprofen regularly, this study tends to unveil whether the use of OTC ibuprofen and naproxen is effective in terms of pain relief and minimal side effects, especially in the high-risk population of OA, viz., the elderly [17].

Knee osteoarthritis is highly prevalent among the elderly and is a major cause of pain, disability, and reduced quality of life. Although both ibuprofen and naproxen are widely available over-the-counter NSAIDs used for symptomatic relief, comparative data focusing specifically on their short-term efficacy and safety profile in elderly Pakistani patients remain limited. Moreover, real-world evidence evaluating both pain reduction and adverse effects in this high-risk age group is scarce. Therefore, a direct comparative assessment of these two commonly used NSAIDs was necessary to guide safer and more effective clinical decision-making. This study aims to evaluate ibuprofen and naproxen in elderly patients suffering from knee OA in terms of pain relief. The primary outcome was to study the relief of pain, while secondary outcomes were the evaluation of adverse effects by the use of drugs.

## METHODS

This comparative analytical study was conducted at the Rheumatology Clinic of Shahida Islam Medical College and Hospital for a period of six months from June 2024 to November 2024. After ethical approval from the Ethical Review Committee of the hospital, IRB no: SIMC/ET.C/00020/24, diagnosed patients with OA (OA of stage I to III) above 50 years of age, willing to participate in the study were included through consecutive sampling while patients with stage IV OA or with other systemic or rheumatologic co-morbidities such as hypertension and diabetes were excluded. Patients already on naproxen sodium and ibuprofen or a history of taking either of the two drugs within the last month were also excluded. Any patient with a history of surgery within the past year was also excluded. The sample size was calculated using G-Power software for sample size calculation. Keeping the test to be applied at a paired t-test (matched pairs) and the following criterion, the sample size came out to be 147. However, due to consecutive sampling, a slightly higher sample size for each group was included, viz. 155 in each group [18]. t-tests - Means: Difference between two dependent means (matched pairs). Analysis (A priori): Compute required sample size. Input (Tail)s: Two, Effect size dz = 0.3, $\alpha$ err prob=0.05 and Power (1-$\beta$ err prob) = 0.95. Output (Non-centrality parameter, $\delta$): = 3.6373067, Critical t = 1.9763457, Df = 146, Total sample size = 147 and Actual power = 0.9508665. For diagnosis of OA, at least one of the following radiological feature were noted: narrowing of joint space, cyst formation in the knee joint, sub-chondral sclerosis or presence of marginal lipping or sub-chondral sclerosis.

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Current pain of patients or maximal pain on the visual analogue pain scale (VAS) at nighttime (where pain is highest) was recorded [3]. Patients were advised against using any medication/s which could interfere with pain evaluation or reduce the effects of NSAIDs. These included anti-inflammatories or aspirin-containing medicines, or any other analgesic medicines such as H2 blockers, proton pump inhibitors, antacids, prostaglandin analogues and sucralfate. They were advised to consult with the clinician whenever any symptom arose before taking any medication mentioned above. Informed consent was sought from each patient before inclusion in the study. Using a pre-designed proforma (annexure), data collection was carried out by the principal investigator. At follow-up, the principal investigator also filled out the proforma. Patients were given a list of side effects (as reported in results) and any other side effects observed by them for the duration of follow-up. A pre-designed case-report form (CRF) was provided to the patients for recording any adverse drug reaction (ADR) and/or any drug-drug interaction (DDI), and was directed on how to fill the form and bring it to their follow-up or whenever symptoms arose. Patients were randomly divided into an equal number of patients receiving naproxen and ibuprofen. A daily dose of naproxen sodium 660 mg in patients below 65 years, while 440 mg in patients >65 years of age was advised [19], while ibuprofen 1200 mg all either age group was advised [20]. Treatment was advised for 7 continuous days, and then asked to return for follow-up. Knee pain was assessed at baseline and at follow-up as well. Pain assessment was carried out using VAS [21] (0-No pain, 1=Slight pain, 2=Mild pain, 3=Moderate pain, 4=Severe pain. The clinician assessed the degree of knee pain on three occasions, viz., at rest, on weight-bearing and on passive motion. Along with pain, patients were assessed for joint stiffness in the morning, during the day and at night. Each change in symptom/s was recorded both at baseline and one week after treatment on follow-up. For analysis of data, SPSS version 22.0 was used. For categorical data, frequency and percentages were used. For numerical data, the mean and standard deviation were reported. Data normality was assessed using the Shapiro-Wilk test. For comparison of baseline versus 7-day follow-up data of patients in each group, a paired t-test was applied, keeping $p<0.05$ as statistically significant.

## RESULTS

The study included 310 participants, with an equal division between the two treatment groups: Naproxen Sodium (440/660 mg, n=155) and Ibuprofen (1200 mg, n=155). The mean age in the Naproxen group was 62.77 ± 11.67 years, while the Ibuprofen group had a slightly younger mean age of 61.59 ± 12.84 years. Weight and height were similar across groups, with Naproxen patients averaging 78.85 ± 17.72 kg and 165.33 ± 8.98 cm, while the Ibuprofen group averaged 80.29 ± 18.22 kg and 167.6 ± 9.21 cm. The BMI values also aligned closely (Naproxen: 29.26 ± 8.2; Ibuprofen: 28.65 ± 8.58). Gender distribution was comparable, with male constituting 46.45% of the Naproxen group and 48.39% of the Ibuprofen group, while female accounted for 53.5% and 51.61%, respectively (Table 1).

**Table 1:** Baseline Demographics of Patients Included in the Study (n=310)

| Variables | | Naproxen Sodium (440/660 mg), n=155 | Ibuprofen (1200 mg), n=155 |
|---|---|---|---|
| Age (Years) Mean ± SD | | 62.77 ± 11.67 | 61.59 ± 12.84 |
| Weight (kg) | | 78.85 ± 17.72 | 80.29 ± 18.22 |
| Height (cm) | | 165.33 ± 8.98 | 167.6 ± 9.21 |
| BMI (kg/m$^2$) | | 29.26 ± 8.2 | 28.65 ± 8.58 |
| Gender | Male | 72 (46.45 %) | 75 (48.39 %) |
| | Female | 83 (53.5 %) | 80 (51.61 %) |

Pain and Stiffness Improvement at Follow-Up: Both treatment groups showed marked improvement in pain and stiffness at the 7-day follow-up. For pain at rest, the Naproxen group showed a reduction from 3.2 ± 0.8 at baseline to 1.5 ± 0.6, while the Ibuprofen group improved from 2.9 ± 0.7 to 1.3 ± 0.5. Pain on passive movement decreased from 4.0 ± 0.9 to 2.1 ± 0.7 in the Naproxen group and from 3.8 ± 0.8 to 2.0 ± 0.6 in the Ibuprofen group. Pain on weight bearing reduced from 4.5 ± 1.0 to 2.7 ± 0.8 for Naproxen and from 4.2 ± 1.1 to 2.5 ± 0.7 for Ibuprofen. For morning stiffness, the mean values in the Naproxen group declined from 3.8 ± 0.7 to 1.9 ± 0.5, and in the Ibuprofen group from 3.5 ± 0.6 to 1.7 ± 0.4. Pain during the day lessened from 4.3 ± 0.6 to 2.3 ± 0.6 in the Naproxen group, and from 4.0 ± 0.7 to 2.1 ± 0.5 in the Ibuprofen group. Similarly, pain at night decreased from 3.6 ± 0.9 to 1.8 ± 0.7 for Naproxen and from 3.3 ± 0.8 to 1.6 ± 0.6 for Ibuprofen (Table 2).

**Table 2:** Symptoms Improvement of Various Variables in Each Group at Baseline Vs 7th-Day Follow-Up (n=310) Assessed by Visual Analogue Scale

| Variables | | Naproxen Sodiu (440/660 mg) n=155, Mean ± SD | Ibuprofen (1200 mg) n=155, Mean ± SD | p-Value |
|---|---|---|---|---|
| Pain at Rest | Baseline | 3.2 ± 0.8 | 2.9 ± 0.7 | 0.004 |
| | Follow up | 1.5 ± 0.6 | 1.3 ± 0.5 | |
| Pain on Passive Movement | Baseline | 4.0 ± 0.9 | 3.8 ± 0.8 | 0.003 |
| | Follow up | 2.1 ± 0.7 | 2.0 ± 0.6 | |
| Pain on Weight Bearing | Baseline | 4.5 ± 1.0 | 4.2 ± 1.1 | 0.003 |
| | Follow up | 2.7 ± 0.8 | 2.5 ± 0.7 | |
| Morning Stiffness | Baseline | 3.8 ± 0.7 | 3.5 ± 0.6 | <0.001 |
| | Follow up | 1.9 ± 0.5 | 1.7 ± 0.4 | |

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| | | | | |
|---|---|---|---|---|
| Pain During Day | Baseline | 4.3 ± 0.6 | 4.0 ± 0.7 | 0.002 |
| | Follow up | 2.3 ± 0.6 | 2.1 ± 0.5 | |
| Pain at Night | Baseline | 3.6 ± 0.9 | 3.3 ± 0.8 | <0.001 |
| | Follow up | 1.8 ± 0.7 | 1.6 ± 0.6 | |

Findings show the frequency and percentage of side effects associated with each treatment group. The most commonly reported side effects in both groups included nausea, dyspepsia, and headache. The Naproxen group had a slightly higher frequency of nausea (12 cases, 34.3%) compared to the Ibuprofen group (10 cases, 28.6%). Dyspepsia was reported by 15 participants (42.9%) in the Naproxen group and 13 (37.1%) in the Ibuprofen group. Headache affected 9 participants (25.7%) in the Naproxen group, slightly lower than the 12 cases (34.3%) in the Ibuprofen group. Additional side effects, such as vomiting, dizziness, and edema, were observed in both groups with relatively lower frequencies and percentages (Figure 1).

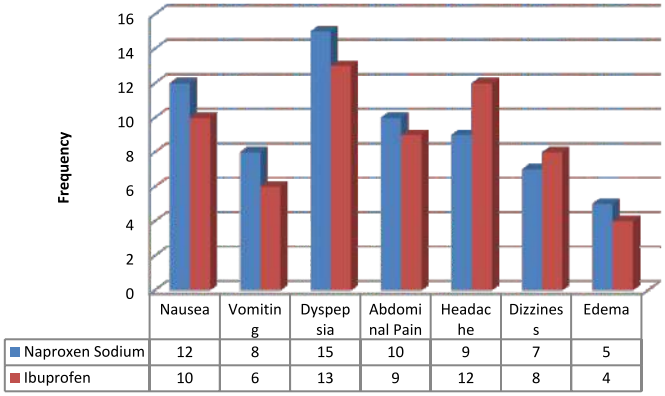


**Figure 1:** Side Effect Associated with Use of Naproxen Sodium Vs Ibuprofen(n=310)

## DISCUSSIONS

The results of the study indicated that both naproxen and ibuprofen were effective in reducing pain in various situations. Both naproxen sodium and ibuprofen were effective in reducing pain at baseline to follow up at the 7th post-medication day in terms of pain at rest, on weight bearing, on passive movements, morning stiffness, pain during the day and at night. A significant difference was observed between the groups ($p<0.010$). Along with that, minimal side effects were reported with both drugs, all of which were tolerable. Similar reports have been reported in other studies as well, wherein the efficacy of various NSAIDs compared to each other and with other lines of treatment for OA, such as opioids and COX-2 inhibitors, was evaluated [19]. In a study on patients administered naproxen sodium and ibuprofen, both demonstrated substantial superior pain relief for mild to moderate knee OA in comparison to placebo [20]. Improvement in pain intensity after 7 days of continuous treatment in this study was observed in between 35-45 %, contrasting with 30 % OA pain improvement in general [21]. In another study, although ibuprofen was effective in alleviating pain in knee OA, some of the side effects were found to be significantly affected in patients [22]. In this regard, naproxen sodium was observed to be highly effective as well as tolerable in terms of side effects [23]. Likewise, results from daily evaluation of naproxen sodium and ibuprofen for reduction of pain-associated symptoms showed that for arthritic pain and control of pain, both ibuprofen and naproxen sodium were significantly beneficial in improving pain in comparison to placebo [24]. In terms of pain evaluation at night, naproxen was reported to show a greater tendency for improving pain, compared to ibuprofen, as evident by the lower pain on VAS by patients on naproxen when compared with ibuprofen [25]. The results were in line with the findings reported in this study. In this study as well, pain relief by naproxen sodium was reported to be for a longer duration than ibuprofen. The possible reason for this might be due to the longer half-life of naproxen sodium as compared to ibuprofen, thereby enabling sustained and optimal relief of pain [26]. The duration of action of naproxen sodium according to published data is long, ranging from 8 to 12 hours [27]. In comparison, the half-life of ibuprofen as reported in literature is around 4-6 hours. Therefore, the use of naproxen sodium for sustained and longer duration of pain relief might be vital in implications such as improving quality of life and day-to-day functioning in knee OA, as naproxen sodium is better than ibuprofen [28]. However, the overall pain relief between naproxen sodium and ibuprofen, as reported in studies, has been equal to each other more or less, with no statistically significant difference between each other. The study highlighted both pain measurements at various timings and situations with the use of naproxen sodium and ibuprofen, both at baseline and at 7th –days follow up along with any side effects observed during the period.

This study was limited by its short duration of follow-up (7 days), which restricts evaluation of long-term efficacy and delayed adverse effects. The single-center design may also limit the generalizability of findings to broader populations. Additionally, long-term gastrointestinal, renal, and cardiovascular safety outcomes were not assessed. Future multicenter randomized controlled trials with extended follow-up periods are recommended to evaluate long-term safety, comparative effectiveness, and impact on quality of life among elderly patients with knee osteoarthritis.

## CONCLUSIONS

It was concluded that both ibuprofen and naproxen were effective in providing pain relief among elderly patients with knee osteoarthritis, with only minimal adverse effects observed for each drug.

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## Authors' Contribution

Conceptualization: SM
Methodology: AK
Formal analysis: MAZ, NN
Writing and Drafting: AK, NN, KA, SI
Review and Editing: AK, NN, KA, SI, MAZ, SM

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Comparison of Large and Small-Bore Chest Tubes in the Management of Malignant Pleural Effusion: A Prospective Cohort Study

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## ABSTRACT

Malignant pleural effusion (MPE) is a common complication in advanced cancers, often requiring chest tube drainage for symptom relief. Both small- and large-bore chest tubes are used, but their comparative effectiveness and patient comfort remain debated. **Objectives:** To compare clinical outcomes and complications of small versus large-bore chest tubes in MPE management. **Methods:** A prospective cohort study included 60 patients with MPE, divided into small-bore (Group A, n=30) and large-bore (Group B, n=30) groups. Outcomes measured were pain scores and duration of tube placement; complications included bleeding, wound infection, and subcutaneous emphysema. Data were analyzed using SPSS version 25.0. **Results:** Small-bore tubes were associated with significantly lower pain scores at 24 hours in patients ≤45 years (1.43 ± 2.15 vs 4.00 ± 1.67, p=0.037) and >45 years (1.17 ± 1.47 vs 2.92 ± 1.77, p=0.001). Pain reduction was consistent across genders and urban/rural groups. However, the duration of drainage was longer with small-bore tubes, particularly in patients >45 years (12.87 ± 3.07 vs 9.00 ± 2.80 days, p<0.001) and in rural patients (13.72 ± 2.96 vs 8.07 ± 2.54 days, p=0.001). Complication rates, including bleeding, subcutaneous emphysema, and wound infection, were similar between groups (p>0.050). **Conclusion:** Small-bore chest tubes provide significantly lower pain while maintaining comparable safety to large-bore tubes. Despite a longer drainage duration, they represent a more comfortable and equally safe option for managing MPE.

## INTRODUCTION

Malignant pleural effusion (MPE) is a frequent issue in advanced cancers, causing significant symptoms like shortness of breath and chest pain that can affect a patient's quality of life [1, 2]. The go-to treatment has been chest tube drainage followed by pleurodesis, but there's still some debate about the best tube size that strikes a balance between effective fluid removal and patient comfort [3, 4]. Larger chest tubes (typically over 14 Fr) can quickly drain thick effusions or blood, but they often come with more severe pain during insertion and while they're in place, which can slow down recovery and make patients less tolerant [5, 6]. On the other hand, smaller tubes (8–14 Fr) have become more popular because they tend to be more comfortable for patients and easier to insert, without significantly compromising drainage efficiency in many situations [7-9]. Recent randomized trials back this up. One study found that patients using smaller tubes reported less pain compared to those with larger tubes, while still achieving similar rates of fluid clearance and success with pleurodesis [10]. Similarly, a randomized controlled trial

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involving MPE patients showed lower pain scores with no difference in effectiveness between small and large bore drains [11]. Even with these promising results, some doctors are concerned that smaller tubes may come with higher risks of complications, such as blockages, dislodgment, or longer dwell times, which could increase the chances of infection or bleeding [12, 13]. However, systematic reviews and meta-analyses published since 2020 have shown that both tube sizes have comparable safety profiles, with low rates of bleeding, infection, and subcutaneous emphysema [14-16]. This study was set up to tackle the ongoing clinical question by directly comparing large and small-bore chest tubes in managing malignant pleural effusion.

Although both small- and large-bore chest tubes are routinely used for the management of malignant pleural effusion (MPE), the optimal tube size remains a subject of clinical debate. While international trials suggest comparable efficacy with improved comfort using small-bore tubes, local evidence from Pakistani tertiary care settings is limited. Additionally, variations in patient demographics, healthcare access, and clinical practices may influence outcomes such as pain perception, drainage duration, and complication rates. This gap highlights the need for context-specific comparative data to guide evidence-based decision-making in our population. This study aims to provide practical evidence to guide personalized treatment options that enhance both patient outcomes and comfort by looking at pain scores, tube duration, and complication rates based on age, gender, and residential status.

## METHODS

This prospective cohort study was conducted in the Pulmonology Department of Khyber Teaching Hospital, Peshawar, from 12th March 2024 to 25th March 2025. Ethical approval was granted by the Institutional Review and Ethics Board (IREB) of Khyber Medical College, Peshawar (Ref. No. 649/DME/KMC), and the study adhered to the Declaration of Helsinki and Good Clinical Practice guidelines. A non-probability consecutive sampling method was employed to select participants. Patients were assigned to either group A or group B based on drain availability as well as the treating physician's discretion. The sample size was calculated using WHO software, with 90% power and a significance level ($\alpha$) of 0.05 (two-tailed). A previous study reported a mean duration of drain placement of 3.0 ± 1.6 days for the small-bore group compared to 7.9 ± 3.8 days for the large-bore group [11]. Using the formula $n = 2(Z1-\alpha/2 + Z1-\beta)^2\sigma^2 / \Delta^2$, where $\sigma$ is the pooled standard deviation and $\Delta$ is the expected mean difference, the required sample size was calculated as 29 per group. This was rounded to 30 participants per group, giving a total sample size of 60. During the study period, all patients with malignant pleural effusion presenting to the Pulmonology Department of Khyber Teaching Hospital, Peshawar, who gave informed consent, were consecutively recruited if they met the inclusion criteria. Both males and females aged 18–70 years, diagnosed with malignant pleural effusion requiring therapeutic drainage, were included. Patients with malignant effusion who were terminally ill, had bleeding diathesis, were immunocompromised, had diabetes, hydropneumothorax, empyema, or were unwilling to participate were excluded. After obtaining informed consent, participants were assigned unique IDs. Baseline assessments were performed, including demographics (age, gender, residence, socioeconomic status, profession, education) and relevant medical history (comorbidities, previous chest interventions). Chest tubes, either small- or large-bore, were selected according to institutional guidelines, considering anticipated drainage volume, patient comfort, and the nature of pleural fluid. To avoid selection bias, all eligible patients were enrolled consecutively. No significant differences in baseline demographics and clinical characteristics were observed between the two groups, indicating appropriate comparability. Chest tubes were inserted by trained physicians according to institutional protocol, which included local anesthesia, sterile preparation, insertion technique, and secure fixation. Air leaks, drainage, and wound checks were monitored uniformly. Outcome measures included duration of tube placement (days in situ), pain assessed using the Visual Analogue Scale (VAS), and complications (bleeding, subcutaneous emphysema, wound infections), which were recorded as binary outcomes based on institutional definitions. Data were collected using a standardized proforma and stored securely to ensure confidentiality. Data analysis was performed using SPSS version 25.0. Descriptive statistics were presented as mean ± standard deviation or median (IQR) for continuous variables (age, pain score, tube placement duration) after testing for normality using the Shapiro–Wilk test. Age and tube placement duration were normally distributed ($p>0.050$), while pain scores were not ($p<0.050$). Categorical variables (gender, residence, socioeconomic status, education, pain, complications) were analyzed as frequencies and percentages. Comparisons between groups were made using the independent sample t-test for normally distributed variables (age, duration of tube placement) and the Mann–Whitney U test for non-normally distributed variables (pain scores). The association between chest tube type and complications (bleeding, emphysema, wound infection) or pain severity was assessed using chi-square or Fisher's exact test at the 5% level of significance. Effect modifiers (age, gender,

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residence, socioeconomic status) were controlled by stratification, followed by chi-square or Fisher's exact test. A p-value ≤ 0.050 was considered statistically significant.

## RESULTS

In total, 60 patients took part, with 30 in each group. The age breakdown revealed that most patients were over 45 years old, making up 80.0% of the large-bore group and 76.7% of the small-bore group. Meanwhile, those aged 45 or younger represented 20.0% and 23.3% in their respective groups. When it comes to gender, the distribution was even, though there were slightly more males in both groups: 60.0% in the large-bore group and 53.3% in the small-bore group, while females accounted for 40.0% and 46.7%, respectively. Looking at where the participants lived, rural patients made up a slightly larger share, with 50.0% in the large-bore group and 60.0% in the small-bore group. Urban patients filled in the rest, at 50.0% and 40%, respectively. As for socioeconomic status, most participants fell into either the middle or lower classes. In the large bore group, 50.0% were middle class and 46.7% were lower class, with just one patient (3.3%) coming from a high socioeconomic background. The small-bore group had 53.3% from the middle class and 46.7% from the lower class, with none from the high-income bracket. Overall, both groups were quite similar across all major demographic factors, which suggests that the randomization process was effective and allows for a fair comparison of clinical outcomes (Table 1).

**Table 1:** Demographics of Patients Based on Large-Bore and Small-Bore Chest Tubes (N = 60)

| Variables | Category | Large Bore Tube (N=30) | Small Bore Tube (N=30) | Total (N=60) |
|---|---|---|---|---|
| Age (years) | ≤ 45 | 6 (20.0%) | 7 (23.3%) | 13 (21.7%) |
| | > 45 | 24 (80.0%) | 23 (76.7%) | 47 (78.3%) |
| Gender | Female | 12 (40.0%) | 14 (46.7%) | 26 (43.3%) |
| | Male | 18 (60.0%) | 16 (53.3%) | 34 (56.7%) |
| Residence | Rural | 15 (50.0%) | 18 (60.0%) | 33 (55.0%) |
| | Urban | 15 (50.0%) | 12 (40.0%) | 27 (45.0%) |
| Socioeconomic Status | High | 1 (3.3%) | 0 (0.0%) | 1 (1.7%) |
| | Middle | 15 (50.0%) | 16 (53.3%) | 31 (51.7%) |
| | Low | 14 (46.7%) | 14 (46.7%) | 28 (46.7%) |

For patients aged 45 and younger, those with large bore tubes reported significantly higher pain scores at the 24-hour mark (mean ± SD: 4.00 ± 1.67) compared to their counterparts with small bore tubes (1.43 ± 2.15), with a p-value of 0.037. Moreover, the duration of tube placement was notably shorter for the large-bore group (6.83 ± 2.99 days) than for the small-bore group (12.43 ± 3.99 days, p = 0.017). A similar pattern emerged for patients over 45, where those with large-bore tubes had a higher average pain score (2.92 ± 1.77) compared to the small-bore group (1.17 ± 1.47), and this difference was highly significant (p = 0.001). Again, tube duration was shorter for the large-bore group (9.00 ± 2.80 days) compared to the small-bore group (12.87 ± 3.07 days, p<0.001). When we break it down by gender, both female and male patients exhibited similar trends. Female patients with large bore tubes reported significantly more pain (3.42 ± 1.51) than those with small bore tubes (1.50 ± 1.87), with a p-value of 0.009. Additionally, the duration of tube placement was significantly longer for females with small-bore tubes (13.36 ± 3.10 days) compared to those with large-bore tubes (8.83 ± 3.27 days, p = 0.001). Likewise, male patients in the large-bore group reported a mean pain score of 2.94 ± 1.96, which was significantly higher than the small-bore group (1.00 ± 1.37, p=0.002). For males, the tube duration was again longer in the small-bore group (12.25 ± 3.36 days) compared to the large-bore group (8.39 ± 2.75 days, p=0.001). In conclusion, across all age and gender categories, small-bore chest tubes were linked to significantly lower pain scores but required a longer duration of placement, indicating a trade-off between patient comfort and the length of intervention (Table 2).

**Table 2:** Stratification of VAS Scores and Tube Duration by Age and Gender Among Patients Undergoing Large and Small-Bore Chest Tube Placement (N=60)

| Stratification Variables | Category | Outcome | Groups | N | Mean ± SD | t (DF) | p-Value |
|---|---|---|---|---|---|---|---|
| Age | ≤45 | VAS (24 h) | Large | 6 | 4.00 ± 1.67 | t (11) = 2.42 | 0.037 |
| | | | Small | 7 | 1.43 ± 2.15 | | |
| | | Tube Duration (days) | Large | 6 | 6.83 ± 2.99 | t (11) = 2.89 | 0.017 |
| | | | Small | 7 | 12.43 ± 3.99 | | |
| | >45 | VAS (24 h) | Large | 24 | 2.92 ± 1.77 | t (44) = 3.69 | 0.001 |
| | | | Small | 23 | 1.17 ± 1.47 | | |
| | | Tube Duration (days) | Large | 24 | 9.00 ± 2.80 | t (44) = -4.51 | 0.001 |
| | | | Small | 23 | 12.87 ± 3.07 | | |
| Gender | Female | VAS (24 h) | Large | 12 | 3.42 ± 1.51 | t (33) = -12.2 | 0.009 |
| | | | Small | 14 | 1.50 ± 1.87 | | |
| | | Tube Duration (days) | Large | 12 | 8.83 ± 3.27 | t (17) = 6.86 | 0.001 |
| | | | Small | 14 | 13.36 ± 3.10 | | |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Male | VAS (24 h) | Large | 18 | 2.94 ± 1.96 | t (22) = -10.39 | 0.002 |
| | | | Small | 16 | 1.00 ± 1.37 | | |
| | | Tube Duration (days) | Large | 18 | 8.39 ± 2.75 | t (29) = -3.64 | 0.001 |
| | | | Small | 16 | 12.25 ± 3.36 | | |

For rural patients, those who had large-bore chest tubes reported an average VAS score of 2.67 ± 1.84, while those with small-bore tubes experienced a lower average score of 1.72 ± 1.90. However, this difference wasn't statistically significant (p=0.160). On the other hand, the duration of tube placement in rural patients showed a significant difference: small-bore tubes were in place for an average of 13.72 ± 2.96 days, compared to just 8.07 ± 2.54 days for the large-bore group (p=0.001). This indicates that small-bore tubes tend to stay in longer among rural patients. In urban patients, the difference in pain scores was quite significant: those with large-bore tubes had an average VAS score of 3.60 ± 1.63, while those with small-bore tubes reported only 0.50 ± 0.52 (p=0.001), suggesting that small-bore tubes provide much greater comfort. However, the difference in tube duration for urban patients, 9.07 ± 3.26 days for large bore and 11.33 ± 3.20 days for small bore, didn't reach statistical significance (p=0.082). To sum it up, small-bore chest tubes were linked to significantly less pain for urban patients and longer tube durations for rural patients, with statistical significance observed in both cases for different outcomes. These results imply that a patient's life might affect how chest tube size impacts their experience, possibly due to differences in pain perception, access to healthcare, or follow-up practices (Table 3).

**Table 3:** Stratification of VAS Scores and Tube Duration by Residence Among Patients Undergoing Large and Small-Bore Chest Tube Placement (N=60)

| Residence | | Group | N | Mean ± SD | t (DF) | p-Value |
|---|---|---|---|---|---|---|
| Rural | VAS (24 hr.) | Large | 15 | 2.67±1.83 | t (31) =1.44 | 0.160 |
| | | Small | 18 | 1.72±1.90 | | |
| | Tube Duration (days) | Large | 15 | 8.07±2.54 | t (31) = -5.91 | 0.001 |
| | | Small | 18 | 13.72±2.96 | | |
| Urban | VAS (24 hr.) | Large | 15 | 3.60±1.63 | t (25) =6.78 | 0.001 |
| | | Small | 12 | 0.50±0.52 | | |
| | Tube Duration (days) | Large | 15 | 9.07±3.26 | t (25) = -1.82 | 0.082 |
| | | Small | 12 | 11.33±3.20 | | |

In patients 45 years and younger, 2/2 (100%) in the large-bore group experienced bleeding, while no patients in the small-bore group had bleeding. This was not statistically significant, but with a p- p-value of 0.192 when performing a Fisher's exact test. Among patients older than 45 years, bleeding occurred in 19 out of 47 patients and was similar between large (n=10) and small-bore (n=9) groups, p=0.859. As for subcutaneous emphysema, in the younger cohort (≤45 years of age), there were 3 total cases, 2 in the large-bore group and 1 in the small-bore group, with no significant difference (p=0.559). Among patients older than 45 years of age, 6 had this complication, again higher prevalence in the large bore cohort (n=4) compared to the small cohort (n=2), although not statistically significant (p=0.666). There was one case of wound infection in the younger age group, while five cases presented in the older group. Of note, in the younger group, only one patient with an infection had a small-bore tube (p=1.000), while, on the contrary, most of the infections in older patients (n=4) were in patients with large-bore tubes. But it was not significantly different either (p=0.348). In summary, Table 4 demonstrates that although bleeding and emphysema were more common in the large-bore chest tube group, complications were not statistically significantly different in either age group, likely secondary to the small sample sizes in these subgroups (Table 4).

**Table 4:** Association of Age Groups with Post-Operative Complications Using Fisher's Exact Test

| Age (years) | | | Group | | Total | p-Value |
|---|---|---|---|---|---|---|
| | | | Large | Small | | |
| 45 or below | Bleeding | No | 4 | 7 | 11 | 0.192 (Fisher's Exact) |
| | | | 36.4% | 63.6% | 100.0% | |
| | | Yes | 2 | 0 | 2 | |
| | | | 100.0% | 0.0% | 100.0% | |
| | Total | | 6 | 7 | 13 | |
| | | | 46.2% | 53.8% | 100.0% | |
| More than 45 | Bleeding | No | 14 | 14 | 28 | 0.859 |
| | | | 50.0% | 50.0% | 100.0% | |
| | | Yes | 10 | 9 | 19 | |
| | | | 52.6% | 47.4% | 100.0% | |
| | Total | | 24 | 23 | 47 | |
| | | | 51.1% | 48.9% | 100.0% | |
| 45 or below | Emphysema | No | 4 | 6 | 10 | 0.559 (Fisher's exact) |
| | | | 40.0% | 60.0% | 100.0% | |
| | | Yes | 2 | 1 | 3 | |
| | | | 66.7% | 33.3% | 100.0% | |
| | Total | | 6 | 7 | 13 | |
| | | | 46.2% | 53.8% | 100.0% | |
| More than 45 | Emphysema | No | 20 | 21 | 41 | 0.666 (Fisher's exact) |
| | | | 48.8% | 51.2% | 100.0% | |
| | | Yes | 4 | 2 | 6 | |
| | | | 66.7% | 33.3% | 100.0% | |
| | Total | | 24 | 23 | 47 | |
| | | | 51.1% | 48.9% | 100.0% | |
| 45 or below | Wound infection | No | 6 | 6 | 12 | 1.000 (Fisher's exact) |
| | | | 50.0% | 50.0% | 100.0% | |
| | | Yes | 0 | 1 | 1 | |
| | | | 0.0% | 100.0% | 100.0% | |

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| | | | | | | |
|---|---|---|---|---|---|---|
| | Total | | 6 | 7 | 13 | |
| | | | 46.2% | 53.8% | 100.0% | |
| More than 45 | Wound infection | No | 20 | 22 | 42 | 0.348 (Fisher's exact) |
| | | | 47.6% | 52.4% | 100.0% | |
| | | Yes | 4 | 1 | 5 | |
| | | | 80.0% | 20.0% | 100.0% | |
| | Total | | 24 | 23 | 47 | |
| | | | 51.1% | 48.9% | 100.0% | |

The study demonstrated post-procedural complications of bleeding, subcutaneous emphysema, and wound infection stratified by gender and chest tube size, either large or small bore. Ten of 26 females bled, again with a trend towards larger numbers in the large bore group (n=6) versus small bore group (n=4), though this was not significant (p=0.422). Of the 34 male patients who presented with bleeding, the majority were similar across both tubes, and there was no statistically significant difference in bleeding between tube types (11/34; p= 1.000). Amongst patients who developed subcutaneous emphysema, 5 out of the 26 females had subcutaneous air, with 4 of these being in the large-bore arm. This difference was not significant and approached the significance level (p=0.148). Among males, 4 of 34 from both groups developed emphysema, with no significant difference (p=1.000). For wound infection, there were 2 female patients in both large tube and small bore, for a p-value of 1.000. Two infections were seen in male patients, in the large-bore group, while there were no infections in the small-bore group; but this was also not statistically significant (p=0.487). In general, no statistically significant differences in complication rates between genders were found, although certain trends, such as an increase in frequency of emphysema in females having large-bore tubes, were noted. This indicates that the size of the chest tube is probably not the most important variable in terms of risk of complications when stratified by gender (Table 5).

**Table 5:** Stratification of Bleeding, Subcutaneous Emphysema, and Wound Infection by Gender and Chest Tube Type (N=60)

| Gender | | | Group | | Total | p-Value |
|---|---|---|---|---|---|---|
| | | | Large | Small | | |
| Female | Bleeding | No | 6 | 10 | 16 | 0.422 (Fisher's exact) |
| | | | 37.5% | 62.5% | 100.0% | |
| | | Yes | 6 | 4 | 10 | |
| | | | 60.0% | 40.0% | 100.0% | |
| | Total | | 12 | 14 | 26 | |
| | | | 46.2% | 53.8% | 100.0% | |
| Male | Bleeding | No | 12 | 11 | 23 | 1.000 (Fisher's exact) |
| | | | 52.2% | 47.8% | 100.0% | |
| | | Yes | 6 | 5 | 11 | |
| | | | 54.5% | 45.5% | 100.0% | |
| | Total | | 18 | 16 | 34 | |
| | | | 52.9% | 47.1% | 100.0% | |
| Female | Emphysema | No | 8 | 13 | 21 | 0.148 (Fisher's exact) |
| | | | 38.1% | 61.9% | 100.0% | |
| | | Yes | 4 | 1 | 5 | |
| | | | 80.0% | 20.0% | 100.0% | |
| | Total | | 12 | 14 | 26 | |
| | | | 46.2% | 53.8% | 100.0% | |
| Male | Emphysema | No | 16 | 14 | 30 | 1.000 (Fisher's exact) |
| | | | 53.3% | 46.7% | 100.0% | |
| | | Yes | 2 | 2 | 4 | |
| | | | 50.0% | 50.0% | 100.0% | |
| | Total | | 18 | 16 | 34 | |
| | | | 52.9% | 47.1% | 100.0% | |
| Female | Wound infection | No | 10 | 12 | 22 | 1.000 (Fisher's exact) |
| | | | 45.5% | 54.5% | 100.0% | |
| | | Yes | 2 | 2 | 4 | |
| | | | 50.0% | 50.0% | 100.0% | |
| | Total | | 12 | 14 | 26 | |
| | | | 46.2% | 53.8% | 100.0% | |
| Male | Wound infection | No | 16 | 16 | 32 | 0.487 (Fisher exact) |
| | | | 50.0% | 50.0% | 100.0% | |
| | | Yes | 2 | 0 | 2 | |
| | | | 100.0% | 0.0% | 100.0% | |
| | Total | | 18 | 16 | 34 | |
| | | | 52.9% | 47.1% | 100.0% | |

## DISCUSSION

The development of malignant pleural effusion is a poor prognostic factor. Recurrent pleural effusion can cause severe, debilitating symptoms and impaired quality of life. In some cases, MPE may coexist with other pulmonary conditions or infections, such as mycobacterial disease, further complicating patient management and outcomes [17, 18]. Treatment of malignant pleural effusion is palliative and therefore should be associated with a low morbidity and mortality rate. Treatment options are variable, and findings in some reports have demonstrated that small-bore catheters (8-10 Fr in one study and 7-24 Fr in another) are as effective as large chest tubes in treating malignant effusions [19]. Interest in the use of small-bore catheters for effusion drainage and sclerotherapy is based on the premise that it may be less invasive as a procedure and thus better tolerated by patients compared to standard large-bore chest tubes, with no Compromise in efficacy [20]. In this study, 60 patients with malignant pleural effusion were enrolled; they were divided into two groups: Group A (30 patients) used a small-bore chest tube, and Group B (30 patients) used a large-bore chest tube. Although males constituted about 75% of the total study cohort but male and female distribution in the two groups was almost the same. The two groups were comparable in their basic characteristics with no significant differences in ages, genders. Many studies [21] had compared the efficacy of small-bore chest tubes against standard large-bore chest

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tubes, and the results showed that the small-bore chest tubes were at least as successful as the traditional large-bore tubes. In our study, there was no casualty reported, and the procedure was well tolerated and resulted in a satisfactory response with minimal complications. This is following a comparative study of small-bore catheter versus traditional large chest tube in the management of malignant pleural effusion [22] and supported the role of small-bore catheter in the management of malignant pleural effusion. In our study, there is no reported case of hemothorax or excessive bleeding. This is supported by studies [23, 24]. In our study, drain dislodgement was monitored through daily clinical examination and drain output assessment, with chest radiography performed when indicated, and managed promptly by repositioning or reinsertion. Drain dislodgement was high in 4 (10%) patients of Group A (SBCD) as compared to 2 (5%) in Group B (LBCD). This is almost like a study where 1 (6.6%) case of dislodgement was reported in Group A (SBCD) only [25]. This may be due to the drain not being securely attached to the chest wall. Pain was measured using the numerical pain rating scale (score from 0 to 10) greater than 3 post-tube insertion. It was significantly higher in Group B (LBCD) as compared to Group A (SBCD). In 6(15%) patients in group B, pain was recorded as compared to 2(5%) patients in group A. This finding is observed in a study that demonstrates that smaller (12F) chest tubes are associated with less pain than larger (24F) tubes [26]. Small-bore chest tubes appear to be at greater risk of blockage, kinking. Studies suggested that a blockage rate of small-bore tubes of 8.1% compared to 5.2% for large-bore tubes in a prospective (non-randomised) study [21], which is consistence with findings of this study. Routine drain flushing was not part of our protocol; however, its use in future practice could further reduce blockage and improve outcomes with small-bore drains. Chest tube quality, number of pores in it, and intubation technique may contribute to this high rate of tube blockage in our setup. Overall, 14 (35%) complications were found in Group A (SBCD) as compared to 10 (25%) complications in Group B (LBCD). This satisfies our result with [13] that both small chest drains and large-bore chest drains have comparable complications. Though complications were high in small-bore chest drain 35% as compared to large-bore chest drain 25% but most of the complications, i.e., 8(20%) in small-bore chest drain, were due to drain blockage, which can be minimized with frequent drain washing. Thus, small-bore chest drains can be opted in the management of in the management of malignant pleural effusions in our setup.

This study was limited by its single-center design, relatively small sample size, and non-randomized allocation of chest tube size, which may introduce selection bias and limit generalizability. Furthermore, long-term outcomes such as recurrence rates, quality of life measures, and pleurodesis success were not assessed. Future multicenter randomized controlled trials with larger sample sizes and extended follow-up are recommended to validate these findings and evaluate long-term efficacy, cost-effectiveness, and patient-reported outcomes associated with different chest tube sizes in malignant pleural effusion management.

## CONCLUSIONS

In conclusion, small-bore chest tubes also provide significantly reduced levels of pain in comparison to large-bore tubes, especially in older and female patients. Placement time is typically longer with small-bore tubes, but complication rates are similar overall. Less painful may help comfort the patient, though longer may be associated with more healthcare resources. In summary, small-bore chest tubes are as safe as and a more comfortable alternative for the treatment of malignant pleural effusion tubing. Based on the findings of this study, it is recommended that small-bore chest tubes be considered a preferred option for the management of malignant pleural effusion, particularly in older female patients and those residing in urban areas, where reduced pain levels were notably observed.

## Authors' Contribution

Conceptualization: MY, AU
Methodology: RA, KR, RS, SS, AY, SA
Formal analysis: MY, AU
Writing and Drafting: AU
Review and Editing: AU, RA, KR, RS, SS, AY, SA, MY

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Prevalence of Methotrexate Intolerance in Patients with Rheumatoid Arthritis, Psoriatic Arthritis and Juvenile Idiopathic Arthritis

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## ABSTRACT

Methotrexate intolerance is frequently encountered, however, seldom studied scientifically in a low-resource setting. Hence, the study was planned to look for the areas for possible early interventions that may assist in decreasing or preventing intolerance, and its early identification may impact treatment, leading to timely changes in medication that may promote patient compliance and better control of the disease. **Objectives:** To determine the prevalence of methotrexate intolerance in patients with rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis. **Methods:** This descriptive comparative study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period 12th February 2025 to 31st May 2025. Male and female patients aged 10 to 70 years diagnosed with rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis were enrolled and evaluated for methotrexate intolerance using the MISS questionnaire, taking a score ≥6 as a cut-off for the presence of intolerance. **Results:** Mean age was 38.85 ± 17.31 years, and the majority of participants had an age of more than 40 years (n=81, 53.6%), while 91 patients (60.3%) were male. Rheumatoid arthritis was the most common clinical diagnosis (n=91, 60.3%). Overall, methotrexate intolerance was observed in 58 (38.4%) patients. Methotrexate intolerance was most common in rheumatoid arthritis patients (n=38, 41.8%) (p-value=0.323). **Conclusions:** Though methotrexate intolerance is fairly common among patients with rheumatic disorders, no statistically significant association was observed between intolerance and background disease or baseline parameters such as route of administration.

## INTRODUCTION

Persistent arthritic conditions are a hallmark of autoimmune diseases such as psoriasis-associated arthritis (PsA) and rheumatoid arthritis (RA) [1]. Methotrexate (MTX) remains the primary disease-modifying anti-rheumatic medication (DMARD) for treating RA and PsA because of its affordability, effectiveness, and tolerable safety record [2]. Despite many beneficial effects, MTX use has been linked to various adverse events such as GI distress (abdominal pain, nausea and vomiting), cytopenias and hepatic enzymes derangements [3]. GI adverse events like nausea and abdominal pain were reported by 85.5% and 59.4% respectively, in a cross-sectional study. Overall, MTX intolerance was reported by 34.5% patients [4]. The greatest rate of methotrexate intolerance was seen in JIA/uveitis patients. The sole predictor of intolerance risk was the subcutaneous injection method [5]. MTX intolerance was found in a significant proportion of rheumatoid arthritis patients [6]. Patients with juvenile idiopathic arthritis (JIA) experienced a wide range of gastrointestinal adverse reactions before and following taking MTX (anticipatory and associative). Following the use of MTX, the latter complaints develop as a conventional conditioning reaction to digestive issues [7]. As a result, MTX-induced gastrointestinal side effects, commonly labelled MTX intolerance, are complicated and may make it much harder to take a medication that might

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usually work. Although gastrointestinal complications from MTX are common in RA and PsA, the nature and extent of these side effects, particularly their presence, have not been evaluated [8]. Methotrexate is a cornerstone of therapy in autoimmune diseases, a valuable chemotherapeutic agent and a potent immunosuppressant in organ transplant patients. Among autoimmune diseases, methotrexate holds a central role in the management of rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis because of its therapeutic effect and cost effectiveness [9]. Despite an acceptable safety profile, a major limitation to its use is intolerance to the drug. Serious adverse effects such as pulmonary toxicity, hepatotoxicity and bone marrow suppression are rare or transient if MTX is stopped. Drug intolerance leads to discontinuation of therapy and the need for novel agents, resulting in more health care and societal costs [10]. The frequency of MTX intolerance in rheumatism has been evaluated in a number of studies. A significantly elevated proportion of MTX intolerance, 50.5%, was noted in the population of 297 patients in a research study in which the MISS score was verified. A greater likelihood of intolerance was linked to a somewhat greater MTX dose, most likely as a result of an elevated plasma level of medication. Additionally, individuals taking parenteral MTX had a 23% greater rate of MTX intolerance [11]. Adult individuals with psoriatic and rheumatoid arthritis were examined for MTX intolerance in a cross-sectional study. In a sample of 291 patients, GI adverse events were reported by 123 patients (42.3%); however, MTX intolerance was shown to be 11% prevalent. Patients receiving parenteral MTX had a greater rate of MTX intolerance (20.6%) compared to those receiving oral MTX (6.2%) [12]. A total of 138 patients with JIA were evaluated for methotrexate intolerance using the MISS questionnaire. Taking a score of 6 as a cut, the prevalence of intolerance was 62.3% [13]. Prompt recognition of intolerance could have a direct effect on treatment, resulting in timely adjustments to medications that could improve adherence by patients and alleviate symptoms.

Although methotrexate (MTX) remains the cornerstone therapy for rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis, intolerance to the drug frequently compromises treatment adherence and clinical outcomes. Most available evidence on MTX intolerance originates from high-income countries, with limited data from resource-limited settings such as Khyber Pakhtunkhwa, Pakistan. Furthermore, variations in demographic characteristics, route of administration, and disease profiles may influence intolerance patterns, yet local comparative data across RA, JIA, and PsA populations remain scarce. This gap underscores the need to determine the prevalence and associated factors of MTX intolerance in our setting to guide early identification and intervention strategies. This study aims to determine the prevalence of methotrexate intolerance in patients with RA, JIA, and PsA who presented to a tertiary care resource-limited setting in Khyber Pakhtunkhwa. To identify potential early measures that could help reduce or prevent intolerance.

## METHODS

This descriptive comparative study was carried out at the Department of Rheumatology, Khyber Teaching Hospital, Peshawar, during the period 12th February 2025 to 31st May 2025, after taking permission from the hospital IRB vide no: 138/DME/KMC. Male and female patients aged 10 to 70 years diagnosed with rheumatoid arthritis, psoriatic arthritis and juvenile rheumatoid arthritis were enrolled. Patients with endoscopically proven peptic ulcer disease, pregnant patients, psychiatric illnesses such as eating disorders, a history of bowel surgery and patients with cytopenias were excluded. Rheumatoid arthritis was confirmed with ACR criteria by the presence of at least four among morning stiffness, soft tissue swelling, small joint arthritis, symmetrical distribution of joint swelling, subcutaneous nodules, raised inflammatory markers such as RA factors and ESR/CRP. Juvenile rheumatoid arthritis was confirmed with similar criteria, with the addition of symptoms in patients aged less than 16 years. Psoriatic arthritis was confirmed with CASPAR criteria scoring 3 or above. CASPAR criteria included clinical presence of psoriasis, psoriatic nail dystrophy, seronegativity, dactylitis and radiologic evidence of bone erosions. Intolerance was confirmed with MISS (Methotrexate Intolerance Severity Score), which comprised four parameters including abdominal pain, nausea, vomiting and behavioural symptoms occurring upon, before (anticipatory) and when thinking of MTX (associative). MTX intolerance was defined as ≥6 on the MISS with ≥1 point on anticipatory and/or associative and/or behavioural items. Sample size was 151, calculated using the WHO sample size calculator using 11% anticipated proportion of methotrexate intolerance, with 5% margin of error and 95% confidence level [12]. Participants were recruited using a nonprobability consecutive sampling technique. Informed consent was taken from enrolled patients before initiating the study. Baseline information like age, gender, body mass index (BMI), smoking history, residence, education and SE status were recorded. Clinical information gathered included diagnosis, mode of methotrexate administration (oral/subcutaneous), drug duration (weeks), disease activity, concomitant disease and medications. An interview was arranged with all patients after comfortably seating them in a quiet room in a chair. History was taken based on the MISS questionnaire about methotrexate related events, including abdominal pain, nausea, vomiting

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and behavioural symptoms. The score was calculated, and a score ≥6 was noted. Data analysis was carried out using IBM SPSS version 26.0. Descriptive statistics were carried out for reporting baseline demographic and clinical parameters. Continuous data like age, BMI, disease duration and MISS score were reported as means and standard deviations and categorical data like gender, family history, residence, education, profession, smoking, comorbidities, disease activity and methotrexate intolerance were presented as frequencies and percentages. Effect modifiers were controlled through stratification. Post-stratification chi-square test was applied at 5% significance level.

## RESULTS

The mean age of participants was 38.85 years, with a standard deviation of 17.311, the mean BMI was 25.179 ± 0.978kg/m$^2$, and the Mean MISS score was 5.059 ± 1.87 as reported in table 1.

**Table 1:** Descriptive Statistics of Study Participants (n=151)

| Parameters | Mean ± SD |
|---|---|
| Age (Years) | 38.9 ± 17.3 |
| BMI (kg/m$^2$) | 25.1 ± 1.0 |
| Duration (Months) | 8.2 ± 2.9 |
| MISS | 5.06 ± 1.9 |

The majority of study participants were more than 40 years (n = 81, 53.6%), while 91 patients (60.3%) were male. 81 patients (53.6%) belonged to rural areas. 39 (25.8%) patients had a family history of rheumatic disease, and 42 patients (27.8%) were smokers. 130 patients (86.1%) were taking methotrexate orally, and 59 (39.1%) had severe disease activity. Rheumatoid arthritis was the most common recorded in 91 patients (60.3%), as shown in Table 2.

**Table 2:** Baseline Clinical and Demographic Information of Study Participants (n=151)

| Parameters | Subgroups | Frequency (%) |
|---|---|---|
| Age (Years) | Below 17 | 32 (21.2%) |
| | 17-40 | 38 (25.2%) |
| | Above 40 | 81 (53.6%) |
| Gender | Male | 91 (60.3%) |
| | Female | 60 (39.7%) |
| BMI (kg/m$^2$) | 24.0 or Below | 23 (15.2%) |
| | More Than 24.0 | 128 (84.8%) |
| Disease Duration (Months) | 6 or Below | 46 (30.5%) |
| | More Than 6 | 105 (69.5%) |
| Residence | Rural | 81 (53.6%) |
| | Urban | 70 (46.4%) |
| Education | No Formal Schooling | 42 (27.8%) |
| | Matric or Below | 77 (51.0%) |
| | Above Matric | 32 (21.2%) |
| Family Hx | Yes | 39 (25.8%) |
| | No | 112 (74.2%) |
| Smoking | Yes | 42 (27.8%) |
| | No | 109 (72.2%) |
| Comorbidities | Yes | 30 (19.9%) |
| | No | 121 (80.1%) |
| Route | Oral | 130 (86.1%) |
| | SC | 21 (13.9%) |
| Disease Activity | Mild | 42 (27.8%) |
| | Moderate | 59 (39.1%) |
| | Severe | 50 (33.1%) |
| Diagnosis | RA | 91 (60.3%) |
| | JIA | 36 (23.8%) |
| | PA | 24 (15.9%) |

32 patients (100.0%) had juvenile rheumatoid arthritis and were aged 16 years or below, while 04 patients (10.5%) with JRA were in the aging more than 16 years or older. 59 patients (64.8%) with rheumatoid arthritis were male compared to 32 (53.3%) female. 28 patients (71.8%) with rheumatoid arthritis had a family history of RA. Moderate disease activity was recorded in 31 RA patients (61.0%), 14 (23.7%) JRA and 09 (15.3%) with psoriatic arthritis, as reported in table 3.

**Table 3:** Patient Distribution with Respect to Diagnosis (n=151)

| Parameters | | Diagnosis | | | Total |
|---|---|---|---|---|---|
| | | RA (n=91) | JRA (n=36) | PA (n=24) | |
| Age (Years) | 16 and Below | 0 (0.0%) | 32 (100.0%) | 0 (0.0%) | 32 (100.0%) |
| | 17 to 40 | 22 (57.9%) | 4 (10.5%) | 12 (31.6%) | 38 (100.0%) |
| | More than 40 | 69 (85.2%) | 0 (0.0%) | 12 (14.8%) | 81 (100.0%) |
| Gender | Male | 59 (64.8%) | 16 (17.6%) | 16 (17.6%) | 91 (100.0%) |
| | Female | 32 (53.3%) | 20 (33.3%) | 8 (13.3%) | 60 (100.0%) |
| BMI (kg/m$^2$) | ≤24.0 | 19 (82.6%) | 4 (17.4%) | 0 (0.0%) | 23 (100.0%) |
| | >24.0 | 72 (56.3%) | 32 (25.0%) | 24 (18.8%) | 128 (100.0%) |
| Smoking | Yes | 33 (78.6%) | 4 (9.5%) | 5 (11.5%) | 42 (100.0%) |
| | No | 58 (53.2%) | 32 (29.4%) | 19 (17.4%) | 109 (100.0%) |
| Family History | Yes | 28 (71.8%) | 4 (10.3%) | 7 (17.9%) | 39 (100.0%) |
| | No | 63 (56.3%) | 32 (28.6%) | 17 (15.2%) | 112 (100.0%) |
| Route | Oral | 79 (60.8%) | 31 (23.8%) | 20 (15.4%) | 130 (100.0%) |
| | SC | 12 (57.1%) | 5 (23.8%) | 4 (19.0%) | 21 (100.0%) |
| Disease Activity | Mild | 25 (59.5%) | 10 (23.8%) | 7 (16.7%) | 42 (100.0%) |
| | Moderate | 36 (61.0%) | 14 (23.7%) | 9 (15.3%) | 59 (100.0%) |
| | Severe | 30 (60.0%) | 12 (24.0%) | 8 (16.0%) | 50 (100.0%) |
| Duration (Months) | 6 or Below | 27 (58.7%) | 14 (30.4%) | 5 (10.9%) | 46 (100.0%) |
| | More Than 6 | 64 (61.0%) | 22 (21.0%) | 19 (18.1%) | 105 (100.0%) |
| Joints | Right | 33 (67.3%) | 8 (16.3%) | 8 (16.3%) | 49 (100.0%) |
| | Left | 29 (56.9%) | 12 (23.5%) | 10 (19.6%) | 51 (100.0%) |
| | Bilateral | 29 (56.9%) | 16 (31.4%) | 6 (11.8%) | 51 (100.0%) |
| Comorbidities | Yes | 17 (56.7%) | 4 (13.3%) | 9 (30.0%) | 30 (100.0%) |
| | No | 74 (61.2%) | 32 (26.4%) | 15 (12.4%) | 121 (100.0%) |

Methotrexate intolerance was observed in 58 (38.4%) patients, while 58 (38.4%) were methotrexate tolerate, as reported in figure 1.

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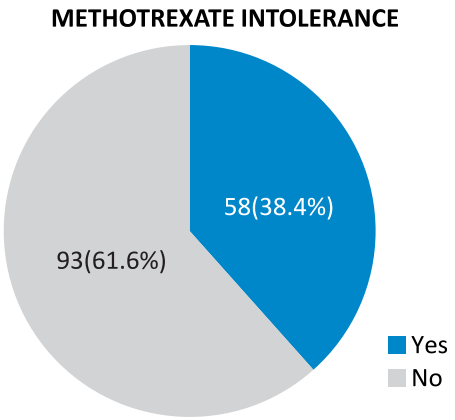


**Figure 1:** Methotrexate Intolerance among Study Participants (n=151)

38 patients (41.8%) with rheumatoid arthritis were intolerant to methotrexate compared to 14 (38.9%) with JIA and 6 (25.0%) with psoriatic arthritis (p-value=0.323), as reported in table 4.

**Table 4:** Subgroup Analysis of Methotrexate Intolerance with Background Diagnosis (n=151)

| Parameters | | Intolerance | | Total | p-Value |
|---|---|---|---|---|---|
| | | No | Yes | | |
| Diagnosis | RA | 53 (58.2%) | 38 (41.8%) | 91 (100.0%) | 0.323 |
| | JIA | 22 (61.1%) | 14 (38.9%) | 36 (100.0%) | |
| | PA | 18 (75.0%) | 6 (25.0%) | 24 (100.0%) | |
| Total | | 93 (61.6%) | 58 (38.4%) | 151 (100.0%) | |

22 patients (64.7%) in the age group (21-40 years) were intolerant to methotrexate compared to 14 (38.9%) and 22 (27.2%) in the age groups 20 or below and more than 40 years respectively (p value 0.001. No other statistically significant association was recorded with other parameters, as reported in table 5.

**Table 5:** Demographic Information of Intolerance

| Parameters | | Intolerance | | Total | p-Value |
|---|---|---|---|---|---|
| | | No | Yes | | |
| Age (Years) | Below 17 | 20 (62.5%) | 12 (37.5%) | 32 (100.0%) | 0.001 |
| | 17 to 40 | 14 (36.8%) | 24 (63.2%) | 38 (100.0%) | |
| | Above 40 | 59 (72.8%) | 22 (27.2%) | 81 (100.0%) | |
| Gender | Male | 58 (63.7%) | 33 (36.3%) | 91 (100.0%) | 0.504 |
| | Female | 35 (58.3%) | 25 (41.7%) | 60 (100.0%) | |
| BMI ($kg/m^2$) | 24.0 or Below | 17 (73.9%) | 6 (26.1%) | 23 (100.0%) | 0.187 |
| | More than 24.0 | 76 (59.4%) | 52 (40.6%) | 128 (100.0%) | |
| Route | Oral | 83 (63.8%) | 47 (36.2%) | 130 (100.0%) | 0.156 |
| | SC | 10 (47.6%) | 11 (52.4%) | 21 (100.0%) | |
| Disease Activity | Mild | 25 (59.5%) | 17 (40.5%) | 42 (100.0%) | 0.849 |
| | Moderate | 38 (64.4%) | 21 (35.6%) | 59 (100.0%) | |
| | Severe | 30 (60.0%) | 20 (40.0%) | 50 (100.0%) | |
| Comor-bidities | Yes | 19 (63.3%) | 11 (36.7%) | 30 (100.0%) | 0.826 |
| | No | 74 (61.2%) | 47 (38.8%) | 121 (100.0%) | |
| Disease Duration (Months) | 6 or Below | 27 (58.7%) | 19 (41.3%) | 46 (100.0%) | 0.628 |
| | More Than 6 | 66 (62.9%) | 39 (37.1%) | 105 (100.0%) | |
| Smoking History | Yes | 24 (57.1%) | 18 (42.9%) | 42 (100.0%) | 0.486 |
| | No | 69 (63.3%) | 40 (36.7%) | 109 (100.0%) | |
| Family History | Yes | 20 (51.3%) | 19 (48.7%) | 39 (100.0%) | 0.124 |
| | No | 73 (65.2%) | 39 (34.8%) | 112 (100.0%) | |

## DISCUSSION

In addition to the widely recognized abdominal discomfort that MTX causes, investigators reported that patients with RA, JIA and PA additionally experienced anticipated and associated digestive and behavioural manifestations. These complaints are all referred to as MTX intolerance. 38.4% of our study cohort had MTX intolerance. Equivalent Intolerant rates comparable to our study have been reported in RA studies [11, 12]. Gastrointestinal toxicity is the primary dose-limiting concern for MTX usage. Intestinal mucositis caused by MTX poses a significant challenge to patients. It can impact the whole alimentary tract and is frequently accompanied by cramps, nausea, and pain in the stomach [14]. The frequency of MTX intolerance in RA was slightly higher compared to JIA and psoriatic arthritis. Our findings demonstrated a higher prevalence of MTX intolerance in adult rheumatoid arthritis (RA) patients compared to adolescents, but the difference was statistically significant (p-value=0.323). Methotrexate intolerance is a complex phenomenon. Three fundamental concepts comprise the complicated belief system associated with methotrexate intolerance: beliefs on the dangers of RA, the advantages of methotrexate, and the risk of methotrexate [15]. In this study, we also found that MTX intolerance was more common in patients receiving parenteral MTX (52.4%) compared to oral MTX (36.8%); however, this difference in intolerance did not reach statistical significance. More behavioural problems in the parenteral group were the reason for this discrepancy. Apart from the route of administration, there are also concerns about the dosing with high doses attributed to severe complications such as malignancies [16]. Given their prior oral MTX complaints, individuals who shifted could have become more likely to experience gastrointestinal and behavioural side effects when taking parenteral MTX, which would have increased the incidence of MTX intolerance in the injectable category. MTX intolerance was substantially correlated with age; specifically, patients in the age group 20 to 40 years had a higher likelihood of having MTX intolerance than those in the extreme ages. MTX-related gastrointestinal and additional problems were not linked to younger or older ages in earlier research [17]. To ascertain if younger age is an independent risk contributor to MTX intolerance, confirmatory research is necessary. In addition to impeding the administration of MTX, intolerance can undermine patients' standard of living [1]. However, strictly speaking, these indications do not seem particularly

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noticeable. As a result, they are difficult to identify by medical evaluation alone, but the MISS can identify them [8]. Thus, it is beneficial to use the MISS as it enables early symptom diagnosis. This could open up an area of possibility for prompt MTX intolerance therapy along with prompt physiological relief of symptoms, which might stop conditioned reactions and MTX intolerance from developing. Reducing the MTX dosage, moving to parenteral MTX, initiating behavioural therapy, or using antiemetics like ondansetron are all possible treatments for (physical) symptoms [18, 19]. Using an established questionnaire, the current research is the initial attempt to show the proportion of patients affected by MTX intolerance. Intolerance was more prevalent in those receiving parenteral (subcutaneous) than oral MTX. Considering the primary explanation for stopping MTX is continuous gastrointestinal issues, intolerant patients may be more inclined to quit taking MTX altogether or switch to costlier biological therapies or (less potent) DMARDs [20]. The MISS can be used in regular clinical settings to closely observe patients and promptly assist by employing the aforementioned strategies to avoid or mitigate the detrimental effects of MTX intolerance on patients' daily activities, adherence, and ability to continue receiving successful therapy.

This study was limited by its single-center design and non-probability consecutive sampling, which may restrict the generalizability of findings to the broader rheumatology population. Additionally, the cross-sectional nature of the study precludes assessment of causal relationships and long-term treatment outcomes related to methotrexate intolerance. Future multicenter longitudinal studies with larger sample sizes are recommended to evaluate predictors of intolerance, assess the impact on treatment adherence and disease control, and explore targeted preventive strategies to optimize methotrexate therapy in patients with rheumatic diseases.

## CONCLUSIONS

The study demonstrated via the internationally accepted MISS assessment that the prevalence of MTX intolerance was 38.4%, and it was more common in patients on parenteral MTX than in those on oral MTX, and it continued after switching from parenteral to oral MTX. Moreover, patients in the third and fourth decades of life were more often intolerant to MTX. Because persistent MTX intolerance can negatively affect a patient's quality of life and interfere with MTX use, RA, JIA and PA patients on MTX, it is recommended to observe them using the MISS for early identification of MTX intolerance.

## Authors' Contribution

Conceptualization: UA
Methodology: IUD, HA, MI, AZ
Formal analysis: MI
Writing and Drafting: UA, AA, IUD, HA, AZ
Review and Editing: UA, AA, IUD, HA, AZ, MI

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Common Clinical Presentation and Outcome of Severe Malaria in Pediatric Age Group (1-12 years) at Allama Iqbal Teaching Hospital, Dera Ghazi Khan, Pakistan

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## ABSTRACT

Malaria remains a significant public health challenge worldwide, particularly in tropical and subtropical regions. **Objectives:** To determine the clinical presentation and outcomes of severe malaria in children aged 1-12 years. **Methods:** This prospective observational study was conducted in the Pediatrics Department, Allama Iqbal Teaching Hospital, DG Khan, from May 2024 to January 2025, including children aged 1–12 years with severe malaria, selected via non-probability consecutive sampling. Demographic and clinical data were recorded at admission, and all patients received IV artesunate. Successful discharge was defined by full clinical recovery and stable vitals. Data analysis was done using SPSS version 26.0, employed chi-square/Fisher's exact tests for categorical and t-tests for continuous variables, with $p<0.050$ considered significant. **Results:** In a total of 120 children, 80 (66.7%) were male. The median age was 7.0 (4.0-10.0) years. Malnutrition was identified in 59 (49.2%) children. *Plasmodium vivax* was the predominant malarial parasite identified in 84 (70.0%) children. The most common clinical presentations were severe anemia, impaired consciousness, seizures, and respiratory distress, observed in 82 (68.3%), 50 (41.7%), 30 (25.0%), and 22 (18.3%), respectively. Mortality was reported, and all children were successfully discharged. Significantly longer hospital stay was noted among children with seizures (8.0 [5.0-11.0] vs. 6.0 [4.0-8.0], p=0.024). **Conclusions:** Severe malaria in children most commonly presents with severe anemia, impaired consciousness, and seizures, with Plasmodium vivax as the predominant causative organism. All enrolled children recovered and were discharged without mortality, indicating favorable short-term outcomes under the current management protocol.

## INTRODUCTION

Malaria remains a significant public health challenge worldwide, particularly in tropical and subtropical regions where the disease is endemic [1]. According to the WHO, malaria is responsible for an estimated 241 million cases and 627,000 deaths annually, with children under five years being the most vulnerable group [1]. However, older children also bear a substantial burden, particularly in endemic regions like Pakistan [2]. Pakistan is among the countries with a high burden of malaria, primarily caused by *Plasmodium vivax (P. vivax)* and *Plasmodium falciparum (P. falciparum)* [3, 4]. The disease is prevalent in rural and low-resource settings, where access to prompt diagnosis and treatment remains a challenge [5]. Severe malaria can result in life-threatening complications such as cerebral malaria, severe anemia, respiratory distress, acute kidney injury, and multi-organ failure [6]. According to WHO estimates, children account for nearly 76% of global malaria-related deaths, with most fatalities due to P. falciparum infection [7, 8]. In Pakistan, malaria accounts for 2-3 million cases annually, with a rising incidence in endemic areas such as South Punjab [9, 10]. *P. falciparum* contributes to 30-40% of malaria cases in Pakistan, with an increasing proportion of severe malaria cases [11]. Although pediatric malaria remains a significant

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contributor to childhood morbidity and mortality in South Punjab, most available literature is either outdated or originates from tertiary care centers in major urban settings, which may not reflect the unique epidemiological, socioeconomic, and healthcare challenges faced by resource-limited districts such as DG Khan [12]. There is a paucity of recent, systematically collected data describing the clinical spectrum, management, and short-term outcomes of severe malaria in children presenting to secondary-level hospitals in this region. This study directly addresses this gap by providing prospective, hospital-based evidence from a representative cohort in South Punjab, focusing on both the clinical characteristics and real-world outcomes following standardized treatment protocols. By delineating the prevailing clinical presentations, complications, and discharge outcomes among children with severe malaria, our findings offer actionable insights for frontline clinicians, local policymakers, and public health authorities to tailor intervention strategies, allocate resources more effectively, and refine region-specific clinical guidelines. This targeted approach is especially important in the context of persistent poverty, malnutrition, and healthcare barriers that can influence disease progression and response to treatment in this population.

Although malaria remains a major contributor to pediatric morbidity in Pakistan, region-specific data on the clinical spectrum and short-term outcomes of severe malaria in South Punjab are limited. Most existing studies originate from large urban tertiary centers or are outdated, potentially overlooking evolving epidemiological trends such as the increasing role of *Plasmodium vivax* in severe disease. Furthermore, systematic prospective evaluations linking clinical manifestations with hospitalization outcomes in secondary-level hospitals are scarce. Therefore, updated local evidence is needed to guide region-specific clinical management and resource allocation. This study aims to determine the clinical presentation and outcomes of severe malaria in children aged 1-12 years.

## METHODS

This prospective observational study was conducted at the Department of Pediatrics, Allama Iqbal Teaching Hospital, DG Khan, Pakistan, from May 2024 to January 2025, after obtaining approval from the Institutional Ethical Review Board (PM. U-I/008/1027/A.I. T Hosp, DGK). Sample selection was done using a non-probability consecutive sampling technique. A sample size of 120 was calculated using the online OpenEPI sample size calculator, considering the proportion of anemia in children with malaria as 87.1% [13], with a 95% confidence level and a 6% margin of error. The inclusion criteria were children of any gender, aged 1-12 years, who were diagnosed with severe malaria based on clinical and laboratory criteria outlined by the WHO 2022 guidelines. The exclusion criteria were known hematological disorders, like sickle cell disease or hemolytic anemia. Children diagnosed with meningitis or encephalitis, or with concurrent infections (e.g., dengue or typhoid fever), were also excluded. Severe malaria was labeled based on the presence of *P. falciparum*, or P. vivax parasitemia on peripheral blood smear or rapid diagnostic test (RDT), along with one or more severe manifestations such as impaired consciousness (Glasgow Coma Scale <11 or Blantyre Coma Scale <3 in younger children), seizures, severe anemia (Hb <7 g/dL), respiratory distress, metabolic acidosis, circulatory collapse (shock), jaundice, renal impairment, or hypoglycemia (<40 mg/dL). Informed consent was obtained from all participants or legal guardians after explanation of study objectives and procedures. Upon admission, demographic information like age, gender, residential status, and vaccination status was obtained. Relevant laboratory investigations were evaluated. All children were treated with IV artesunate at a weight-based dosage according to WHO 2022 guidelines, as 3.0 mg/kg for children weighing <20 kg, and 2.4 mg/kg for those >20 kg. Artesunate was administered at 0, 12, and 24 hours, followed by once-daily dosing thereafter. Treatment continued with IV artesunate until the patient was clinically stable and able to tolerate oral therapy, typically within 48 to 72 hours. After that, a full 3-day course of oral artemisinin-based combination therapy was initiated to complete the antimalarial regimen. Supportive treatment, including IV fluids, blood transfusions, anticonvulsants, oxygen therapy, or mechanical ventilation (for respiratory failure), was provided as per clinical requirements. Outcomes were recorded in terms of in-hospital mortality or discharge, and duration of hospital stay. Once children were able to tolerate oral therapy, they were transitioned to a full course of oral artemisinin-based combination therapy to complete the antimalarial treatment as per WHO guidelines. Successful discharge was defined as clinical resolution of severe malaria features, including restoration of consciousness, cessation of seizures, correction of anemia and metabolic disturbances, and stabilization of vital parameters, allowing the child to be safely discharged home. Data were collected using a structured proforma. Statistical analysis was performed using IBM-SPSS Statistics, version 26.0. Normal distribution of the data was checked using the Shapiro-Wilk test. Odds ratio with 95 confidence interval (CI) was calculated to measure the effect size. The chi-square test or Fisher's exact test, and the independent t-test or Mann-Whitney U test were used, taking $p<0.050$ as significant.

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## RESULTS

In a total of 120 children, 80 (66.7%) were male. The median age was 7.0 (4.0-10.0) years, while the mean weight was 18.8 (15.5-23.5) kg. The residential status of 74 (61.7%) children was rural. Malnutrition was identified in 59 (49.2%) children. *P.vivax* was the predominant malaria parasite identified in 84 (70.0%) children. The most common clinical presentations were severe anemia, impaired consciousness, seizures, and respiratory distress, observed in 82 (68.3%), 50 (41.7%), 30 (25.0%), and 22 (18.3%), respectively (Figure 1).

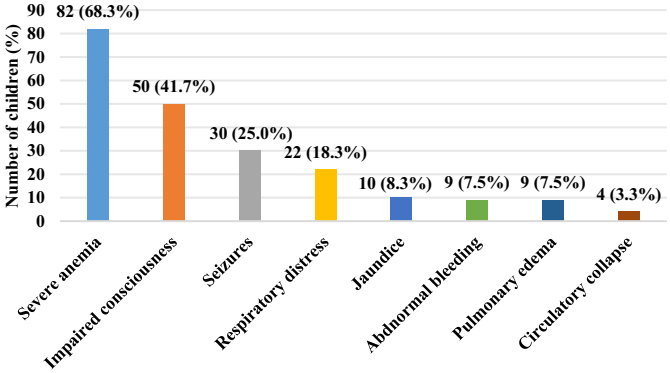


**Figure 1:** Most Common Clinical Manifestations of Severe Malaria (N=120)

No mortality was reported in this study, and all children were successfully discharged. Overall, the median duration of hospital stay was 7.0 (4.0-9.0) days. Evaluation of seizures to demographic, clinical, and laboratory parameters (Table 1) showed no significant associations except for malarial agent (p=0.033), lower haemoglobin (p=0.006), and a significantly longer hospital stay (p=0.024), table 1.

**Table 1:** Association of Seizures with Various Demographic, Clinical, and Laboratory Parameters (N=120)

| Characteristics | | Seizures | | Chi-square Value | p-value |
|---|---|---|---|---|---|
| | | Yes (n=30) | No (n=90) | | |
| Gender | Male | 21 (70.0%) | 59 (65.6%) | 1.22 (0.50-2.95) | 0.655 |
| | Female | 9 (30.0%) | 31 (34.4%) | Reference | |
| Age (Years) | 1-5 | 11 (36.7%) | 34 (37.8%) | Reference | 0.913 |
| | 6-12 | 19 (63.3%) | 56 (62.2%) | 1.05 (0.46-2.41) | |
| Residence | Rural | 17 (56.7%) | 57 (63.3%) | 0.76 (0.33-1.78) | 0.515 |
| | Urban | 13 (43.3%) | 33 (36.7%) | Reference | |
| Malnutrition | | 18 (60.0%) | 41 (45.6%) | 1.79 (0.79-4.06) | 0.171 |
| Malarial Agent | *P. vivax* | 19 (63.3%) | 65 (72.2%) | Reference | 0.033 |
| | *P. falciparum* | 11 (36.7%) | 16 (17.8%) | 2.35 (0.98-5.61) | |
| | *P. falciparum + P. vivax* | - | 9 (10.0%) | 0.15 (0.01-2.66) | |
| Hemoglobin (g/dl) | | 6.4 (5.8-6.9) | 6.8 (6.3-9.0) | - | 0.006 |
| Hematocrit (%) | | 32.3±6.5 | 34.1±6.3 | - | 0.176 |
| Platelets (109/L) | | 115.5 (66.0-170.5) | 118.5 (70.3-169.3) | - | 0.966 |
| Blood Glucose (mg/dl) | | 87.8±13.7 | 84.0±14.3 | - | 0.202 |
| Blood Urea (mg/dl) | | 32.0±9.7 | 34.8±10.6 | - | 0.201 |
| Serum Creatinine (mg/dl) | | 0.88±0.27 | 0.8±0.3 | - | 0.104 |
| Alanine Aminotransferase (U/L) | | 37.8 (29.7-55.0) | 36.3 (27.4-48.3) | - | 0.532 |
| Aspartate Transaminase (U/L) | | 44.3 (29.5-61.8) | 48.3 (30.8-59.7) | - | 0.689 |
| Serum Bilirubin (mg/dl) | | 1.6 (1.3-2.1) | 1.6 (0.9-2.2) | - | 0.759 |
| Hospital Stays (days) | | 8.0 (5.0-11.0) | 6.0 (4.0-8.0) | - | 0.024 |

No demographic or laboratory parameters demonstrated a significant association between children with and without respiratory distress, table 2.

**Table 2:** Association of Respiratory Distress with Various Demographic, Clinical, and Laboratory Parameters (N=120)

| Characteristics | | Respiratory Distress | | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| | | Yes (n=22) | No (n=98) | | |
| Gender | Male | 11 (50.0%) | 69 (70.4%) | 0.42 (0.16-1.08) | 0.067 |
| | Female | 11 (50.0%) | 69 (70.4%) | Reference | |
| Age (Years) | 1-5 | 6 (27.3%) | 39 (39.8%) | Reference | 0.273 |
| | 6-12 | 16 (72.7%) | 59 (60.2%) | 1.76 (0.63-4.90) | |
| Residence | Rural | 12 (54.5%) | 62 (63.3%) | 0.70 (0.27-1.77) | 0.447 |
| | Urban | 10 (45.5%) | 36 (36.7%) | Reference | |
| Malnutrition | | 9 (40.9%) | 50 (51.0%) | 0.66 (0.26-1.70) | 0.391 |
| Malarial Agent | *P. vivax* | 15 (68.2%) | 69 (70.4%) | Reference | 0.215 |
| | *P. falciparum* | 7 (31.8%) | 20 (20.4%) | 1.61 (0.58-4.49) | |
| | *P. falciparum + P. vivax* | - | 9 (9.2%) | 0.24 (0.01-4.27) | |
| Hemoglobin (g/dl) | | 6.8 (6.4-9.5) | 6.5 (6.2-8.2) | - | 0.229 |
| Hematocrit (%) | | 32.7±6.7 | 33.9±6.3 | - | 0.433 |
| Platelets (109/L) | | 120.5 (63.0-170.5) | 118.5 (70.3-169.3) | - | 0.962 |
| Blood Glucose (mg/dl) | | 83.7±11.4 | 85.2±14.8 | - | 0.658 |
| Blood Urea (mg/dl) | | 38.1±10.8 | 34.2±10.2 | - | 0.066 |
| Serum Creatinine (mg/dl) | | 0.9±0.2 | 0.8±0.3 | - | 0.352 |
| Alanine Aminotransferase (U/L) | | 40.9 (32.8-57.5) | 36.3 (27.8-47.1) | - | 0.160 |
| Aspartate Transaminase (U/L) | | 45.7 (33.3-60.6) | 46.5 (29.9-59.9) | - | 0.908 |
| Serum Bilirubin (mg/dl) | | 1.6 (0.9-2.2) | 1.6 (1.1-2.1) | - | 0.984 |
| Hospital Stays (days) | | 8.0 (5.0-10.0) | 6.5 (4.0-9.0) | - | 0.521 |

Details about the association between anemia and demographic, clinical, and laboratory parameters, table 3.

**Table 3:** Association of Severe Anemia with Various Demographic, Clinical, and Laboratory Parameters (N=120)

| Characteristics | | Severe Anemia | | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| | | Yes (n=82) | No (n=38) | | |
| Gender | Male | 55 (67.1%) | 25 (65.8%) | 1.06 (0.48-2.34) | 0.890 |
| | Female | 27 (32.9%) | 13 (34.2%) | Reference | |

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| | | | | | |
|---|---|---|---|---|---|
| Age (Years) | 1-5 | 29 (35.4%) | 16 (42.1%) | Reference | 0.478 |
| | 6-12 | 53 (64.6%) | 22 (57.9%) | 1.31 (0.60-2.85) | |
| Residence | Rural | 49 (59.8%) | 25 (65.8%) | 0.78 (0.35-1.72) | 0.527 |
| | Urban | 33 (40.2%) | 13 (34.2%) | Reference | |
| Malnutrition | | 36 (43.9%) | 23 (60.5%) | 0.51 (0.24-1.09) | 0.090 |
| Malarial Agent | *P. vivax* | 55 (67.1%) | 29 (76.3%) | Reference | 0.207 |
| | *P. falciparum* | 22 (26.8%) | 5 (13.2%) | 2.32 (0.81-6.68) | |
| | *P. falciparum + P. vivax* | 5 (6.1%) | 4 (10.5%) | 0.66 (0.17-2.60) | |
| Hemoglobin (g/dl) | | 6.4 (6.1-6.8) | 9.5 (8.6-10.0) | - | <0.001 |
| Hematocrit (%) | | 34.0±6.0 | 32.9±7.2 | - | 0.390 |
| Platelets (109/L) | | 119.5 (68.0-170.8) | 112.5 (70.6-162.3) | - | 0.716 |
| Blood Glucose (mg/dl) | | 86.3±14.0 | 82.0±14.3 | - | 0.120 |
| Blood Urea (mg/dl) | | 33.1±9.9 | 36.2±11.3 | - | 0.130 |
| Serum Creatinine (mg/dl) | | 0.8±0.3 | 0.8±0.2 | - | 0.940 |
| Alanine Aminotransferase (U/L) | | 37.7 (28.8-48.3) | 36.5 (25.0-50.5) | - | 0.771 |
| Aspartate Transaminase (U/L) | | 44.4 (29.1-61.8) | 49.4 (34.9-56.6) | - | 0.531 |
| Serum Bilirubin (mg/dl) | | 1.5 (0.9-2.1) | 1.9 (1.5-2.7) | - | 0.009 |
| Hospital Stays (days) | | 7.0 (4.0-9.0) | 7.0 (4.8-8.3) | - | 0.880 |

Details about the evaluation of impaired consciousness about demographic, clinical, and laboratory parameters, and no significant associations were found, table 4.

**Table 4:** Association of Impaired Consciousness with Study Variables in Children with Severe Malaria (N=120)

| Characteristics | | Impaired Consciousness | | OR (95% CI) | p-value |
|---|---|---|---|---|---|
| | | Yes (n=50) | No (n=70) | | |
| Gender | Male | 33 (66.0%) | 47 (67.1%) | 0.95 (0.45-2.03) | 0.897 |
| | Female | 17 (34.0%) | 23 (32.9%) | Reference | |
| Age (Years) | 1-5 | 18 (36.0%) | 27 (38.6%) | Reference | 0.774 |
| | 6-12 | 32 (64.0%) | 43 (61.4%) | 1.12 (0.54-2.32) | |
| Residence | Rural | 32 (64.0%) | 42 (60.0%) | 1.18 (0.57-2.46) | 0.657 |
| | Urban | 18 (36.0%) | 28 (40.0%) | Reference | |
| Malnutrition | | 30 (60.0%) | 29 (41.4%) | 2.07 (1.02-4.22) | 0.045 |
| Malarial Agent | *P. vivax* | 32 (64.0%) | 52 (74.3%) | Reference | 0.071 |
| | *P. falciparum* | 16 (32.0%) | 11 (15.7%) | 2.37 (0.99-5.67) | |
| | *P. falciparum + P. vivax* | 2 (4.0%) | 7 (10.0%) | 0.46 (0.09-2.27) | |
| Hemoglobin (g/dl) | | 6.4 (6.1-8.2) | 6.8 (6.3-8.4) | - | 0.025 |
| Hematocrit (%) | | 33.0±6.5 | 34.1±6.3 | - | 0.313 |
| Platelets (109/L) | | 132.0 (71.0-169.3) | 111.0 (68.0-166.3) | - | 0.270 |
| Blood Glucose (mg/dl) | | 82.6±15.3 | 86.6±13.2 | - | 0.130 |
| Blood Urea (mg/dl) | | 33.7±9.4 | 34.3±11.1 | - | 0.767 |
| Serum Creatinine (mg/dl) | | 0.8±0.3 | 0.8±0.3 | - | 0.921 |
| Alanine Aminotransferase (U/L) | | 33.9 (26.2-45.8) | 39.9 (30.5-61.0) | - | 0.070 |
| Aspartate Transaminase (U/L) | | 46.2 (27.6-61.0) | 48.0 (31.2-59.7) | - | 0.960 |
| Serum Bilirubin (mg/dl) | | 1.5 (1.1-2.1) | 1.6 (1.0-2.1) | - | 0.616 |
| Hospital Stays (days) | | 7.0 (4.0-8.0) | 7.0 (4.8-9.0) | - | 0.365 |

## DISCUSSION

It was found that 66.7% children with severe malaria were male, while the mean age was 6.99±3.51 years. These findings align closely with those reported by Murmu *et al.*, who similarly found a male predominance and a high incidence among younger children (1–5 years, 40.29%) [14]. This demographic similarity highlights the vulnerability of relatively younger children, particularly males, possibly reflecting gender-based disparities in exposure or healthcare-seeking behaviors in South Asian contexts [15]. Malnutrition was identified in nearly half of the children (49.2%) in the current study. Nutritional status is crucial in influencing susceptibility and severity of infections, particularly malaria [16]. The high rate of malnutrition observed is reflective of the socioeconomic status and healthcare infrastructure prevalent in rural South Punjab, similar to Chiabi *et al.*, who documented malnutrition as a significant risk factor affecting clinical outcomes in severe malaria cases in Cameroon [17]. Data from Northeast Ethiopia is also consistent with the present findings, where Debash et al. reported both malaria and undernutrition as a common entity among children [18]. *P. vivax* infection accounted for 70.0% of cases. Global literature exhibits *P. falciparum* to be the dominant species associated with severe malaria. Murmu *et al.* reported 80.5% *P. falciparum* involvement, reinforcing the pathogenic severity of this species [14]. Contemporary regional data by Babar *et al.* and Gehlawat *et al.* have shown increasingly recognized *P. vivax* as a significant contributor to severe malaria [19, 20]. The most common clinical presentations were severe anemia, impaired consciousness, seizures, and respiratory distress, observed in 68.3%, 41.7%, 25.0%, and 18.3%, respectively. Murmu *et al.* documented altered sensorium, seizures, and jaundice as common presentations [14]. In this study, 41.7% exhibited impaired consciousness compared to studies from Murmu *et al.* (50%) and Voloc *et al.* (75.4% cerebral malaria) [14, 21]. The variation in clinical manifestations of severe malaria in the pediatric population could be attributed to regional differences in parasite virulence, host genetic factors, or timing of healthcare-seeking behavior, which might influence the early diagnosis and thus mitigate severe neurological complications. Seizures and respiratory distress are significantly associated with prolonged hospital stays to Kalinga *et al.*, where respiratory distress and neurological manifestations were predictors of prolonged hospitalization [22]. Namayanja *et al.* reported acidosis as the

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major determinant of hospital stay, highlighting that variability in clinical presentations influences hospital resource utilization and management strategies [23]. Clinically significant hypoglycemia (<40 mg/dL) was not found in this study, with the mean blood glucose levels maintained above the critical range (84.93±14.17 mg/dL). This contrasts with Manning *et al.*, who documented higher prevalence rates of hypoglycemia in African children [24]. Variations in nutritional status, early glucose monitoring, or protocol-driven clinical management differences may explain these discrepancies. Previous study highlighted that prompt diagnosis and immediate artesunate administration are crucial in preventing metabolic complications, a practice possibly adhered to rigorously in the present study context [25]. Regarding laboratory parameters, not much significant association was found between platelet count, serum creatinine, alanine aminotransferase, or aspartate transaminase and severe clinical manifestations. This contrasts with Murmu *et al.* and Voloc *et al.*, where thrombocytopenia and hepatic dysfunction correlated significantly with severe outcomes [14, 21]. The relatively mild derangement in laboratory parameters herein might reflect early presentation and prompt management, reducing severe organ dysfunction. Genetic variability in host responses or differences in parasite strains could contribute to these variations [26]. Although global trends identify *P. falciparum* as the main cause of severe malaria, this study indicated a substantial burden of severe disease due to *P. vivax* [27]. While rigorous diagnostic protocols were followed, the possibility of species misidentification cannot be entirely excluded due to morphological overlaps, especially in mixed or low-density infections. The absence of mortality in the current study contrasts markedly with global reports. Namayanja *et al*. observed a mortality rate of 6.3%, Chiabi *et al.*, 3.8%, and Voloc et al. reported a considerably higher rate of 18.6% [17, 23]. The zero-mortality observed herein could reflect early hospital presentation, prompt and appropriate treatment protocols involving intravenous artesunate, and effective supportive care, including intensive monitoring and management practices. Conversely, higher mortality rates in other studies might reflect late healthcare-seeking behavior, delayed initiation of antimalarial treatment, or limited availability of critical care facilities. The clinical implications of the findings of this study are substantial. The recognition of *P. vivax* as a significant cause of severe malaria emphasizes the need for revised public health guidelines and awareness campaigns in South Punjab. High malnutrition rates underline the necessity of addressing underlying nutritional deficiencies through integrated pediatric care and community interventions. The study's single-center design limits generalizability to broader populations. Long-term outcomes post-discharge were not evaluated, precluding insights into chronic sequelae such as neurological deficits or recurrent infections. Genetic factors influencing host susceptibility were not assessed, which could provide valuable insights into disease severity variation.

This study was limited by its single-center design and non-probability sampling technique, which may restrict the generalizability of findings to other endemic regions. The absence of long-term follow-up prevented assessment of post-discharge complications or neurological sequelae. Additionally, molecular confirmation of parasite species was not performed, which may limit precise species differentiation. Future multicenter, longitudinal studies incorporating molecular diagnostics and long-term outcome assessment are recommended to better understand disease patterns and optimize pediatric malaria management strategies.

## CONCLUSIONS

Severe malaria in children most commonly presents with severe anemia, impaired consciousness, and seizures, with Plasmodium vivax as the predominant causative organism. All enrolled children recovered and were discharged without mortality, indicating favorable short-term outcomes under the current management protocol.

## Authors' Contribution

Conceptualization: SI,
Methodology: SI, SAL, AA, IJ, AU
Formal analysis: SI, AA, IJ, AU
Writing and Drafting: SI, MSA
Review and Editing: SI, MSA, SAL, AA, IJ, AU

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# CLEC3B Expression in Saliva and Serum: A Promising Biomarker Approach for Oral Squamous Cell Carcinoma

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## ABSTRACT

Metastasis, considered the most important factor for determining the survival rate of oral squamous cell carcinoma (OSCC). Therefore, a useful biomarker is needed to classify patients with OSCC in order to ensure effective treatment. Although CLEC3B has been mentioned in the literature, its relationship to OSCC has not yet been studied. **Objectives:** To evaluate the potential of CLEC3B expression in saliva and blood as a diagnostic biomarker for oral squamous cell carcinoma. **Methods:** A case-control study comprised of 80 samples (40 blood and 40 saliva) from 40 participants was conducted. Both Ziauddin University Hospital and Abbasi Shaheed Hospital served as the recruitment sites for all samples. RT qPCR was used to determine the expression levels of CLEC3B in OSCC and healthy individuals after obtaining written informed consent. Ziauddin University Ethical Review Committee approved this project. SPSS version 20.0 was used to analyze the data. **Results:** When compared to healthy people, OSCC patients' saliva had considerably lower levels of CLEC3B (p-value 0.001). Moreover, the expression was comparatively lower in the saliva of OSCC patients as compared to blood, suggesting that this marker can be better evaluated in saliva. **Conclusions:** Low expression of CLEC3B with the progression of OSCC depicts its tumor suppressive role in the tumor microenvironment. Its high yield in saliva can make it a suitable and easily assessable biomarker for determining OSCC progression.

## INTRODUCTION

Oral squamous cell carcinoma gained eighth place among the major cancers that have spread worldwide. The incidence of OSCC is estimated to be highest in the developing countries, particularly in the Southeastern region [1, 2]. The prevalence was reported to be 18.6% in Pakistan, with the majority of cases being caused by the concomitant use of alcohol and cigarettes [3]. Prolonged exposure to tobacco, alcohol, addictive substances, and oncogenic infections can induce genetic alterations, including chromosomal damage, which contribute to the development of premalignant lesions that may progress to invasive carcinoma [4]. Certain cytological and tissue architectural features of squamous cell differentiation are displayed by the uncontrolled proliferation of epithelial cells. This condition can proceed from mild to severe dysplasia, depending on the quantity and severity of these cytological changes. Although science and technology have advanced, the prognosis for OSCC has remained same for more than three decades with a 50% 5-year survival rate [5]. Recent advancements in the application of molecular

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and biochemical methods have made it simpler to identify biomarkers for the diagnosis and prognosis of OSCC. The Hanahan and Weinberg's proposed Hallmarks of cancer development include invasion and metastasis as the main mechanisms for cancer progression [6]. This crucial feature is governed by the expression of certain biomarkers. Research has identified C-type lectin domain family 3-member B (CLEC3B) as a promising biomarker with potential diagnostic and prognostic significance in oral squamous cell carcinoma (OSCC) [7]. The literature had shown that CLEC3B serves many different functions as It played an oncogenic part in some tumors, but other research indicated that it had a tumor suppressing impact in cases such as hepatocellular carcinoma and pancreatic cancer [8]. Additionally, through the signals of AMP-activated protein kinase and vascular endothelial growth factor, CLEC3B participates in the invasion and metastasis of tumor cells [9]. Given the complexity of OSCC pathogenesis and the urgent need for reliable, non-invasive biomarkers, investigating CLEC3B expression in blood and saliva offers significant approach. This study aims to clarify its diagnostic and prognostic potential in OSCC, helping to resolve its ambiguous role by focusing on a single, well-defined cancer type. Tissue biopsy has continued to be the gold standard method for diagnosing OSCC. However, it is an intrusive approach, some patients might be reluctant to it [10]. For the diagnosis and prognosis of OSCC, saliva is a noninvasive and easily accessible bodily fluid that offers potential indicators [11]. As a result, tissue biopsy may be able to be replaced. However, various saliva collecting methods, including draining, spitting, and suction processes, have an impact on the recovery of particular biomarkers. Additionally, a number of researchers have found that saliva has a higher output of biomarkers than blood [12]. There are significant challenges in identifying prospective blood and salivary biomarkers in OSCC despite continued research on the clinical application of diagnostic biomarkers. Even though saliva is a non-invasive medium, it is not typically employed for diagnostic purposes [13]. There is currently a dearth of information showing how accurately saliva represents the serum levels of particular biomarkers. In the context of OSCC, limited but emerging evidence suggests a potential tumor-suppressive role, particularly through its involvement in extracellular matrix remodeling and immune regulation.

Although CLEC3B has been investigated in several malignancies, its diagnostic relevance in oral squamous cell carcinoma (OSCC), particularly using non-invasive samples such as saliva, remains insufficiently explored. Most previous studies have focused on tissue-based or serum biomarkers, with limited comparative evaluation of salivary and blood gene expression in OSCC patients. Furthermore, there is a lack of region-specific data from Pakistan examining CLEC3B expression in clinically confirmed OSCC cases. Therefore, investigating CLEC3B expression in both saliva and serum is necessary to determine its potential as a reliable and minimally invasive biomarker. This study aims to evaluate the importance of saliva and blood in identifying CLEC3B expression in OSCC patients and control.

## METHODS

This was a case control study comprised of a total of 80 samples, 40 samples were taken from OSCC patients and 40 samples from healthy individuals as controls Using the Open Epi platform, the preliminary calculation indicated that a minimum of 18 participants per group was required, based on a 95% confidence level and a 5% margin of error. Additionally, a prior power analysis was performed to assess the adequacy of the sample size for detecting potential differences in gene expression between groups. This analysis, set at a two-tailed significance level of 0.05 and 80% statistical power, assumed a moderate-to-large effect size (Cohen's d ≈ 0.75). To further enhance the reliability of the results, account for variability in saliva and blood transcript levels, and minimize the risk of data loss due to sample degradation or low-quality RNA, the sample size was increased to 40 subjects per group (total n = 80). Blood and saliva samples from each case and control subject were collected after obtaining written informed consent from June 2023 till January 2024. All the samples were recruited from the Dental Outpatient Departments of Ziauddin University Hospital and Abassi Shaheed Hospital. OSCC patients were diagnosed on the basis of histopathological report. This study was conducted in accordance with the Code of Ethics of the World Medical Association and the Ethics Review Committee (ERC) of Ziauddin (Ref code: 2941220ZAPAT) and data gave its approval. Data collection was given by Abassi Shaheed Hospital (DIRS/ASH/ESTT/3145/2020). Sample size for comparing two means was calculated (Table 1).

**Table 1:** Sample Size for Comparing Two Means

| Variables | Input Data | | |
|---|---|---|---|
| Confidence Level (2-Sided) | 95% | | |
| Power | 80% | | |
| Ratio of Sample Size (Group 2/Group 1) | 1% | | |
| **Variables** | **Group 1** | **Group 2** | **Differences*** |
| Mean | 10.8 | 7.33 | 3.47 |
| SD | 2.8 | 2.23 | – |
| Variance | 7.84 | 4.9729 | – |
| Sample Size | 9 | 9 | – |
| Total Sample Size | 18 | | |

*Difference between the means. Results from Open Epi, version 3,

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open source calculator—SS Mean. Print from the browser with Ctrl-P, or select text to copy and paste to other programs

OSCC patients were confirmed by histology. Healthy controls were verified through a detailed medical history and a clinical oral examination to confirm the absence of any oral lesions, systemic illnesses, or recent infections. Individuals with autoimmune diseases or other malignancies. Each individual had 5 ml of entire, unstimulated saliva taken from them, and 5 ml of blood was collected at the same time in morning. To minimize pre-analytical variability, saliva samples were collected under standardized conditions: participants were asked to refrain from eating, drinking, or brushing teeth for at least 30 minutes prior to sample collection. Unstimulated whole saliva was collected in sterile tubes, immediately placed on ice, and processed within 2 hours of collection. All samples underwent identical RNA extraction protocols. However, inherent variability in saliva composition remains a potential limitation. All of the obtained samples underwent a 15-minute, 2600 x g centrifugation at 4°C. Then, these samples were kept at -80 degrees Celsius. Blood and saliva samples were utilized to conduct qPCR tests on CLEC3B expression. For gene expression analysis, Trizol technique was used to extract the RNA. For phase separation, 200 µL of chloroform was added. RNA precipitation was carried out by adding 2 mL of isopropanol, followed by centrifugation. The resulting supernatant was discarded, and the RNA pellets were air-dried and subsequently resuspended in 20 µL of nuclease-free water. Samples were stored at -80°C until further use. The concentration and purity of the extracted RNA were assessed using the MultiScan Sky Spectrophotometer. cDNA synthesis was performed using the RevertAid First Strand cDNA Synthesis Kit, following the manufacturer's protocol. Primer 3 software was used to design the primer sequence. GAPDH was taken as an internal control. To ensure the specificity and efficiency of the primers designed for CLEC3B and GAPDH, a pilot study was conducted prior to the main experiment. This involved testing the primers on representative saliva and blood samples. Primer specificity was confirmed through melt curve analysis and gel electrophoresis. The following primers were used: Forward 5′-CCAGAACATCATCCCTGCCT-3′ for GAPDH, Reverse: 3′- 5′- CCTGCTTCACCTTCTTG, Forward 5′-TGGTGTAACCTCAGAAGTG- 3′; CLEC3B; Backwards: 5′-GTCAACTCCAGGCTTGTA- 3′. RT-qPCR was used to analyze the expression of CLEC3B. To make a 20 µL volume, 10 µL of SYBR green master mix and 10 µL of cDNA and primer combination were combined. 40 cycles of denaturation (92C),annealing, and extension (72C) were performed The relative fold change was estimated for the study of expression using the CT values. The 2^-ΔΔCt was used to quantify relative expression. The data were analyzed using SPSS version 20.0. Kruskal Wallis and pairwise comparison was performed and median and interquartile ranges were calculated for nonparametric data at a 95% confidence interval. The p-value less than 0.050 was considered statistically significant.

## RESULTS

The study analyzed the expression of CLEC3B in 40 blood and saliva samples by determining the relative gene expression. The study observed the highest median (IQR) values in cases of saliva, 5.1 (2.06%), compared with blood samples, 2.7 (0.4%), at a confidence interval of 95% (Figure 1).

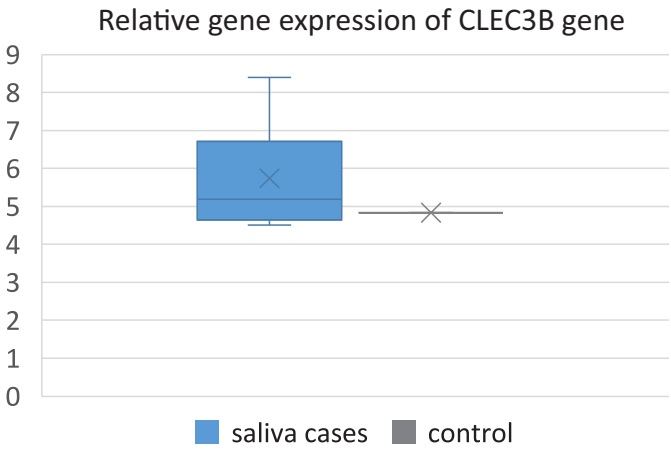


**Figure 1:** Relative Gene Expression of CLEC3B in Saliva OSCC Cases Compared with Controls

The Kruskal-Wallis test was applied to compare CLEC3B expression between OSCC cases and controls. These Boxplots represent the median and Interquartile ranges. The p-value less than 0.05 considered significant.

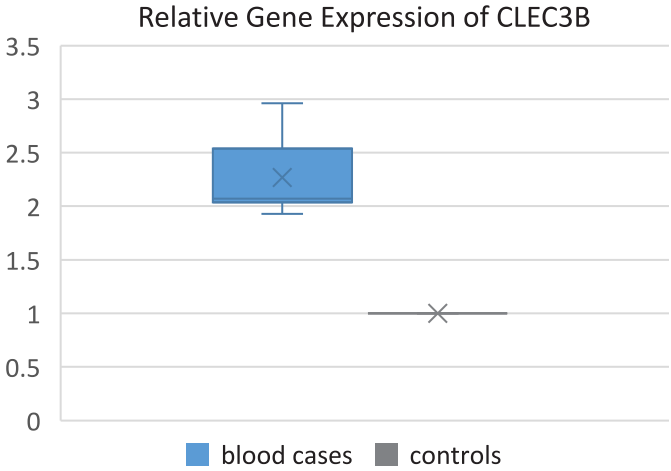


**Figure 2:** Relative Gene Expression of OSCC Cases and Controls in Blood

In both saliva and blood samples, significantly increased relative gene expression was observed in OSCC cases compared with controls(p-value=0.001).

Test result variable (s) for saliva and blood was applied (Table 2).

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**Table 2:** Test Result Variable(s): Saliva and Blood

| Area | Std. Errora | Asymptotic Sig.[b] | Asymptotic 95% Confidence Interval | |
|---|---|---|---|---|
| | | | Lower Bound | Upper Bound |
| 0.953 | 0.035 | 0.000 | 0.885 | 1. |
| 0.90 | 0.085 | 0.03 | 0.812 | 0.988 |

To evaluate the significance of CLEC3B in blood and saliva, ROC curve was generated and area under the curve was calculated. The study found significantly increased area under the curve in blood samples (AUC 0.9) and in saliva samples as (AUC 0.95). If study allow the cutoff point to be 3, the sensitivity would be 100% and 1 - specificity would be 94% for saliva samples and for blood cut off point is 0.4 and 1 - specificity would be 100%. The study shows ROC analysis in AUC (0.953), at point 3 we observed 100% sensitivity and 1-specificity was 94% in saliva (a). Analysis shows ROC analysis in AUC (0.90), at point 0.4 we observed 95% sensitivity and 1-specificity was 100% in blood samples (b) (Figure 3).

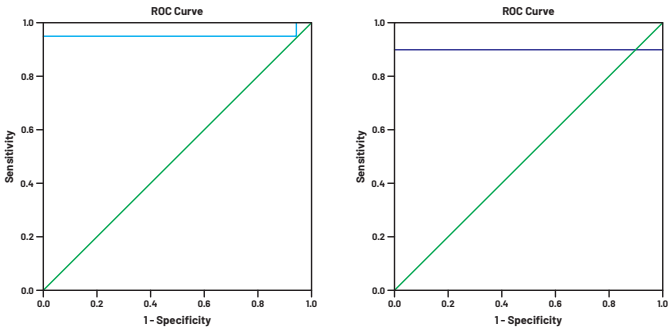


**Figure 3:** ROC Curve Analysis in Blood and Saliva Samples

## DISCUSSION

Genetic mutations and uncontrolled tumor cell proliferation cannot be the only causes of cancer progression. The development of tumors and their spread are greatly influenced by a variety of growth factors and signaling pathways. The delayed diagnosis is the primary cause of the OSCC patient's poor prognosis, though. Numerous studies have explored differences in salivary transcriptome profiles between healthy individuals and those with disease, contributing to disease detection and monitoring of its progression [14, 15]. In the present research, we examined the potential of saliva as a non-invasive diagnostic tool and evaluated the diagnostic relevance of CLEC3B in identifying OSCC through salivary biomarker analysis. Our findings revealed that blood and saliva samples from OSCC cases had considerably lower levels of CLEC3B expression than samples from controls (p-value=0.001). In blood and saliva samples from OSCC patients, Arellano *et al.* demonstrated the expression of CLEC3B and contrasted it with healthy control subjects. When compared to a healthy person, he had a lower level of CLEC3B in OSCC [16]. Another case-control research on saliva samples from OSCC patients found that CLEC3B was downregulated relative to healthy people [17, 18]. These findings might point to OSCC's tumor-suppressive properties. Studies using blood samples from patients with ovarian cancer, lung, breast, and colon carcinoma revealed similar findings, with considerable downregulation of CLEC3B [19-21]. Additionally, hepatocellular carcinoma tissue samples showed comparable outcomes [8]. The earlier investigations were supported by our study. The delayed expression of CLEC3B observed in OSCC samples in this study and in previous studies indicated the fact that decreased expression leads to decreased phosphorylation of AMP activated kinases that inhibits cell growth and proliferation, resulting in the activation of VEGF signaling, leading to invasion and progression of OSCC [9]. This work would suggest that CLEC3B expression reduced in the blood and saliva of OSCC patients compared to healthy people, can be thought of as a potential diagnostic biomarker (p-value=0.001). Compared to blood CLEC3B levels, the differences in salivary CLEC3B levels between OSCC and healthy participants seemed more significant. This may be due to the fact that the salivary environment is flooded with oral cancer cells. Tetranectin, a translational byproduct, seems to be ingested within the tumor microenvironment. The extracellular matrix must be broken down by proteases for metastasis to occur. Tetranectin is therefore present in lower concentrations in OSCC patients compared to healthy persons [22]. Therefore, this study may aid in the classification of OSCC patients. While CLEC3B expression was evaluated in OSCC patients, correlation with clinical staging and histopathological grading was not included in this study. Future investigations incorporating these parameters would be valuable to confirm CLEC3B's utility as a prognostic biomarker and to understand its potential role in tumor progression. However, it suffers some limitation due to its limited sample size , potential variability in saliva collection and composition, which may affect CLEC3B expression levels and the utility of this gene should further be validated and studied with large samples in future.

This study has certain limitations, too. Its single-center design and relatively small sample size may limit the generalizability of the findings. Furthermore, the lack of correlation with clinical staging, histopathological grading, and long-term patient outcomes restricts the ability to establish the prognostic significance of CLEC3B in OSCC. Variability in saliva collection and inherent differences in salivary composition may also influence gene expression levels. Future multicenter studies with larger cohorts, longitudinal follow-up, and comprehensive clinicopathological correlation are recommended to further validate CLEC3B as a reliable diagnostic and prognostic biomarker and to clarify its role in tumor progression.

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## CONCLUSIONS

It was concluded that CLEC3B is downregulated in OSCC and may act as a diagnostic biomarker. In addition, low expression of CLEC3B with progression of the disease depicts its tumor suppressive role in tumor microenvironment. Furthermore, its high yield in saliva can make it a suitable and easily assessable biomarker for determining OSCC progression.

## Authors' Contribution

Conceptualization: SZA
Methodology: SZA, SU, AAB, AIS
Formal analysis: UZ
Writing and Drafting: SZA, FS, AIS
Review and Editing: SZA, FS, AIS, UZ, SU, AAB

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Evaluation of Temporomandibular Joint Disorder in Dental Undergraduates Using the Fonseca Questionnaire

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## ABSTRACT

A basic component of general well-being and health is oral health. One common problem influencing populations worldwide is temporomandibular dysfunction (TMD). **Objectives:** To determine the occurrence of temporomandibular disorders in dental undergraduates using the Fonseca index. **Methods:** A cross-sectional analytical study was carried out with undergraduate dental students enrolled at Watim Medical and Dental College, Rawalpindi, Pakistan. The sample size was determined using the WHO sample size calculator, and participants were selected through non-probability judgmental sampling. Assessment of temporomandibular disorders was performed using the validated Fonseca Anamnestic Questionnaire. Data management and statistical analysis were conducted with SPSS version 26. **Results:** A total of 186 participants were included, with 149 females (80.10%) and 37 males (19.90%). Using the Fonseca Clinical Index, TMD classification revealed that 104 participants had present TMD (55.90%), while 82 had absent TMD (44.10%). Severity levels ranged from no TMD (44.09%) to mild TMD (43.01%), moderate TMD (9.68%), and severe TMD (3. 23%). Gender and TMD were statistically significantly associated (p=0.004), indicating that gender may contribute to TMD occurrence, with females being more affected. Additionally, there was a correlation between gender and TMD severity (p=0.038), suggesting that severity may vary based on an individual's gender. However, no correlation was found between age and TMD (p=0.397). **Conclusions:** TMD was prevalent among dental undergraduates, with a statistically significant association with gender, particularly affecting females.

## INTRODUCTION

TMD refers to a range of disorders that impact the muscles of mastication, the temporomandibular joint, and related tissues [1, 2]. Temporomandibular disorders (TMDs) are now widely acknowledged as the primary source of chronic orofacial pain of non-dental origin, occupying the third position among dental conditions responsible for pain and functional impairment [3]. Myofascial disorders represent the most frequently encountered subtype of TMD, primarily characterized by muscle-related pain, whereas internal derangements, including disc displacement and TMJ arthralgia, are reported less often [4]. The approximate prevalence of TMD in adults is around 31-38%, and 11% in children [5-7]. Epidemiological studies indicate that TMDs disproportionately affect women, occurring about five times more frequently than in men, with the highest prevalence reported in younger individuals [6, 8]. Nevertheless, signs of TMDs appear to increase with advancing age. Among healthcare professionals,

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particularly dental undergraduates, awareness and understanding of TMD are crucial due to their role in diagnosing and managing these disorders in future practice. Dental undergraduates represent a particularly significant population for assessing temporomandibular disorders due to their dual role as both potential sufferers and future frontline professionals in diagnosing and managing TMD. Research indicates that dental students may be especially vulnerable to TMD symptoms due to high academic stress, prolonged postural strain during clinical training, and increased awareness of orofacial symptoms, which may lead to self-reporting bias or early identification [6, 7]. This makes them an ideal group for studying the interplay between psychosocial and physiological contributors to TMD. The Fonseca Anamnestic Index (FAI), or Fonseca Questionnaire, is a well-established, validated tool widely used in epidemiological studies to assess TMD symptoms and severity across diverse populations [9]. Its simplicity, cost-effectiveness, and ability to categorize TMD into mild, moderate, and severe forms make it particularly suitable for large-scale screenings in academic settings. By applying this tool to dental undergraduates, this study not only aims to quantify the prevalence and types of TMD within a high-risk, knowledgeable cohort but also seeks to inform curriculum enhancements and stress management interventions targeted at mitigating TMD onset during professional training. Psychosocial, environmental, biological, and neurophysiological factors play significant roles in the development of TMD symptoms. These factors include emotional stress (such as anxiety and depression), bruxism, occlusal discrepancies, orthodontic interventions, issues with chewing function, and postural irregularities, all contributing to an increased susceptibility to TMDs [6, 8]. The Fonseca Questionnaire, developed by Dr. Luciano Fonseca, serves as a valuable tool in screening and assessing TMD symptoms [9]. This questionnaire comprises a set of structured questions designed to evaluate various aspects of TMJ dysfunction, including pain, joint noises, and functional limitations. Its utility lies in providing a systematic approach to gathering clinical data, aiding in both early detection and comprehensive evaluation of TMD among dental professionals. Although considerable research has been conducted on temporomandibular disorders (TMDs), there is a lack of evidence focusing on the prevalence and awareness of TMD symptoms among dental undergraduates, particularly through the use of standardized screening instruments such as the Fonseca Questionnaire. There is also limited data assessing how well dental undergraduates recognize, self-report, and interpret TMD-related symptoms, despite being future providers expected to manage such disorders. This study addresses this gap by evaluating the prevalence and characteristics of temporomandibular disorder (TMD) symptoms among dental undergraduates using the Fonseca Questionnaire. In addition, it seeks to assess students' awareness and knowledge of TMD, thereby providing insights that may support early detection, management, and the integration of targeted educational and wellness strategies within dental institutions.

Temporomandibular disorders (TMD) represent a significant source of orofacial pain and functional limitation worldwide, yet their early identification in high-risk student populations remains insufficiently explored. Although several international studies report variable prevalence rates among university students, there is limited region-specific evidence assessing TMD among dental undergraduates in Pakistan using standardized and validated screening tools such as the Fonseca Anamnestic Index. Furthermore, few studies have evaluated the association between demographic variables and TMD severity within this cohort. Addressing this gap is essential to inform preventive, educational, and stress-management strategies in dental institutions. This study aims to determine the occurrence of temporomandibular disorders in dental undergraduates using the Fonseca index.

## METHODS

This analytical cross-sectional study was carried out among undergraduate dental students at Watim Medical and Dental College, Rawalpindi, Pakistan, to investigate temporomandibular disorders (TMD). Data collection took place over six months, from May to October 2022. Ethical clearance was obtained from the Institutional Ethical Review Board of Watim Medical and Dental College (Ref. No. 06 ERB/April/2022). Written informed consent was secured from all participants in accordance with the Helsinki Declaration. The sample size was estimated using the WHO calculator, considering a student population of about 350, a 95% confidence interval, 5% margin of error, and an expected prevalence of 63% based on prior literature. An additional 10% was added to account for possible non-response, yielding a total of 186 participants. Students from all four professional years were included to ensure representation across different stages of the program. Sampling was performed using a non-probability purposive strategy. Temporomandibular disorders were assessed with the Fonseca Anamnestic Index (FAI), a validated and frequently used screening tool. The instrument evaluates symptoms such as restricted mouth opening, difficulty in jaw movement, fatigue or discomfort during mastication, headaches, neck or ear pain, joint sounds, bruxism, difficulty biting, and psychological stress. Each of the ten questions is scored as 10 points for "Yes," 5

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points for "Sometimes," and 0 points for "No," producing a total score ranging from 0–100. Scores are interpreted as: 0–15 (no TMD), 20–40 (mild), 45–65 (moderate), and 70–100 (severe). To reduce confounding, students with systemic illnesses (e.g., autoimmune disease, rheumatoid arthritis, neurological disorders) or those receiving any TMD treatment (pharmacological, surgical, or physiotherapy) were excluded. Data were collected through the FAI, a brief sociodemographic questionnaire (age, gender), and relevant medical/dental history. The psychometric properties of the FAI are well established, with reported high reliability (Cronbach's alpha = 0.849; ICC = 0.837), good concurrent validity against DC/TMD, and acceptable sensitivity (≈78%) and specificity, with an AUC of 0.852. Statistical analyses were performed using IBM SPSS version 26.0. Normality of continuous data was examined with the Shapiro–Wilk test. Group differences in mean FAI scores across age categories were assessed using independent samples t-test, while associations between gender and TMD severity were evaluated with the chi-square test.

## RESULTS

This study assessed temporomandibular disorder (TMD) prevalence and severity among 186 students (mean age 21.60 ± 1.65 years), with a significant female majority (80.1%). Over half (55.9%) of the participants exhibited TMD symptoms, with 43% classified as mild, 9.7% as moderate, and 3.2% as severe based on the Fonseca clinical index. Common symptoms included frequent headaches (34.9%), neck pain (23.7%), and jaw fatigue during chewing (16.7%). Statistical analysis revealed a significant association between gender and both TMD presence (p=0.004) and severity (p=0.038), while age showed no significant correlation with TMD (p=0.397). These findings suggest a notable gender disparity in TMD prevalence and highlight the importance of early screening in young adult populations. Table 1 presents students' demographic and Temporomandibular Disorder (TMD) statistics. Of the 186 participants, 149 are female (80.10%) and 37 are male (19.90%). Based on the Fonseca Clinical Index, 104 participants (55.90%) were found to have TMD, while 82 participants (44.10%) did not show signs of the disorder. The severity of TMD among the participants was distributed as follows: 44.09% had no TMD, 43.01% had mild TMD, 9.68% had moderate TMD, and 3.23% had severe TMD (Table 1).

**Table 1:** Demographic Characteristics and Temporomandibular Disorder Classification

| Variables | n (%) |
|---|---|
| Students | 186 (100) |
| **Gender** | |
| Male | 37 (19.90) |
| Female | 149 (80.10) |
| **Temporomandibular Disorder (TMD)** | |
| Present | 104 (55.90) |
| Absent | 82 (44.10) |
| **Classification of Temporomandibular disorder using Fonseca's clinical index** | |
| NO TMD | 82 (44.09) |
| Mild TMD | 80 (43.01) |
| Moderate TMD | 18 (9.68) |
| Severe TMD | 06 (3.23) |

Various symptoms related to Temporomandibular Disorder (TMD) were observed in the study population. These symptoms include difficulty opening the mouth wide, jaw movement issues, fatigue or muscle pain during chewing, headaches, neck pain, earaches, joint noises, teeth clenching or grinding habits, and perceived tension (Table 2).

**Table 2:** Fonseca Questionnaire for Temporomandibular Disorder

| Variables | Yes N (%) | No N (%) | Sometimes N (%) |
|---|---|---|---|
| Is it hard for you to open your mouth? | 5 (2.7) | 168 (90.30) | 13 (7) |
| Is it hard for you to move your mandible from side to side? | 7 (3.0) | 169 (90.9) | 10 (5.4) |
| Do you get tired /muscular pain while chewing? | 31 (16.7) | 112 (60.2) | 43 (23.1) |
| Do you have frequent headaches? | 65 (34.9) | 81 (43.5) | 40 (21.5) |
| Do you have pain in the nape or a stiff neck? | 44 (23.7) | 98 (52.7) | 44 (23.7) |
| Do you have earaches or pain in the craniomandibular joints? | 8 (4.3) | 160 (86) | 18 (9.7) |
| Have you noticed any TMJ clicking while chewing or when you open your mouth? | 36 (19.4) | 120 (64.5) | 30 (16.1) |
| Do you clench or grind? | 29 (15.6) | 129 (69.4) | 28 (15.1) |
| Do you feel your teeth do not articulate well? | 14 (7.5) | 165 (88.7) | 7 (3.8) |
| Do you consider yourself a tense (nervous) person? | 58 (31.2) | 78 (41.9) | 50 (26.9) |

Information on the variables associated with Temporomandibular Disorder (TMD). Gender and TMD are statistically significantly associated (p=0.004), indicating that gender may contribute to the occurrence of TMD, and females are more affected. Moreover, there is a correlation between gender and the severity of TMD, as evidenced by a p-value of 0.038. This suggests that the severity of TMD may vary depending on an individual's gender. There is no meaningful correlation between age and TMD (p-value = 0.397). Age is not the sole predictor of TMD incidence (Table 3).

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**Table 3:** Associations Between Gender, Age, TMD, and TMD Severity

| Variables | $\chi^2$ / t-value | DF | p-Value |
|---|---|---|---|
| Gender and TMD | 8.09 | 1 | 0.004* |
| Gender and TMD severity | 8.44 | 3 | 0.038* |
| Age and TMD (t-test) | -0.85 | 184 | 0.397 |

*Statistically significant at p≤0.050

## DISCUSSION

This study examined temporomandibular disorders (TMD) in dental students using demographic data and the Fonseca Clinical Index. Among the 186 participants, 55.9% were diagnosed with TMD, classified into mild (43.01%), moderate (9.68%), and severe (3.23%) levels. Common symptoms included difficulty in mouth opening (2.7%), jaw movement limitations (3%), chewing fatigue (16.7%), headaches (34.9%), neck pain (23.7%), earaches (4.3%), and teeth clenching or grinding (15.6%). These findings confirm that TMD is relatively frequent among dental students and may affect daily functioning. When compared with previous research, our results were largely consistent. Nazir *et al.* reported a prevalence of 66.9% among dental students [9], while other studies using the same questionnaire documented rates of 62% and 53.21%, respectively [10, 12]. One study reported that within its 53.21% TMD-positive population, 35.78% had mild, 11.93% moderate, and 5.5% severe TMD, which closely aligns with our classification. Research conducted in Saudi Arabia also demonstrated that 45% of dental students experienced TMD, with 62.8% of females exhibiting mild to severe forms [13, 14]. These comparative findings underscore that dental students across diverse settings consistently exhibit a high burden of TMD. A systematic review and meta-analysis of 21 studies further demonstrated the broader impact of TMD, showing that 19.1% of affected individuals experience disc displacement and 9.8% suffer from degenerative joint disease [8, 15]. Such evidence suggests that dental students with TMD may be at risk of progressive functional limitations and oral parafunctions. Additionally, studies indicate that TMD prevalence is significantly higher among dental students (80%) compared to peers in non-dental fields (62%) [16–18], highlighting the need for preventive measures tailored to this group. Stress emerged as a key associated factor, with 31.2% of our study population identifying it as a perceived root cause of TMD. This aligns with previous findings reporting psychological stress in 29.6% of dental students with TMD. However, a Pakistani study found a much lower rate (12.3%), which may reflect differences in population characteristics, stress assessment tools, or cultural factors influencing reporting. Given the demanding academic, clinical, and patient care responsibilities faced by dental students, chronic stress likely plays a significant role in TMD development, with potential negative consequences for academic performance, health, and quality of life [19, 20]. The analysis demonstrated a statistically significant relationship between gender and temporomandibular disorders, both in terms of occurrence (p=0.004) and severity (p=0.038), with higher susceptibility observed among female students. In contrast, age showed no meaningful association with TMD (p=0.397). These results align with earlier studies that implicate hormonal influences in the greater prevalence of TMD among women. Jedynak *et al.* proposed that persistent endocrine disruptions may contribute to this gender disparity [21]. Meta-analytical evidence further reinforces that TMDs are more prevalent among women, possibly influenced by hormonal mechanisms. Taken together, our results and prior evidence highlight that TMD is common among dental students, with stress and female gender being significant associated factors. Preventive and interventional strategies, particularly stress management and early screening, should be prioritized to reduce the burden of TMD in this high-risk population.

This study was limited by its single-center design and non-probability sampling technique, which may restrict generalizability to other dental institutions. The reliance on self-reported questionnaire data may also introduce response bias and over- or under-estimation of symptoms. Additionally, clinical examination based on DC/TMD criteria was not performed to confirm diagnoses. Future multicenter studies incorporating clinical assessments, longitudinal follow-up, and evaluation of psychosocial and hormonal factors are recommended to better understand TMD progression and to design targeted preventive interventions for dental students.

## CONCLUSIONS

The study concluded a significant prevalence of Temporomandibular Disorder (TMD) among dental students, with symptoms ranging from jaw dysfunction to psychological stress. Gender was found to significantly influence TMD presence and severity, favoring females. Age, however, did not show a significant association with TMD incidence. These findings underscore the need for targeted preventive measures and further research into the complex interplay of gender, age, and hormonal factors in TMD development among student populations.

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## Authors' Contribution

Conceptualization: AK
Methodology: SA[1], AS
Formal analysis: SA[1], AS
Writing and Drafting: ABK
Review and Editing: AK, SA[1], AS, ABK, DA, SA[2]

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Efficacy of Trichloroacetic Acid Versus Cryotherapy in Patients with Xanthelasma Palpebrarum: A Randomized Controlled Trial

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## ABSTRACT

Xanthelasma palpebrarum is a common benign eyelid lesion with multiple treatment options. **Objectives:** To compare the efficacy and safety of 100% trichloroacetic acid (TCA) versus cryotherapy in its management. **Methods:** A randomized controlled trial was conducted at the Department of Dermatology, Nishtar Hospital, Multan, from November 2024 to April 2025. Sixty patients with untreated bilateral xanthelasma palpebrarum were enrolled using non-probability consecutive sampling and randomly assigned using a computer-generated simple randomization technique (1:1) to receive either 100% trichloroacetic acid or cryotherapy. Treatment efficacy and adverse effects were evaluated at six weeks using standardized clinical criteria. Data were analyzed using SPSS version 26. A confidence level of 95% was used for all statistical analyses. Results were considered statistically significant at a p-value≤0.05. **Results:** A total of 60 patients (30 patients in each group) with xanthelasma palpebrarum were enrolled, with a mean age of 40.10 ± 7.40 years and a mean disease duration of 11.18 ± 2.94 months. Females comprised 60.0% of the sample, and 63.3% were aged 36–55 years. Excellent treatment response was observed in 53.3% of patients treated with 100% TCA and 20.0% with cryotherapy (p=0.023). Hyperpigmentation (p=0.020) and scarring (p=0.010) were significantly higher in the TCA group. Age, gender, and lesion location showed no significant association with efficacy or adverse effects. **Conclusions:** TCA offers superior clinical efficacy compared to cryotherapy but with a higher risk of adverse cosmetic effects, underscoring the need for individualized treatment planning in xanthelasma management.

## INTRODUCTION

Xanthelasma palpebrarum (XP) is the most commonly encountered type of cutaneous xanthoma, marked by yellowish plaques over the medial aspects of the eyelids [1]. These lesions are typically bilateral, symmetrical, and localized to the upper eyelids, although they may also involve the lower eyelids in some cases. XP is a benign condition with no malignant potential, but it frequently prompts patients to seek medical attention due to its prominent cosmetic impact, particularly when lesions are large or disfiguring [2]. The reported prevalence of XP ranges from 0.3% to 4.4%, with a higher incidence observed among middle-aged women [3, 4]. While XP has traditionally been associated with hyperlipidemia, recent studies suggest that up to 34.5–58% of patients may have normal lipid profiles, though isolated low HDL or altered lipoprotein metabolism may still be present [5, 6]. Other contributing factors include hypothyroidism, diabetes mellitus, and familial dyslipidemia. The underlying pathology involves dermal infiltration by cholesterol-laden macrophages (foam cells), which are influenced by both systemic metabolic dysfunction and local factors such as trauma or friction [7]. Several therapeutic options are

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available for the treatment of XP, including surgical excision, electrosurgery, laser ablation, radiofrequency, cryotherapy, and chemical cauterization using trichloroacetic acid (TCA). However, there is no consensus on the most effective first-line treatment [8]. Surgical excision offers low recurrence rates but is invasive and may result in scarring or ectropion, especially in periorbital lesions. Laser therapies require specialized equipment and carry a risk of pigmentary changes and prolonged erythema. Consequently, there is a growing preference for minimally invasive, cost-effective outpatient procedures such as TCA cautery and cryotherapy [9]. TCA induces epidermal and superficial dermal coagulation, resulting in protein denaturation and lesion resolution. Its use in concentrations ranging from 50% to 100% has demonstrated clearance rates between 61% and 100% depending on lesion size and number of sessions. However, treatment-related complications such as hypopigmentation, erythema, and recurrence have also been reported, especially with lower concentrations [10, 11]. In one study using 95% TCA, complete lesion resolution was achieved in 33% of patients, while others required multiple sessions [10]. Another trial using 100% TCA reported lesion clearance in 95% of cases, suggesting improved efficacy with higher concentrations [12]. In contrast, cryotherapy causes tissue necrosis via rapid freezing and thawing, but has historically been underutilized due to concerns over periorbital edema. More recent studies using very short freeze times have reported promising results with minimal complications and excellent patient tolerability [13]. Despite the availability of both TCA and cryotherapy, direct comparative data assessing their efficacy remain sparse. Previous studies have either focused on single-arm interventions or lacked standardized outcome assessment.

Despite the availability of multiple treatment modalities for xanthelasma palpebrarum, there is no clear consensus regarding the most effective and cosmetically acceptable first-line therapy. Although both 100% trichloroacetic acid (TCA) and cryotherapy are widely used due to their accessibility and cost-effectiveness, direct randomized comparisons between these two modalities remain limited. Most previous studies have been single-arm or split-face designs with small sample sizes and inconsistent outcome measures. Therefore, robust comparative data evaluating both efficacy and safety profiles are needed to guide evidence-based clinical decision-making. This study aimed to compare the efficacy, safety, and tolerability of 100% TCA versus cryotherapy in xanthelasma palpebrarum, with the hypothesis that 100% TCA would yield superior lesion clearance with acceptable side effects.

## METHODS

This randomized controlled trial (RCT No. NCT06839638) was carried out at the Department of Dermatology, Nishtar Hospital, Multan, from November 2024 to April 2025. Ethical approval was obtained from the Institutional Ethical Review Board of Nishtar Medical University, Multan (Reference No. 21456/NMU). A non-probability consecutive sampling technique was used to enroll eligible patients presenting with xanthelasma palpebrarum. The sample size was calculated using OpenEpi software, assuming a treatment success rate of 61% for 100% TCA and 18% for cryotherapy. With a two-sided significance level of 0.01, power of 80%, and equal group allocation (1:1), the sample size was determined to be 30 participants per group, yielding a total of 60 participants [10, 14]. Patients aged 20 to 55 years of either gender with clinically diagnosed bilateral xanthelasma palpebrarum (0.5–3.0 cm), no prior treatment history, and currently receiving anti-lipidemic therapy for systemic control of disease were included. Only those who provided informed consent and agreed to follow-up were enrolled. Patients with hypersensitivity to trichloroacetic acid or cryotherapy, active periorbital skin conditions, bleeding disorders, or a history of keloid formation were excluded. After obtaining informed consent, participants were assigned to one of two treatment groups using a computer-generated simple randomization technique in a 1:1 allocation ratio. Baseline demographic and clinical characteristics, including age, gender, duration of xanthelasma, and area of lesion, were documented before initiating treatment. Participants in Group A received 100% trichloroacetic acid (TCA), while those in Group B underwent cryotherapy with liquid nitrogen. Both treatment procedures were performed by a qualified dermatologist under standardized clinical conditions. In Group A, TCA 100% was applied directly to the lesion using a fine-tipped wooden applicator after cleaning the skin with normal saline with a rotatory motion from the periphery toward the center. The acid was applied until a uniform white frosting appeared over the lesion surface, indicating adequate protein coagulation. To protect the surrounding healthy skin, white soft paraffin was applied around the lesion margins to prevent accidental spillage of the acid. In Group B, cryotherapy was administered using one freeze-thaw cycle of liquid nitrogen until a narrow halo of white ice formed around the lesion. Patients were instructed to keep the area clean and to report any signs of blistering or infection. All patients were prescribed topical fusidic acid 2% to be applied twice daily over the treated area for one week following the procedure. Participants in both groups were followed up at six weeks after the intervention. At the follow-up visit, the primary outcome, which includes treatment efficacy and secondary outcomes, included the frequency of adverse

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effects (edema, erythema, pigmentary changes, scarring) were assessed using standardized clinical examination. Efficacy was graded based on percentage reduction in lesion: mild (<50%), moderate (50–75%), or excellent (>75%) response [12]. Side effects, including edema, erythema, hypopigmentation, hyperpigmentation, and scarring, were evaluated and recorded. All assessments were performed by a blinded evaluator to reduce observer bias. Data were collected using a predesigned, structured data collection form developed specifically for this study. The data were analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation and compared between the treatment groups using the Independent Samples t-test. Categorical variables were presented as frequencies and percentages. The association between categorical variables and treatment groups was analyzed using the Pearson Chi-square test. A confidence level of 95% was used for all statistical analyses. Results were considered statistically significant at a p-value ≤ 0.050 (Figure 1).

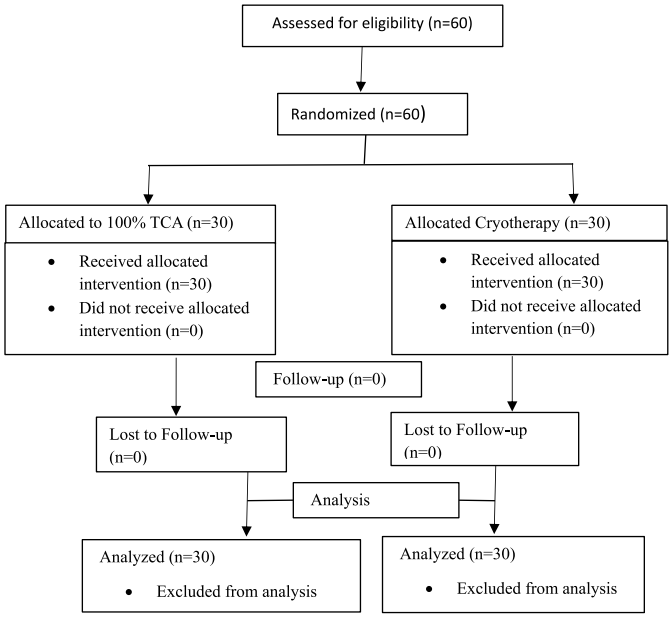


**Figure 1:** CONSORT Flow Diagram

## RESULTS

The mean age of participants was 40.10 ± 7.40 years, while the average duration of xanthelasma was 11.18 ± 2.94 months. There was no statistically significant difference in baseline characteristics between the two treatment groups. The mean age in the TCA group was 41.17 ± 7.80 years, compared to 39.03 ± 6.95 years in the cryotherapy group (p=0.268). The average duration of xanthelasma was 10.80 ± 3.18 months in Group A and 11.57 ± 2.69 months in Group B (p=0.317). The age distribution (p=0.176), gender composition (p=0.598), and lesion location (p=0.941) were also comparable across both groups. Baseline lesion size (mean ± SD) was 1.73 ± 0.86 cm in the TCA group and 1.83 ± 0.89 cm in the cryotherapy group, with no statistically significant difference (p=0.660) (Table 1).

**Table 1:** Baseline Demographic and Clinical Characteristics of Patients

| Variables | Group A (TCA 100%) n = 30 | Group B (Cryotherapy) n = 30 | p-Value |
|---|---|---|---|
| Age (years) (Mean ± SD) | 41.17 ± 7.80 | 39.03 ± 6.95 | 0.268 |
| **Age Group** | | | |
| 20–35 years | 8 (26.7%) | 13 (43.3%) | 0.176 |
| 36–55 years | 22 (73.3%) | 17 (56.7%) | |
| **Gender** | | | |
| Male | 13 (43.3%) | 11 (36.7%) | 0.598 |
| Female | 17 (56.7%) | 19 (63.3%) | |
| **Area of Lesion** | | | |
| Upper Eyelid | 17 (56.7%) | 16 (53.3%) | 0.941 |
| Lower Eyelid | 5 (16.7%) | 6 (20.0%) | |
| Both Upper and Lower Eyelid | 8 (26.7%) | 8 (26.7%) | |
| Duration of Xanthelasma (months) (Mean ± SD) | 10.80 ± 3.18 | 11.57 ± 2.69 | 0.317 |
| Baseline lesion size (cm) (mean ± SD) | 1.73 ± 0.86 | 1.83 ± 0.89 | 0.660 |

Chi-square test was used for dichotomous variables, and the Independent Samples t-test was applied for continuous variables. A p-value < 0.050 was considered statistically significant

At 6 weeks post-treatment, mean lesion size reduced to 0.47 ± 0.40 cm in the TCA group compared to 0.77 ± 0.45 cm in the cryotherapy group, with a statistically significant difference favoring TCA (p=0.010). Post-intervention, treatment response differed significantly between groups ($\chi^2$=7.52, df=2, p=0.023). In Group A (TCA), 53.3% achieved excellent response compared to 20.0% in Group B (Cryotherapy). Conversely, moderate responses were more common in Group B (43.3% vs. 30.0%), while mild responses were also higher in Group B (36.7% vs. 16.7%). This indicates that the statistical difference was driven primarily by a relative shift in Group B from excellent responses toward moderate and mild outcomes (Figure 2).

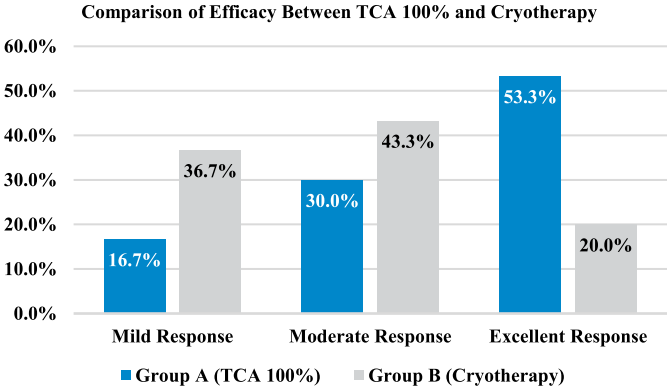


**Figure 2:** Comparison of Efficacy Between TCA 100% and Cryotherapy in Patients with Xanthelasma Palpebrarum (N=60)

In Group A, edema was reported in 5 (16.7%), erythema in 7

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(23.3%), hypopigmentation in 5 (16.7%), hyperpigmentation in 9 (30.0%), and scarring in 6 (20.0%) patients. In contrast, Group B (Cryotherapy) showed edema in 3 (10.0%), erythema in 4 (13.3%), hypopigmentation in 3 (10.0%), hyperpigmentation in 2 (6.7%), and no cases of scarring. Statistically significant differences were observed for hyperpigmentation (p = 0.020) and scarring (p=0.010), indicating a higher frequency of these adverse events in the TCA-treated group (Table 2).

**Table 2:** Comparison of Treatment-Related Side Effects Between TCA 100% and Cryotherapy in Patients with Xanthelasma Palpebrarum (N=60)

| Variables | Group A (TCA 100%) n = 30 | Group B (Cryotherapy) n = 30 | p-Value |
|---|---|---|---|
| Edema | 5 (16.7%) | 3 (10.0%) | 0.448 |
| Erythema | 7 (23.3%) | 4 (13.3%) | 0.317 |
| Hypopigmentation | 5 (16.7%) | 3 (10.0%) | 0.448 |
| Hyperpigmentation | 9 (30.0%) | 2 (6.7%) | 0.020* |
| Scarring | 6 (20.0%) | 0 (0.0%) | 0.010* |

The Pearson Chi-square test was applied to assess statistical significance. A p-value <0.050 was considered statistically significant

## DISCUSSION

This randomized comparative study evaluated the efficacy and safety of 100% trichloroacetic acid (TCA) versus cryotherapy in the treatment of xanthelasma palpebrarum (XP). The two treatment groups in this randomized trial were comparable at baseline, with no significant differences in age, gender distribution, lesion location, or lesion duration. The mean age of participants was 40.10 ± 7.40 years, with Group A (TCA 100%) averaging 41.17 ± 7.80 years and Group B (Cryotherapy) 39.03 ± 6.95 years (p = 0.268), which aligns with previous studies that report XP most frequently affects individuals between 40 and 60 years of age [12, 15]. Gender distribution in our study showed a female predominance (60% overall), with 56.7% females in Group A and 63.3% in Group B (p=0.598), which is consistent with earlier studies reporting a higher prevalence of XP in women [4, 14]. Lesions most frequently involved the upper eyelids in both groups, also mirroring typical patterns noted in literature (upper lids are more often affected than lower lids) [16]. These similarities in baseline characteristics between groups ensure that any differences in outcomes can be attributed to the treatment effects rather than confounding demographic factors. Moreover, the study's patient profile (middle-aged adults with bilateral xanthelasma) is representative of the general xanthelasma population, enhancing the relevance of the findings. Each group's mean lesion duration was around 11 months, indicating that most patients had relatively recent plaques; this is somewhat shorter than in some series, possibly reflecting earlier cosmetic concern and treatment seeking in our cohort [17]. Our findings demonstrate that high-strength TCA is significantly more efficacious than cryotherapy for xanthelasma palpebrarum. After a single treatment session and follow-up evaluation, the TCA group showed a markedly higher rate of substantial lesion reduction: 53.3% of patients achieved an "excellent" response (>75% reduction in lesion size) with TCA, compared to only 20.0% with cryotherapy (with the majority of cryotherapy patients having only mild-moderate improvement). This difference was statistically significant (p=0.023), confirming the superior efficacy of TCA in lesion clearance. These results closely parallel those of Tahir *et al.*, who reported complete resolution of lesions in 75% of sites treated with a single session of 100% TCA, versus only 17.5% complete clearance with cryotherapy (p<0.001) [14]. Notably, this superiority of TCA is also reflected in other comparative studies: for example, a systematic review by Malekzadeh et al. noted that one trial found 100% TCA to be more effective than cryosurgery for xanthelasma resolution [18]. Similarly, Faysal and Rehman compared 100% TCA to another chemical cautery (silver nitrate) and observed 95% of patients achieving ≥75% lesion clearing with TCA, against only 20% with the alternative agent after one treatment [12]. This further underscores the potent efficacy of concentrated TCA, even relative to other destructive modalities. Güngör *et al.* reported that application of TCA (70% concentration) produced similar efficacy to erbium: YAG laser ablation when each was applied to separate lesions in the same patients [19]. This suggests that chemical peeling at sufficient strength can achieve lesion clearance comparable to laser ablation, at least for superficial to moderately thick plaques. Taken together, the evidence positions 100% TCA as one of the most effective single-session treatments for xanthelasma, often outperforming cryotherapy and matching the efficacy of more resource-intensive options in appropriate lesions. Our trial's efficacy data are in line with this consensus. It should be noted that cryotherapy can still gradually reduce xanthelasma with repeat sessions, but its initial impact is clearly less pronounced, as also reflected in Tahir *et al.*'s study, where 80% of cryotherapy-treated lesions needed a second session for full clearance. Although 100% trichloroacetic acid (TCA) demonstrated superior efficacy in lesion clearance, it was associated with a significantly higher frequency of pigmentary alterations and scarring. In the present study, post-treatment hyperpigmentation occurred in 30.0% of TCA-treated patients versus 6.7% of cryotherapy cases (p=0.020). This high incidence represents a potential limitation to the cosmetic use of TCA, particularly in patients with darker skin phototypes, where pigmentary alteration may be more

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pronounced and persistent. The absence of scarring in the cryotherapy group, compared with 20.0% incidence in the TCA group (p=0.010), indicates a statistically significant safety advantage of cryotherapy. Clinically, this finding reinforces cryotherapy's safer cosmetic profile, particularly in periorbital regions where scarring is highly undesirable. These findings are consistent with those reported by Tahir *et al.*, where hyperpigmentation was noted in 37.5% and scarring in 30% of lesions treated with 100% TCA, compared to 10% and 0%, respectively, with cryotherapy [14]. These results align with the known mechanism of TCA, a caustic agent that induces coagulative necrosis extending variably into the dermis, increasing the risk of post-inflammatory pigmentary changes and fibrosis [18]. In our study, minor transient side effects such as erythema and edema were observed in both groups (TCA: 23.3% erythema, 16.7% edema; cryotherapy: 13.3% and 10.0%, respectively), but these were not statistically significant. Previous studies support this trend. Arora *et al.* reported post-treatment hyperpigmentation in 25% and hypopigmentation in 10% of patients treated with 50% TCA [17]. Similarly, Sapra *et al.* found lower rates (hyperpigmentation 7.8%, hypopigmentation 2.6%) with TCA 80%, potentially due to more conservative application in lighter phototypes [11]. Nassief also compared 30% and 70% TCA and observed a clear concentration-dependent increase in both efficacy and adverse effects, with 70% TCA providing greater lesion clearance but a higher incidence of transient pigmentary changes [20]. In contrast, Labandeira *et al.* demonstrated that brief, low-pressure liquid nitrogen cryotherapy caused minimal pigmentary disturbance, reinforcing its favorable safety profile [13]. Thus, while TCA remains effective, its use warrants caution, particularly in patients with darker skin tones or cosmetic sensitivity. Cryotherapy may be preferred when minimizing pigmentation risk is paramount. This study provides comparative clinical evidence on the efficacy and safety of 100% trichloroacetic acid versus cryotherapy in the treatment of xanthelasma palpebrarum. Its strengths include a randomized design, balanced group characteristics, and objective outcome assessment. However, limitations include the single-center setting, short-term follow-up, and absence of lipid profile analysis or quality-of-life evaluation. The study's scope did not extend to long-term recurrence tracking or patient satisfaction. Future multicenter trials with extended follow-up, dermoscopic documentation, and correlation with systemic lipid parameters are recommended to better guide individualized treatment selection and assess the durability of lesion clearance across diverse patient subgroups.

This study has certain limitations, including its single-center design, relatively small sample size, and short-term follow-up period, which precludes assessment of long-term recurrence and sustained cosmetic outcomes. Additionally, patient satisfaction scores and objective lipid profile correlations were not evaluated. Future multicenter randomized trials with larger cohorts, longer follow-up durations, and inclusion of quality-of-life assessments are recommended to better determine long-term efficacy, recurrence rates, and optimal patient selection for each treatment modality.

## CONCLUSIONS

The findings of this randomized trial indicate that 100% trichloroacetic acid provides superior lesion clearance compared to cryotherapy in the management of xanthelasma palpebrarum, albeit with a higher incidence of adverse cosmetic outcomes. However, its use is associated with a greater frequency of adverse effects, particularly pigmentary changes and scarring. The findings emphasize the importance of balancing efficacy with cosmetic outcomes when selecting a therapeutic approach. Clinical decision-making should be individualized, taking into account patient expectations, skin type, and tolerance for potential treatment-related complications.

## Authors' Contribution

Conceptualization: SI, MIJ
Methodology: AB[1], ST
Formal analysis: RT, AB[2]
Writing and Drafting: RT, AB[2], ST, SI, MIJ
Review and Editing: RT, AB[2], ST, SI, MIJ, AB[1]

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Risk Assessment of Breast Cancer Through BI-RADS Category Using Digital Mammography Technique Among Symptomatic and Asymptomatic Women

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## ABSTRACT

Breast cancer is the second leading cause of death among women globally. Risk factors include BRCA1 gene mutations, age, early menopause, and family history. Digital mammography is the gold standard for symptomatic women presenting with chest pain, lumps, nipple discharge, or skin changes, while asymptomatic women undergo routine screening from age 45. Risk assessment is based on correlating BI-RADS findings with patient history and socioeconomic factors. **Objectives:** To assess breast cancer risk through BI-RADS categories using digital mammography among symptomatic and asymptomatic women. **Methods:** This comparative cross-sectional study included 384 women aged 15–75 years. Data were collected using a structured questionnaire covering demographics, lifestyle, reproductive history, family cancer history, breast tissue density, and BI-RADS category. Non-probability convenience sampling was used, and analysis was performed via IBM SPSS version 26.0. **Results:** Most participants were aged 46–65 years, housewives, and postmenopausal. Moderate physical activity (59%), symptoms (80.3%), and prior screening mammography (61.3%) were common. While 88.1% performed self-examinations and 82.1% had professional exams, 53.2% had never undergone a mammogram. Family history of breast cancer (34.3%) was notable. Scattered fibro-glandular breast tissue predominated. Awareness of BI-RADS (43.1%) and digital mammography (62.1%) was limited. Most had no prior cancer treatment (77.4%) or radiation exposure (92.7%), with 29.9% diagnosed with breast cancer. **Conclusions:** Menstrual changes and early post-menopause influenced malignancy risk, with increasing age being a significant factor. Higher parity correlated with benign categories.

## INTRODUCTION

Breast cancer is the second most common cause of death among women worldwide, with one in nine women in Pakistan developing it at some point in their lives [1]. The disease has a high incidence globally, with around 280,000 new cases diagnosed annually and 40,000 deaths recorded in the United States alone. Various risk factors contribute to the development of breast cancer, including increasing age, a positive family history, genetic mutations such as BRCA1 and BRCA2, early menstruation (before 12 years), late menopause (after 55 years), dense breast tissue, nulliparity, late pregnancy, prolonged estrogen use, early radiation exposure, and lifestyle factors such as obesity, alcohol consumption, and sedentary behavior [2]. Breast cancer diagnosis primarily relies on mammographic imaging techniques. Several imaging methods exist, including digital mammography (DMT), contrast-enhanced mammography (CEM), magnetic resonance imaging (MRI), magnification mammography, and stereo mammography. However, in Pakistan, only digital mammography is widely available, and it remains the gold standard for screening symptomatic and asymptomatic women aged 45 and above [3]. Standard mammographic views include right

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craniocaudal (RCC), left craniocaudal (LCC), right mediolateral oblique (RMLO), and left mediolateral oblique (LMLO). Additional or extended views, such as lateral/medial craniocaudal, spot compression, axillary tail, cleavage view, and tangent views, are useful for dense breast tissue, enhancing diagnostic accuracy by reducing tissue overlap [4, 5]. The risk of breast cancer is categorized using the Breast Imaging Reporting and Data System (BI-RADS), which classifies findings from B0 (indeterminate) to BVI (biopsy-confirmed cancer). Breast tissue density is another crucial factor in risk assessment, classified into four types: A (fatty tissue), B (scattered fibroglandular density), C (heterogeneously dense), and D (extremely dense breast tissue). High breast density not only increases cancer risk but also reduces mammographic sensitivity, making detection more challenging due to the masking effect [6]. Traditionally, radiologists visually assess breast density using BI-RADS, but this method is subjective and prone to variability, leading to inconsistencies in risk classification [7]. To address these limitations, automated and semi-automated techniques have been introduced for more accurate and reproducible breast density assessment. Studies such as WISDOM, My Personalized Breast Screening (MyPeBS), and the Tailored Breast Screening Trial are investigating risk-based screening approaches, integrating breast density with other risk factors to determine the need for additional imaging, such as ultrasound. The DenSeeMammo system (DSM) is one such automated tool designed to measure breast density and assess its masking effect on cancer detection [8]. This study aims to evaluate the effectiveness of DSM compared to conventional radiological assessments. Mammographic density plays a crucial role in breast cancer risk prediction, influencing both the sensitivity of screenings and the likelihood of interval cancers. In several U.S. states, women are now informed about their breast density after screenings. Traditional density assessment methods, like the Cumulus approach, are well-established risk predictors. However, with the widespread adoption of full-field digital mammography (FFDM), new volumetric techniques have emerged, offering a more automated approach. Pakistan has the highest breast cancer incidence rate in Asia and ranks eighth globally. Many young women present with late-stage disease, significantly affecting their prognosis. Early detection is critical, and Digital Breast Tomosynthesis (DBT) is emerging as a superior imaging modality for identifying breast cancer, particularly in women with dense breast tissue. Unlike conventional mammography, which struggles with overlapping tissue, DBT provides cross-sectional images, improving sensitivity while reducing false positives [9]. Despite its advantages, DBT is under-researched in Pakistan. Another crucial aspect of breast cancer screening is the evaluation of BI-RADS category III, which indicates a "probably benign" finding requiring follow-up. However, previous research validating BI-RADS III often excluded patients with a personal history of breast cancer (PHBC), who are at a higher risk of recurrence. With growing preference for DBT over FFDM, this study assesses the accuracy of BI-RADS III classifications in PHBC patients, comparing outcomes between the two imaging modalities [10]. Advancements in deep learning (DL) have shown potential to enhance mammography accuracy, aiding in risk assessment. Additionally, research has established a link between sedentary behavior and breast cancer, with observational studies indicating a slight increase in risk due to prolonged inactivity [11].

Although digital mammography and BI-RADS classification are widely used for breast cancer risk stratification, limited region-specific data are available comparing BI-RADS-based risk distribution among symptomatic and asymptomatic women in Pakistan. Most local studies focus on imaging findings alone without integrating demographic, reproductive, and lifestyle factors into risk interpretation. Additionally, evidence exploring the relationship between menstrual changes, parity, and BI-RADS categorization remains insufficient. However, limited literature is available on the association between breast cancer risk and women's parity or menstrual cycle changes This gap highlights the need for a comprehensive assessment combining clinical history and mammographic findings to refine breast cancer risk evaluation. This study, therefore, seeks to assess the relationship between breast cancer risk, lifestyle factors, menstrual cycle changes, and parity among symptomatic and asymptomatic women. By addressing these knowledge gaps, the study aspires to refine breast cancer screening strategies and contribute to more personalized risk-based screening protocols. This study aimed to assess the risk of breast cancer through BI-RADS category using the digital mammography technique among symptomatic and asymptomatic women.

## METHODS

This comparative cross-sectional study was conducted at the Combined Military Hospital Diagnostic Center, Lahore, over four months (September to December 2024). Ethical approval was granted by the Ethical Review Committee (ERC) of Combined Military Hospital Lahore Medical College (Ref. No: #91/ERC/CMH/LMC). Participants were categorized into symptomatic and asymptomatic groups based on clinical history and physical examination, where symptomatic women presented with breast-related complaints such as palpable lumps, nipple discharge, pain, or skin changes, and asymptomatic women underwent routine mammographic screening without prior symptoms. Inclusion criteria comprised women aged 15–75

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years undergoing mammography, while exclusion criteria included confirmed pregnancy, prior mastectomy, and contraindications to mammography, such as severe breast trauma or refusal of the procedure. Mammographic imaging was performed using a Full-Field Phillips Digital Mammography (FFDM) system calibrated according to international radiological standards, including MQSA guidelines, with routine quality assurance tests. Standard Craniocaudal (CC) and Mediolateral Oblique (MLO) views were obtained for all participants, and breast density and lesion classification were assessed using BI-RADS 5th Edition criteria, categorizing findings as BI-RADS 1–2 (normal or benign), BI-RADS 3 (probably benign, requiring short-term follow-up), and BI-RADS 4–5 (suspicious for malignancy, biopsy recommended). The primary outcome variable was BI-RADS classification, with secondary outcomes including breast density, age distribution, and associations with risk factors. Breast cancer risk was assessed using relative risk (RR) and odds ratio (OR) calculations for symptomatic versus asymptomatic groups, along with logistic regression analysis adjusting for age, family history, breast density, and hormone therapy exposure. The sample size was calculated using the World Health Organization Geneva Calculator, applying a conservative anticipated population proportion of 50% due to the absence of reliable local prevalence data for BI-RADS 4–5 findings in young women, yielding a final sample size of 385 participants with sufficient power for comparative analysis. Non-probability convenience sampling was employed, with efforts to minimize selection bias by recruiting participants from diverse backgrounds and age groups. Data collection involved a self-structured questionnaire and mammography reports. Women aged 15–75 years, both symptomatic and asymptomatic, were enrolled after pre-screening counseling explaining radiation risks and benefits, possible BI-RADS outcomes, follow-up recommendations, and counseling was conducted by radiologists and medical imaging technologists, followed by written informed consent. The mammography procedure involved non-invasive X-ray imaging with breast compression lasting approximately 20 minutes. Data collection included four sections: demographics, personal information, knowledge of mammography, and BI-RADS-based diagnosis, with self-reported medical history used to assess prior radiation exposure; medical records were reviewed when available, though dosimetry estimates were not performed due to limited access to historical imaging data. Mammograms were interpreted by multiple radiologists with at least five years of breast imaging experience, and in cases of discordance, consensus reporting was used to reduce subjective bias; breast density was visually assessed based on BI-RADS categorization without automated tools, acknowledging potential inter-observer variability. Statistical analysis was conducted using SPSS version 26.0, with descriptive statistics including mean and standard deviation for quantitative data and frequency and percentages for qualitative data, while comparisons between groups were performed using Chi-square or Fisher's exact tests as appropriate. A p-value of <0.05 was considered statistically significant, and all findings were reported at the 95% confidence interval.

## RESULTS

A total of 385 women were included in the study, of whom 310 (80.5%) were symptomatic and 75 (19.5%) were asymptomatic. The mean age of participants was concentrated between 46–65 years, with 53.6% of women falling into this range. Most participants were married (76.1%), multiparous (87.5%), and in menopause (72.5%). Regarding lifestyle, 59.0% reported moderate physical activity, while 28.6% were physically inactive. Almost two-thirds (65.7%) were housewives, and only 7.3% had a history of radiation exposure (Table 1).

**Table 1:** Demographic, Educational, Lifestyle, Marital Status, and Parity Distribution of Study Participants (N=385)

| Variables | Category | N (%) |
|---|---|---|
| Age (years) | 15–25 | 23 (6.0%) |
| | 26–35 | 20 (5.2%) |
| | 36–45 | 76 (19.7%) |
| | 46–55 | 110 (26.8%) |
| | 56–65 | 103 (25.1%) |
| | 66–75 | 53 (13.8%) |
| Education | Illiterate | 41 (10.6%) |
| | Primary | 44 (11.4%) |
| | Intermediate | 115 (29.9%) |
| | Graduation | 167 (43.4%) |
| | PhD | 18 (4.7%) |
| Lifestyle | Inactive | 110 (28.6%) |
| | Moderate | 227 (59.0%) |
| | High activity | 48 (12.5%) |
| Marital status | Married | 293 (76.1%) |
| | Unmarried | 41 (10.6%) |
| | Widow | 51 (13.2%) |
| Parity | Yes | 337 (87.5%) |
| | No | 48 (12.5%) |

Breast cancer awareness and screening practices were variable. While 82.1% of women had undergone clinical breast examination and 88.1% performed self-examination, only 46.8% had ever undergone a mammogram. Among those who had mammography, 61.3% were for screening, 10.6% for diagnostic purposes, and 28.1% for follow-up. A family history of breast cancer was present in 34.5% of participants, predominantly from the maternal side (21.3%). A smaller subset (16.1%) reported oral contraceptive pill use (Table 2).

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**Table 2:** Distribution Of Breast Cancer Screening Practices, Family History, And Prior Diagnosis Among Study Participants (N=385)

| Variables | Category | N (%) |
|---|---|---|
| Professional breast exam | Yes | 316 (82.1%) |
| Self-exam | Yes | 339 (88.1%) |
| Family history of breast cancer | Yes | 132 (34.5%) |
| Prior breast cancer diagnosis | Yes | 115 (29.9%) |

Among the study participants, 310 (80.5%) were symptomatic and 75 (19.5%) were asymptomatic. The most common presenting symptoms were breast pain (36.3%) and palpable lump (26.2%) (Table 3).

**Table 3:** Symptom Distribution Among Participants (N=385)

| Symptoms | N (%) |
|---|---|
| Pain | 140 (36.3%) |
| Lump | 101 (26.2%) |
| Nipple discharge | 21 (5.4%) |
| Itching | 23 (5.9%) |
| Skin/tissue thickening | 8 (2.0%) |
| Nipple retraction | 6 (1.5%) |
| Other (orange peel, scar, etc.) | 5 (1.2%) |
| Asymptomatic | 75 (19.5%) |

The BI-RADS classification revealed important differences between symptomatic and asymptomatic groups. Among symptomatic women, 93 (30.0%) were BI-RADS 1, 121 (39.0%) BI-RADS 2, 64 (20.6%) BI-RADS 3, and 32 (10.3%) were abnormal (BI-RADS 4–5). By contrast, among asymptomatic women, 22 (29.3%) were BI-RADS 1, 29 (38.7%) BI-RADS 2, 16 (21.3%) BI-RADS 3, and only 7 (9.3%) were abnormal (BI-RADS 4–5). A further 4 symptomatic (1.3%) and 1 asymptomatic (1.3%) participant were BI-RADS 6, representing biopsy-proven malignancy. Overall, the prevalence of abnormal findings (BI-RADS 4–5) was 9.1%, while biopsy-proven cancer (BI-RADS 6) was confirmed in 1.3% of participants. Although abnormal findings were more frequent among symptomatic women compared to asymptomatic (10.3% vs. 9.3%), the difference did not reach statistical significance ($p > 0.050$) (Table 4).

**Table 4:** Distribution of BI-RADS Categories Among Symptomatic and Asymptomatic Women

| BI-RADS Category | Symptomatic (N=310) | Asymptomatic (N=75) | Total (N=385) | p-Value* |
|---|---|---|---|---|
| BI-RADS 0 – Incomplete | 6 (1.9%) | 2 (2.7%) | 8 (2.1%) | 0.620 |
| BI-RADS 1 – Negative | 93 (30.0%) | 22 (29.3%) | 115 (29.9%) | 0.910 |
| BI-RADS 2 – Benign | 121 (39.0%) | 29 (38.7%) | 150 (39.0%) | 0.960 |
| BI-RADS 3 – Probably benign | 64 (20.6%) | 16 (21.3%) | 80 (20.8%) | 0.880 |
| BI-RADS 4 – Suspicious (A–C) | 21 (6.8%) | 5 (6.7%) | 26 (6.8%) | 0.970 |
| BI-RADS 5 – Highly suggestive of malignancy | 11 (3.5%) | 2 (2.7%) | 13 (3.4%) | 0.770 |
| BI-RADS 6 – Known biopsy-proven | 4 (1.3%) | 1 (1.3%) | 5 (1.3%) | 0.990 |
| Abnormal (BI-RADS 4–5) | 32 (10.3%) | 7 (9.3%) | 39 (10.1%) | 0.820 |

*Chi-square/Fisher's exact test

Chi-square analysis demonstrated significant associations between BI-RADS categories and several risk factors (Table 5.5). Age was significantly associated with BI-RADS classification in the left breast ($p < 0.001$). Radiation exposure was strongly associated with abnormal BI-RADS findings in both breasts ($p=0.003$ right, $p<0.001$ left). Menstrual cycle status was significantly associated with BI-RADS categories for both breasts ($p = 0.038$ right, $p = 0.007$ left). Parity showed significance for the right breast ($p=0.023$), while marital status was significant for the left breast ($p = 0.010$). In contrast, family history of breast cancer and lifestyle factors were not significantly associated with BI-RADS categories (Table 5).

**Table 5:** Prevalence of Abnormal BI-RADS Findings (4–5) and Biopsy-Proven Malignancy (6) in Symptomatic Vs. Asymptomatic Women

| Category | Symptomatic (N=310) | Asymptomatic (N=75) | Total (N=385) | p-Value* |
|---|---|---|---|---|
| Abnormal BI-RADS (4–5) | 32 (10.3%) | 7 (9.3%) | 39 (10.1%) | 0.820 |
| Biopsy-proven malignancy (6) | 4 (1.3%) | 1 (1.3%) | 5 (1.3%) | 0.990 |

*Chi-square/Fisher's exact test

## DISCUSSION

This study evaluated breast cancer risk using patient history and BI-RADS categories from digital mammography. Most participants (52.5%) had BI-RADS BI-negative, indicating no significant findings, while others had higher BI-RADS categories (IV–VI), reflecting malignancy risks. Older women (56–75 years) had higher BI-RADS categories, while younger women (15–25 years) showed biopsy-proven malignancies, suggesting aggressive cancer types. However, no statistically significant link between age and BI-RADS was found ($p = 0.060$), highlighting multifactorial risk factors [12]. Extended mammography views and digital breast tomosynthesis (DBT) improve cancer detection, especially in younger women with dense breast tissue [13, 14]. The study highlights the role of extended digital mammography views and DBT in improving breast cancer detection, especially in high-risk populations. While BI-RADS categories help stratify risk, combining them with patient history enhances accuracy [15]. A key finding is the strong link between sedentary behavior and breast cancer risk, with prolonged inactivity increasing the likelihood of cancer, even among physically active individuals [16].

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Regional variations show a higher risk in Asia (21.6%) than in North America (8.26%). Though no direct link between lifestyle and BI-RADS classifications was found, physically active women had lower malignancy rates [14]. The study underscores the need for a holistic risk assessment, emphasizing physical activity as a key prevention strategy [12, 16]. The study found a significant link between occupational radiation exposure and higher BI-RADS malignancy classifications, emphasizing the need for protective measures. Women with irregular menstrual cycles and early menopause had increased breast cancer risk due to hormonal imbalances. Regular cycles were associated with lower malignancy rates. The study found a significant association between parity and BI-RADS classifications, with women who had given birth more likely to be in the BI-negative category, suggesting a lower risk of suspicious findings [17]. However, the correlation was weak, indicating that other factors like age, family history, and lifestyle play a more significant role in breast cancer risk. Marital status showed no significant impact on BI-RADS classifications, though widows had higher percentages in concerning categories, possibly due to healthcare access barriers [18]. Age was significantly related to BI-RADS findings, with older women more likely to have benign results, while younger women showed a broader distribution, including more cases requiring further imaging [12]. Physical activity levels did not significantly influence BI-RADS classifications, suggesting that other risk factors, such as genetics and hormonal changes, have a greater impact on breast health. Overall, while certain factors showed associations with breast cancer risk, none were sole determinants, highlighting the need for comprehensive screening strategies. The analysis highlights a statistically significant association between radiation exposure and BI-RADS classification for the left breast, with exposed individuals showing a higher percentage of B VI-known biopsy-proven malignancies. While this aligns with previous studies on the carcinogenic effects of ionizing radiation, the weak negative correlation (Pearson's R = -0.115) suggests that other factors, such as genetics and lifestyle, also play a role [13]. Similarly, menstrual cycle status showed a significant relationship with BI-RADS categorization, particularly among post-menopausal individuals, who were more likely to fall into higher malignancy categories. However, the weak correlation (Pearson's R = -0.058) indicates that menstrual status alone is not a strong predictor of breast tissue changes. Parity, on the other hand, did not show a statistically significant association with BI-RADS classification, as both parous and nulliparous women exhibited similar patterns in breast tissue findings. This suggests that while reproductive history may influence breast cancer risk, it does not necessarily correlate with BI-RADS categorization [16]. In contrast, marital status was found to be statistically associated with BI-RADS classification (p=0.010), with widowed individuals displaying a higher proportion of B V-highly suggestive of malignancy cases [18]. Despite this, the weak correlation values (Pearson's R= 0.009, Spearman's correlation =-0.039) imply that marital status alone is not a strong determinant of breast tissue classification. Overall, while radiation exposure and menstrual cycle status demonstrate significant associations with BI-RADS classification, their weak correlations indicate the influence of multiple interacting factors [19]. Parity does not appear to be a significant determinant, whereas marital status, despite showing statistical significance, lacks a strong predictive value. These findings underscore the complexity of breast cancer risk factors, emphasizing the need for further research incorporating multivariate analyses to better understand the interplay of genetic, lifestyle, and environmental influences on BI-RADS outcomes [17, 20]. The analysis finds no significant relationship between family history of breast cancer and BI-RADS classification for both the right and left breasts [18, 19]. Statistical tests (Chi-Square and correlation) show weak or no association, suggesting that family history alone does not strongly influence BI-RADS categorization. Interestingly, individuals without a family history had slightly higher proportions in high-risk categories (B V and B VI), indicating that other factors such as genetics, lifestyle, and age may play a more critical role. While some studies suggest a link between family history and malignancy risk, others find no direct correlation, aligning with this study's findings [12, 15, 16]. Further research incorporating genetic testing and additional risk factors is needed for a more comprehensive understanding of breast cancer risk assessment. The study had several limitations. First, it was conducted at a single center, CMH Hospital Diagnostic Center, Lahore, which may limit the generalizability of the findings. The study relied on standard craniocaudal (CC) and mediolateral oblique (MLO) views for classification. CEM and DBT were not included due to availability constraints. However, these advanced techniques could enhance lesion detection, particularly in dense breasts, reducing the rate of BI-RADS III and IV misclassifications. This is acknowledged as a limitation. Lastly, a lack of awareness about breast cancer and cultural hesitancy to discuss symptoms likely led to delays in diagnosis, highlighting the need for better public education and screening initiatives.

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## CONCLUSIONS

The study showed associations between breast cancer risk and patients' history, lifestyle, and working environment. Changes in the female menstrual cycle and early post-menopausal women were found to influence higher malignancy categories and increasing age as a significant risk factor for breast cancer. Parity was found to play a modest role, with women who had given birth more likely to fall into benign categories. Marital status was found to be a weak predictor of breast health outcomes, while radiation exposure was associated with higher categories.

## Authors' Contribution

Conceptualization: UER, ZR
Methodology: UER, ZR
Formal analysis: ZS
Writing and Drafting: UER, ZR
Review and Editing: UER, ZR, ZS

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Association between Maternal Vitamin B-12 Deficiency and Early Neuro-developmental Biomarkers in Breastfed Neonates

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## ABSTRACT

Vitamin B-12 plays a vital role in fetal brain development and early neurological function. Exclusively breastfed neonates are highly dependent on maternal B-12 stores and are at increased risk for early neurodevelopmental deficits in cases of maternal deficiency. However, evidence on this association during the neonatal period remains limited, especially in low-resource settings. **Objectives:** To assess the association between maternal vitamin B-12 deficiency and early neurodevelopmental outcomes in exclusively breastfed neonates within the first month of life. **Methods:** This cross-sectional analytical study was conducted on 91 mother-infant pairs. Maternal serum B-12 levels were measured postpartum, and infants were evaluated within the first 28 days using standardized neurodevelopmental assessments, including cognitive, motor, and language scores, as well as clinical markers like visual tracking, muscle tone, and developmental reflexes. Data were analyzed using SPSS, version 26.0 and associations were tested through independent t-tests and Chi-square analyses ($p<0.050$ considered significant). **Results:** Vitamin B-12 deficiency was found in 35.2% of mothers. Among the exclusively breastfed subgroup (n=46), no statistically significant differences were observed in cognitive (p=0.480), motor (p=0.473), or language scores (p=0.544) between neonates of B-12-deficient and B-12-sufficient mothers. Similarly, visual tracking deficits, abnormal muscle tone, and neurodevelopmental delay showed no significant associations with maternal B-12 status. **Conclusions:** Maternal vitamin B-12 deficiency did not demonstrate a measurable impact on early neurodevelopmental biomarkers in exclusively breastfed neonates during the first month of life. Larger longitudinal studies are needed to determine long-term consequences and guide maternal nutrition policies.

## INTRODUCTION

Optimal maternal nutrition during pregnancy plays a critical role in fetal growth and neurological development [1]. Among the essential micronutrients, vitamin B-12 (cobalamin) is indispensable for neurogenesis, myelination, and the synthesis of neurotransmitters. It supports DNA synthesis and red blood cell formation, but more importantly, it influences brain structure and function through its role in methylation pathways. Maternal vitamin B-12 deficiency is widely prevalent in developing countries, with estimates ranging from 25% to over 70% in South Asia, including Pakistan, due to low intake of animal-sourced foods and poor dietary diversity [2, 3]. Neonates rely heavily on maternal B-12 stores acquired during gestation and through breast milk in early infancy. This makes exclusively breastfed infants particularly vulnerable to the consequences of maternal deficiency [4]. Clinical

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manifestations of B-12 deficiency in infants can range from subtle developmental delays to severe neurological impairments, including hypotonia, irritability, growth failure, and even regression of milestones if not addressed in time. Despite this, early signs are often nonspecific and may go unrecognized, particularly in the neonatal period [5]. The neonatal period, defined as the first 28 days of life, is a critical window for early brain development and synaptic organization. Nutritional insults during this stage can disrupt neurodevelopmental trajectories, and even mild deficiencies may lay the foundation for later impairments in cognition and language. As such, early identification of deficits, even if subclinical, may help predict long-term developmental outcomes and allow timely intervention [3, 6]. While the impact of severe maternal B-12 deficiency on long-term child development is well established, evidence remains inconclusive regarding its effect on early neurodevelopmental markers, especially within the first few weeks after birth [7]. This gap is even more pronounced in low-resource settings where B-12 deficiency often coexists with other nutritional and socioeconomic challenges. Moreover, most available studies focus on developmental outcomes at 6 to 12 months or later, with limited research addressing the neonatal stage, particularly among breastfed infants who depend exclusively on maternal nutritional reserves. By evaluating clinical biomarkers such as cognitive, motor, and language scores alongside neurosensory reflexes and muscle tone, this research aims to provide context-specific evidence that could guide early nutritional interventions in maternal and infant health.

Although maternal vitamin B-12 deficiency is highly prevalent in South Asia, evidence regarding its immediate impact on neonatal neurodevelopment remains inconsistent and limited. Most existing studies focus on developmental outcomes at 6–12 months or later, with minimal data addressing the neonatal period, particularly within the first 28 days of life. Furthermore, region-specific data from Pakistan examining early neurodevelopmental biomarkers in exclusively breastfed neonates are scarce. This gap highlights the need for context-specific evidence to clarify whether maternal B-12 deficiency exerts measurable effects during the critical early neonatal window. This study aims to examine the association between maternal serum vitamin B-12 status and early neurodevelopmental outcomes in breastfed neonates within the first month of life.

## METHODS

This cross-sectional analytical study was conducted at the Department of Pediatrics, Combined Military Hospital Rawalakot, affiliated with Poonch Medical College. Ethical approval was granted by the Institutional Review Committee under reference number 2445/SK132A N/CMH/Rawalakot. Data collection was conducted over six months, from October 2024 to March 2025. A minimum sample size of 91 mother-infant pairs was calculated using Open Epi software, based on an anticipated prevalence of vitamin B12 deficiency in pregnant women of approximately 30%, with a 95% confidence level and 10% margin of error. A non-probability consecutive sampling method was used to recruit eligible participants. Inclusion criteria included mothers aged 18–40 years delivering live-born neonates. Neonates aged ≤28 days at the time of developmental screening. Infants who were exclusively or predominantly breastfed. And provision of written informed consent by the mother or guardian. Exclusion criteria were neonates with major congenital anomalies or a history of birth asphyxia. Mothers with diagnosed chronic illnesses (e.g., diabetes, renal disease, autoimmune disorders). Neonates receiving postnatal vitamin B12 supplementation and neonates born before 34 weeks of gestation (late preterm and term infants were included). After informed consent, maternal and neonatal data were recorded using a structured proforma and supplemented with hospital records. Maternal data included age, parity, education, socioeconomic status, diet type, pregnancy supplement use, and mode of delivery. Maternal venous blood samples (5 ml) were collected within 48 hours postpartum. Serum vitamin B12 levels were measured using the Chemiluminescent Micro-Particle Immunoassay (CMIA) technique in the institutional biochemistry laboratory. The cutoff for deficiency was set at <200 pg/mL, consistent with international clinical guidelines, including the World Health Organization (WHO) [6] and regional studies conducted in South Asia [3], where this threshold is commonly used for identifying functionally deficient levels in pregnant and postpartum women. Neonatal data included gestational age, birth weight, Apgar score, head circumference, body length, and weight at the time of assessment. Neurodevelopment was evaluated using the Trivandrum Developmental Screening Chart (TDSC) and a structured neurological examination performed by a single trained pediatrician to ensure inter-rater consistency. The TDSC tool, validated for use in South Asia, measures cognitive, motor, and language domains, as well as visual tracking, auditory startle, muscle tone, and signs of global developmental delay. Since infants aged up to 28 days were eligible, age-standardization was addressed by assessing all milestones relative to the infant's exact postnatal age in days, and referencing the age-specific TDSC benchmarks for each developmental parameter. This ensured comparability across infants of different neonatal ages. Potential confounding variables such as maternal age, education, socioeconomic status, exclusive breastfeeding, and birth weight were pre-

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specified and assessed for association with maternal B12 status using Chi-square and t-tests. No statistically significant differences were observed between the B12-deficient and normal groups on these variables, suggesting that confounding was unlikely. Data were analyzed using IBM SPSS version 26.0. Descriptive statistics were presented as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Independent t-tests were used to compare mean neurodevelopmental scores across groups. Chi-square tests were applied for categorical comparisons (e.g., neurodevelopmental delay, abnormal tone). Normality of data was assessed using the Explore function, histogram inspection, and boxplots. Subgroup analysis was conducted on exclusively breastfed neonates. A p-value of <0.050 was considered statistically significant. To support clinical interpretation, mean differences and 95% confidence intervals (CIs) were reported. Laboratory analyses were conducted in duplicate, and standard internal quality control procedures were followed throughout.

## RESULTS

The sample showed a near-equal distribution of maternal age, with 46 (50.5%) aged ≤25 years and 45 (49.5%) aged >25 years. Parity was similarly balanced, with 49.5% being primiparas and 50.5% multiparas. Education levels varied, with 24.2% of mothers being illiterate and 27.5% being graduates. A majority of participants belonged to the middle or high socioeconomic strata, and 54.9% delivered vaginally. Notably, 50.5% of mothers did not take supplements during pregnancy. Vitamin B12 deficiency (<200 pg/mL) was observed in 32 (35.2%) of the mothers. The mean maternal BMI was 22.82 ± 2.70 kg/m$^2$, indicating overall adequate nutritional status. The demographic and clinical profile of mothers is presented in Table 1.

**Table 1:** Maternal Demographic and Clinical Characteristics (n=91)

| Variables | Category | Frequency (%) |
|---|---|---|
| Maternal Age | ≤25 Years | 46 (50.5%) |
| | >25 Years | 45 (49.5%) |
| Parity | Primipara | 45 (49.5%) |
| | Multipara | 46 (50.5%) |
| Maternal Education | Illiterate | 22 (24.2%) |
| | Primary | 23 (25.3%) |
| | Secondary | 21 (23.1%) |
| | Graduate | 25 (27.5%) |
| Socioeconomic Status | Low | 27 (29.7%) |
| | Middle | 29 (31.9%) |
| | High | 35 (38.5%) |
| Mode of Delivery | Normal/Vaginal | 50 (54.9%) |
| | Cesarean | 41 (45.1%) |
| Dietary Intake | Vegetarian | 48 (52.7%) |
| | Non-Vegetarian | 43 (47.3%) |
| Supplement Use in Pregnancy | Yes | 45 (49.5%) |
| | No | 46 (50.5%) |
| Serum Vitamin B-12 Status | Deficient | 32 (35.2%) |
| | Normal | 59 (64.8%) |
| Maternal BMI (kg/m$^2$) | Mean ± SD | 22.82 ± 2.70 |

47 (51.6%) of neonates were full term, while 44 (48.4%) were preterm. The gender distribution was balanced. Exclusive breastfeeding was reported in 46 (50.5%) neonates. The mean age at assessment was 17.69 ± 5.60 days. Mean birth weight was 3056.66 ± 325.63 grams, and the Apgar score at 5 minutes was 8.45 ± 0.48. Head circumference, length, and weight were within normal neonatal ranges. Mean scores for cognition, motor, and language domains were 89.3 ± 10.7, 85.8 ± 9.0, and 82.8 ± 10.8, respectively. Visual tracking delays were noted in 48.4% of neonates, and auditory startle response was delayed in 46.2%. Muscle tone abnormalities were observed in 69.3% of neonates (hypertonia: 39.6%, hypotonia: 29.7%). Overall, 57.1% of neonates met the criteria for early neurodevelopmental delay, as shown in table 2.

**Table 2:** Neonatal Characteristics of Study Participants and Early Neurodevelopmental Biomarkers (n=91)

| Variables | Category / Statistic | Frequency (%) or Mean ± SD |
|---|---|---|
| **Neonatal Characteristics of Study Participants** | | |
| Gestational Age | Preterm | 44 (48.4%) |
| | Term | 47 (51.6%) |
| Gender | Female | 47 (51.6%) |
| | Male | 44 (48.4%) |
| Exclusively Breastfed | Yes | 46 (50.5%) |
| | No | 45 (49.5%) |
| Neonatal Age (days) | Mean ± SD | 17.69 ± 5.60 |
| Birth Weight (grams) | Mean ± SD | 3056.66 ± 325.63 |
| Apgar Score at 5 min | Mean ± SD | 8.45 ± 0.48 |
| Head Circumference (cm) | Mean ± SD | 33.85 ± 1.58 |
| Length at Assessment (cm) | Mean ± SD | 48.83 ± 2.14 |
| Weight at Assessment (kg) | Mean ± SD | 3.19 ± 0.42 |
| **Early Neurodevelopmental Biomarkers** | | |
| Cognitive Score | Mean ± SD | 89.3 ± 10.7 |
| Motor Score | Mean ± SD | 85.8 ± 9.0 |
| Language Score | Mean ± SD | 82.8 ± 10.8 |
| Visual Tracking | Normal | 47 (51.6%) |
| | Delayed | 44 (48.4%) |
| Auditory Startle Response | Normal | 49 (53.8%) |
| | Delayed | 42 (46.2%) |
| Muscle Tone | Normal | 28 (30.8%) |
| | Hypotonia | 27 (29.7%) |
| | Hypertonia | 36 (39.6%) |
| Neurodevelopmental Delay | Yes | 52 (57.1%) |
| | No | 39 (42.9%) |

To evaluate possible confounding effects, maternal and neonatal variables were compared between the B12-deficient and normal groups. No significant associations

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were found for maternal age, education, socioeconomic status, breastfeeding status, or birth weight (all p>0.050). These results indicate that maternal B12 status in this cohort was not confounded by the demographic or perinatal variables assessed, as shown in table 3.

**Table 3:** Association of Confounding Variables with Maternal Vitamin B12 Status (n=91)

| Variables | Category | Deficient n (%) | Normal n (%) | p-value |
|---|---|---|---|---|
| Maternal Age | >25 Years | 14 (43.8%) | 31 (52.5%) | 0.423 |
| | ≤25 Years | 18 (56.3%) | 28 (47.5%) | |
| Maternal Education | Graduate | 10 (31.3%) | 15 (25.4%) | 0.880 |
| | Illiterate | 7 (21.9%) | 15 (25.4%) | |
| | Primary | 7 (21.9%) | 16 (27.1%) | |
| Socioeconomic Status | Secondary | 8 (25.0%) | 13 (22.0%) | 0.230 |
| | High | 16 (50.0%) | 19 (32.2%) | |
| | Middle | 9 (28.1%) | 20 (33.9%) | |
| | Low | 7 (21.9%) | 20 (33.9%) | |
| Exclusively Breastfed | Yes | 14 (43.8%) | 32 (54.2%) | 0.339 |
| | No | 18 (56.3%) | 27 (45.8%) | |
| Birth Weight (grams) | Mean ± SD | 3062.63 ± 29 2.37 | 3053.42 ± 34 4.70 | 0.898 |

The mean cognitive score was 90.78 ± 9.60 in the deficient group vs. 88.43 ± 11.22 in the normal group (mean difference = +2.34, 95% CI: -7.01 to 2.32, p=0.320). Motor and language scores also showed no statistically significant differences (p=0.637 and p=0.403, respectively). Neurodevelopmental delay occurred in 59.4% of deficient vs. 55.9% of normal neonates (p=0.751). These results suggest no significant relationship between maternal B12 status and early neurodevelopmental performance, as shown in table 4.

**Table 4:** Association of Maternal B12 Status with Early Neurodevelopmental Outcomes (n=91)

| Outcome Variables | Deficient (n=32) | Normal (n=59) | Mean Difference (95% CI) | p-value |
|---|---|---|---|---|
| Cognitive Score (Mean ± SD) | 90.78 ± 9.60 | 88.43 ± 11.22 | +2.34 (-7.01 to 2.32) | 0.320 |
| Motor Score (Mean ± SD) | 86.41 ± 8.73 | 85.47 ± 9.17 | +0.94 (-4.87 to 3.00) | 0.637 |
| Language Score (Mean ± SD) | 81.52 ± 9.61 | 83.52 ± 11.41 | -1.99 (-6.71 to 2.73) | 0.403 |
| Neuro-developmental Delay | 19 (59.4%) | 33 (55.9%) | — | 0.751 |

Among exclusively breastfed neonates (n=46), no statistically significant differences were found in cognitive, motor, or language scores between the B12-deficient and normal groups. Visual tracking deficits, abnormal tone, and neurodevelopmental delay were more frequent in the B12-deficient group, but these trends did not reach statistical significance (all p>0.050), as shown in Table 5.

**Table 5:** Neurodevelopmental Outcomes by B12 Status in Exclusively Breastfed Neonates (n=46)

| Outcome Variables | B12 Deficient (n=14) | B12 Normal (n=32) | p-value |
|---|---|---|---|
| Cognitive Score (Mean ± SD) | 90.35 ± 11.81 | 87.55 ± 12.47 | 0.480 |
| Motor Score (Mean ± SD) | 88.86 ± 9.06 | 86.79 ± 8.84 | 0.473 |
| Language Score (Mean ± SD) | 81.49 ± 11.88 | 83.70 ± 11.03 | 0.544 |
| Visual Tracking Deficit | 6 (42.9%) | 11 (34.4%) | 0.584 |
| Abnormal Muscle Tone† | 9 (64.3%) | 21 (65.7%) | 0.768 |
| Neurodevelopmental Delay | 9 (64.3%) | 17 (53.1%) | 0.482 |

†Abnormal tone includes both hypotonia and hypertonia

## DISCUSSION

This study investigated the association between maternal vitamin B-12 deficiency and early neurodevelopmental biomarkers in breastfed neonates. Among 91 participants, 35.2% of mothers were vitamin B-12 deficient, yet no statistically significant associations were found between maternal B-12 status and neonatal cognitive, motor, or language scores, nor with neurodevelopmental delays. Even in the subgroup of exclusively breastfed neonates, neurodevelopmental outcomes did not differ significantly by maternal B-12 levels. Additionally, no significant associations were observed between maternal B-12 deficiency and perinatal confounding factors such as maternal age, education, or birth weight. These findings suggest that maternal B-12 status during late pregnancy may not independently predict neurodevelopmental outcomes within the first month of life. This aligns and contrasts with existing literature in several ways. In other studies, our study found no significant difference in cognitive, motor, or language scores based on B-12 status. This is consistent with Cruz-Rodríguez *et al.* and Keskin et al. who noted that infant neurodevelopment at 6 weeks and 3 months was not significantly influenced by maternal B-12 alone, especially in the absence of folate or iron co-deficiencies [8, 7]. The RCT by Solvik *et al.* provided high-dose maternal B-12 during pregnancy and lactation but found no significant improvement in Bayley-III scores at 6 and 12 months of age, even though maternal and infant B-12 levels improved markedly [9]. Wirthensohn *et al.* also reported that short-term developmental outcomes in neonates did not significantly differ by maternal B-12 intake, especially in middle-income populations with borderline but not severe deficiency [10]. Curremt findings were also consistent with Kumar *et al.* who concluded that routine B-12 supplementation in pregnancy may improve hematological and biochemical markers, but does not consistently lead to measurable cognitive gains in early infancy [5]. It is important to consider that B-12-related neurodevelopmental deficits often manifest after 6 to 12 months of age. As noted by Bjørkevoll *et al.* delayed onset of symptoms is common, particularly in mild or subclinical

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deficiency states [11]. In our cohort, visual tracking and auditory startle responses were not significantly related to B-12 status. Similarly, Siddiqua *et al.* found no relationship between maternal B-12 and sensory-motor integration at birth in a large South Indian sample [12]. A Czech cohort study found that while B-12 intake during pregnancy predicted language development and IQ at age 8, early infancy assessments were poor predictors, again supporting our finding of non-significance in the neonatal period [13]. Our study's lack of association between exclusive breastfeeding and neurodevelopmental delay mirrors findings by Ljungblad *et al.* who noted that B-12 content in breastmilk is often insufficient to influence early milestones unless maternal deficiency is severe [14]. Because our assessments were conducted within the first 28 days of life, it is plausible that this early timing limited our ability to detect subtle developmental differences that might emerge later in infancy. This limitation is supported by another longitudinal study, which found that early infancy assessments are poor predictors of longer-term neurocognitive function [15]. Another consideration is the potential for subclinical or subtle neurodevelopmental impairments to go undetected using the TDSC screening tool. Although TDSC is validated for early developmental delay, its sensitivity for detecting mild neurocognitive deficits or emerging executive function delays in neonates may be limited. As such, it is possible that early B-12-related effects existed but were not captured due to the tool's screening nature rather than diagnostic depth. Ulak *et al.* observed that while long-term cognitive development was related to prenatal B-12 status, no difference was seen in anthropometry or milestones at birth or 1 month, aligning directly with our data [15]. Reischl-Hajiabadi et al. assessed infants at 4 months using the Denver II scale and found only mild differences in motor and language development in B-12-deficient mothers, none of which were statistically significant [16]. St-Cyr emphasizes that deficiency thresholds and timing matter; deficiency in early pregnancy or pre-conception is more predictive of outcomes than late third-trimester values, which our study captured [17]. Bakken *et al.* noted that early postpartum B-12 status (≤1 month postpartum) had no significant association with development at 1 month, but stronger associations appeared at 6–12 months [18]. A study by Garzone and Zanella in Guatemala concluded that neurodevelopmental markers at 2 weeks were weakly associated with any nutritional biomarker, reinforcing the idea that postnatal age at assessment limits sensitivity [19]. Studies argued for longitudinal neurodevelopmental surveillance when studying micronutrient deficiencies, as effects often take time to manifest in expressive language and problem-solving domains [20].

This study was limited by its single-center design and cross-sectional nature, which restrict causal inference and generalizability to broader populations. Neurodevelopmental assessment was performed within the first month of life, which may be too early to detect subtle or delayed effects of maternal vitamin B-12 deficiency. Additionally, infant serum B-12 or functional biomarkers such as methylmalonic acid were not measured. Future longitudinal, multicenter studies incorporating biochemical follow-up and extended neurodevelopmental tracking beyond 6–12 months are recommended to better understand the long-term implications of maternal B-12 deficiency.

## CONCLUSIONS

Despite a high prevalence of maternal vitamin B-12 deficiency (35.2%) in our cohort, no significant impact was found on early neonatal neurodevelopmental outcomes such as cognitive, motor, or language scores. These results suggest that neurodevelopmental assessment in the first month of life may not be sensitive enough to detect subtle effects of prenatal B-12 deficiency. In light of global and regional evidence, our findings highlight the importance of early gestational or pre-conception B-12 correction rather than late third-trimester interventions, longer follow-up periods into infancy or childhood to capture latent developmental impacts, and the need to integrate B-12 with other nutritional interventions, particularly in resource-limited or vegetarian populations. Future research should focus on multi-nutrient interventions, time-sensitive supplementation, and neurocognitive tracking beyond 6–12 months to more accurately assess the full impact of maternal B-12 deficiency on child development.

## Authors' Contribution

Conceptualization: JI
Methodology: JI, AH, MUS, SI, MAJ, FR
Formal analysis: JI, AH, MUS, SI
Writing and Drafting: JI, AH, MUS, SI, MAJ, FR
Review and Editing: JI, AH, MUS, SI, MAJ, FR

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Impact of Integrated Vs. Traditional Curriculum Models on Long-Term Clinical Skills Retention

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## ABSTRACT

Integrating basic and clinical sciences has been promoted to enhance clinical reasoning and long-term retention in medical education. **Objectives:** To compare six-month retention of knowledge and interpretation-based clinical reasoning skills among undergraduate medical students taught through integrated versus traditional curriculum models. **Methods:** A quasi-experimental study was conducted among final-year medical students (Integrated curriculum: n=53; Traditional curriculum: n=48). Baseline and six-month follow-up assessments included multiple-choice questions (MCQs) for knowledge and interpretation tasks for clinical reasoning. Objective Structured Clinical Examination (OSCE) scores were also recorded. Independent samples t-tests were applied for normally distributed data and Mann–Whitney U tests for non-normal data, based on Shapiro–Wilk normality results. Effect sizes and 95% confidence intervals (CIs) were calculated. A p-value <0.05 was considered statistically significant. **Results:** Baseline MCQ and interpretation scores were comparable between groups. At six months, knowledge retention (MCQ scores) declined in both groups without a significant between-group difference (p=0.074). Interpretation scores were higher in the integrated group (mean difference 0.48, 95% CI 0.11–0.85, p=0.012), representing a small but statistically significant advantage. OSCE performance was slightly better in the integrated group but did not reach statistical significance (p=0.083). **Conclusions:** The integrated curriculum was associated with a small but statistically significant advantage in preserving interpretation-based clinical reasoning over six months, despite similar knowledge and procedural skill retention. While the effect size is modest, these findings support the relevance of curriculum integration for fostering higher-order reasoning, particularly when coupled with reinforcement strategies.

## INTRODUCTION

In recent years, medical education has undergone a global shift from discipline-based, teacher-centered models to more integrated, learner-centered approaches [1]. Integrated curricula aim to link basic sciences with clinical application, thereby fostering deeper understanding and longer retention of clinical skills. Studies conducted in the United States and Europe have demonstrated the effectiveness of integrated models in enhancing clinical reasoning, critical thinking, and long-term competence [2, 3]. International evidence further supports this trend. Paul *et al.* reported improved cognitive retention in integrated settings [4], while Weimer *et al.* emphasized the role of spaced reinforcement within such curricula [5]. A systematic review by Alharbi *et al.* also concluded that integration enhances diagnostic accuracy and application of knowledge in real-life scenarios [6]. In contrast, traditional medical curricula, which separate basic sciences from clinical exposure, continue to be widely used in developing countries due to institutional inertia and resource limitations. In Pakistan, several public and private

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medical colleges still follow traditional models, raising questions about their adequacy in preparing students for modern clinical demands. While local studies, such as those by Alharbi *et al.* and Fatima *et al.* have explored knowledge acquisition under traditional formats, few have examined long-term retention of clinical skills or directly compared integrated and traditional models over time [6, 7].

Despite the global shift toward integrated medical curricula, evidence comparing their long-term effectiveness with traditional models in low- and middle-income countries remains limited. Most local studies have focused primarily on immediate knowledge acquisition rather than sustained retention of clinical reasoning and procedural skills over time. Furthermore, there is a scarcity of longitudinal data evaluating objective measures such as OSCE performance and interpretation-based assessments after clinical rotations. This gap highlights the need for comparative research examining how curriculum structure influences long-term clinical competence in the Pakistani medical education context. This lack of evidence poses a challenge for educators and policymakers striving to reform curriculum design in Pakistan. With limited studies evaluating retention of core competencies such as OSCE performance and interpretation ability, especially after clinical rotations, there remains a critical gap in understanding how curriculum structure influences long-term outcomes. This study aimed to compare the impact of integrated versus traditional curriculum models on the retention of clinical knowledge and skills over a six-month interval.

## METHODS

This was a prospective quasi-experimental study designed to compare the long-term retention of clinical skills among medical students taught through integrated versus traditional curriculum models. The quasi-experimental design was chosen because students were already enrolled in pre-assigned curricula at their institutions; random allocation was not feasible due to administrative constraints and ethical considerations. This non-random assignment introduces a potential risk of selection bias; however, baseline equivalence for demographics, prior clinical exposure, and self-reported confidence was assessed to minimize the impact of possible confounders on internal validity. The study was conducted from March 2024 to August 2024 at Health Net Hospital, Peshawar, in collaboration with affiliated medical colleges implementing both curriculum models. Formal approval was obtained from the Ethics Review Committee of Health Net Hospital, Peshawar (Reference No. 3088/HNH/HR). Written informed consent was obtained from all participants. Sample size was calculated using G*Power version 3.1 for an independent samples t-test, with an expected moderate effect size ($d = 0.5$), $\alpha = 0.05$, and power $(1 - \beta) = 0.80$. The effect size assumption was based on findings from comparable published studies examining curriculum-based differences in clinical skill retention, which reported effect sizes in the moderate range. The minimum sample required per group was 48; to account for potential attrition, 101 final-year MBBS students were enrolled, 53 from the integrated curriculum and 48 from the traditional curriculum. A purposive sampling method was used, focusing on students who had completed their clinical rotations exclusively under one curriculum type. This approach improved feasibility but carries the risk of sampling bias, which may limit the generalizability of findings to other settings. The study included final-year MBBS students who had documented exposure to either the integrated or traditional curriculum, had completed both baseline and six-month follow-up assessments, and had provided written informed consent. Students were excluded if they had incomplete academic records, failed to attend the follow-up assessment, were enrolled in hybrid curriculum models, or had participated in supplemental clinical workshops within three months before the baseline assessment. Knowledge retention was assessed using a validated 20-item multiple-choice question (MCQ) test mapped to core clinical competencies. Clinical skills performance was measured through an Objective Structured Clinical Examination (OSCE) using standardized checklists, with two faculty assessors independently rating each station. Although complete blinding to group allocation was not feasible due to scheduling constraints, assessors were not informed of the study hypothesis to minimize potential assessment bias. Interpretation ability was evaluated through structured scenario-based questions scored by trained faculty, while self-rated confidence was measured at baseline using a 10-point Likert scale to assess perceived clinical competence. Baseline assessments (MCQ, OSCE, and interpretation) were conducted at the end of the students' final clinical training block. Identical assessments were repeated six months later without any interim reinforcement, allowing measurement of natural skill decay or retention. Data were anonymized using unique participant codes. Content validity of assessment tools was established via expert panel review. Internal consistency was confirmed with Cronbach's $\alpha = 0.82$ for the MCQ test and $\alpha = 0.85$ for the OSCE checklists. Inter-rater reliability for OSCE scoring was high (intra-class correlation coefficient = 0.89), indicating consistent scoring between assessors. Data were analyzed using IBM SPSS Statistics, version 26.0. Continuous variables were summarized as mean ± standard deviation (SD) when normally distributed and as median

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with interquartile range (IQR) when non-normally distributed. Categorical variables were presented as frequencies and percentages. The Shapiro–Wilk test was used to assess normality for each continuous variable, and the choice between parametric and non-parametric tests was explicitly based on these results and the distributional characteristics of the data. Between-group comparisons were performed using independent samples t-tests for normally distributed variables and Mann–Whitney U tests for non-normal variables (e.g., six-month MCQ scores). For Mann–Whitney U tests, Hodges–Lehmann median differences with 95% confidence intervals (CIs) were reported to provide an estimate of effect size. Within-group comparisons were conducted using paired samples t-tests for normally distributed outcomes and Wilcoxon signed-rank tests for non-normal data. Chi-square tests were used to assess associations between categorical variables. Effect sizes were calculated for statistically significant results, and exact p-values were reported, with $p < 0.050$ considered statistically significant.

## RESULTS

Baseline demographic characteristics were similar between the integrated and traditional curriculum groups. The proportion of female students was 47.2% in the integrated group and 43.8% in the traditional group (p=0.730). Distribution by academic year did not differ significantly (p=0.231), and prior clinical exposure was slightly more common in the traditional group (72.9%) compared to the integrated group (62.3%), but without statistical significance (p=0.254). Mean age was almost identical between groups (23.07 ± 2.10 vs. 23.17 ± 1.24 years; p=0.772), and self-reported confidence scores were comparable (6.97 ± 1.09 vs. 7.28 ± 1.45; p = 0.222). These findings confirm that the groups were demographically balanced at the study outset, table 1.

**Table 1:** Comparison of Participant Demographics and Background Variables Between Curriculum Groups (n=101)

| Variables | Category | Integrated (n=53) | Traditional (n=48) | Test Statistic | df | p-value | 95% CI (Difference) |
|---|---|---|---|---|---|---|---|
| Gender | Female | 25 (47.2%) | 21 (43.8%) | $x^2 = 0.119$ | 1 | 0.730 | – |
| | Male | 28 (52.8%) | 27 (56.2%) | | | | |
| Year of Study | 3rd Year | 28 (52.8%) | 31 (64.6%) | $x^2 = 1.432$ | 1 | 0.231 | – |
| | 4th Year | 25 (47.2%) | 17 (35.4%) | | | | |
| Prior Clinical Exposure | Yes | 33 (62.3%) | 35 (72.9%) | $x^2 = 1.299$ | 1 | 0.254 | – |
| | No | 20 (37.7%) | 13 (27.1%) | | | | |
| Age (Years) | Mean ± SD | 23.07 ± 2.10 | 23.17 ± 1.24 | t = –0.290 (Welch's test) | 85.82 | 0.772 | –0.77 to 0.58 |
| Self-Reported Confidence | Mean ± SD | 6.97 ± 1.09 | 7.28 ± 1.45 | t = –1.230 (Welch's test) | 86.58 | 0.222 | –0.83 to 0.18 |

At baseline, MCQ knowledge scores were slightly higher in the integrated group than in the traditional group (6.44 ± 1.22 vs. 6.15 ± 1.14; p=0.222). At six months, median scores were 5.91 (IQR = 5.04–6.31) in the integrated group and 5.26 (IQR = 4.64–6.14) in the traditional group. This difference was not statistically significant (Mann–Whitney U = 1008.5, Z = –1.792, p=0.074; Hodges–Lehmann median difference = 0.42, 95% CI: –0.03 to 0.88). Both groups experienced similar declines in knowledge over time, with no significant difference in change scores (p=0.976), table 2.

**Table 2:** Knowledge Retention Outcomes by Curriculum Group

| Variables | Integrated (n=53) | Traditional (n=48) | Test Statistic / U | df/U | p-value | 95% CI (Diff.) | Median (IQR) Integrated | Median (IQR) Traditional | HL Δ (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Baseline MCQ Score | 6.44 ± 1.22 | 6.15 ± 1.14 | t = 1.228 | 98.87 | 0.222 | -0.18 to 0.75 | – | – | – |
| MCQ Score at 6 Months | 5.75 ± 0.85 | 5.45 ± 1.19 | Mann-Whitney U=1008.5 | – | 0.074 | – | 5.91 (5.04-6.31) | 5.26 (4.64-6.14) | 0.42 (-0.03, 0.88) |
| Change Score (6mo-base) | -0.69 ± 1.62 | -0.70 ± 1.78 | t = 0.030 | 95.37 | 0.976 | -0.66 to 0.68 | – | – | – |

Baseline OSCE scores were slightly higher in the integrated group but not significantly different (7.70 ± 1.26 vs. 7.46 ± 1.34; p=0.363). At six months, OSCE scores again favored the integrated group (7.47 ± 1.02 vs. 7.09 ± 1.19; p=0.084), though the difference was not statistically significant. Interpretation skills were nearly identical at baseline, but at six months, the integrated group scored significantly higher (6.75 ± 1.21 vs. 6.28 ± 0.99; p = 0.036, indicating better preservation of clinical reasoning, table 3.

**Table 3:** Comparison of OSCE and Interpretation Scores Between Integrated and Traditional Curriculum Groups

| Outcome Measures | Group | Mean ± SD | 95% CI (Lower–Upper) | p-value |
|---|---|---|---|---|
| OSCE Baseline Score | Integrated | 7.70 ± 1.26 | 7.35 – 8.04 | 0.363 |
| | Traditional | 7.46 ± 1.34 | 7.07 – 7.85 | |
| OSCE at 6 Months | Integrated | 7.47 ± 1.02 | 7.19 – 7.76 | 0.084 |
| | Traditional | 7.09 ± 1.19 | 6.74 – 7.43 | |

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| | | | | |
|---|---|---|---|---|
| Interpretation Baseline | Integrated | 7.20 ± 0.96 | 6.94 – 7.47 | 0.991 |
| | Traditional | 7.21 ± 1.04 | 6.90 – 7.51 | |
| Interpretation at 6 Mo | Integrated | 6.75 ± 1.21 | 6.42 – 7.09 | 0.036 |
| | Traditional | 6.28 ± 0.99 | 5.99 – 6.57 | |

In the integrated group, OSCE scores decreased slightly over six months, but the change was not statistically significant (mean difference = 0.22 ± 1.58; p=0.305). Interpretation scores showed a greater decline (mean difference = 0.45 ± 1.66), with a p-value of 0.052, suggesting a possible reduction in performance without reinforcement, table 4.

**Table 4:** Within-Group Change in OSCE and Interpretation Scores in Integrated Curriculum (n=53)

| Outcome Comparison | Mean ± SD | 95% CI (Lower–Upper) | p-value |
|---|---|---|---|
| OSCE Baseline vs. 6 Months | 0.22 ± 1.58 | -0.21 – 0.66 | 0.305 |
| Interpretation Baseline vs. 6 Months | 0.45 ± 1.66 | -0.003 – 0.91 | 0.052 |

This 3D clustered column chart illustrates the mean interpretation scores achieved by students at 6 months, comparing the integrated curriculum group (6.75 ± 1.21) to the traditional group (6.28 ± 0.99). Error bars (represented as stacked SDs) indicate variability within each group. The graph demonstrates that participants in the integrated curriculum achieved slightly higher mean interpretation scores at the 6-month follow-up compared to those in the traditional curriculum. The difference in mean scores was statistically significant (p=0.036). Although both groups exhibited variability in performance, the integrated group not only outperformed the traditional group in terms of average score but also had slightly greater score dispersion, as indicated by a higher standard deviation (1.21 vs. 0.99). This suggests that while the integrated approach was more effective on average, individual performance varied more widely, figure 1.

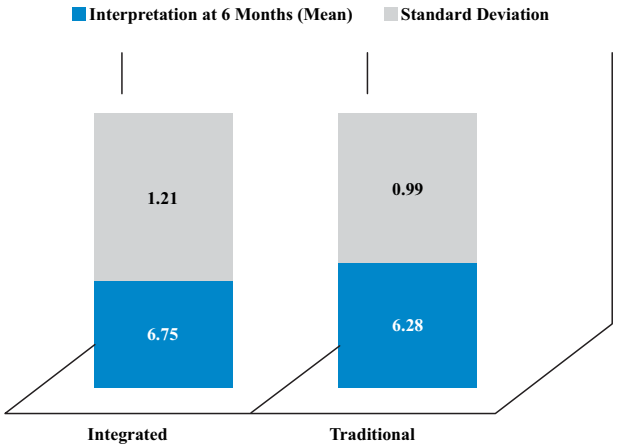


**Figure 1:** Comparison of Mean Interpretation Scores at 6 Months with Standard Deviation Between Integrated and Traditional Curriculum Groups

## DISCUSSION

This study aimed to evaluate the long-term retention of clinical skills among undergraduate medical students taught through integrated versus traditional curriculum models. While knowledge retention (MCQ scores) declined modestly in both groups over six months, the integrated group demonstrated a small but statistically significant advantage in interpretation scores, which reflect higher-order clinical reasoning. Given the modest magnitude of this difference, the result should be interpreted cautiously, acknowledging statistical significance but also its practical limitations. The baseline comparability of both groups in terms of demographics and confidence levels adds strength to the internal validity of this quasi-experimental design. However, the quasi-experimental nature and purposive sampling limit causal inferences and generalizability, a limitation common to curriculum comparison studies. The lack of significant group differences in knowledge retention at six months aligns with studies by Veer *et al.* and Ji *et al.* both of which emphasized that factual knowledge deteriorates over time unless actively reinforced [8, 9]. In contrast, interpretation skills were better preserved in the integrated curriculum group. This finding, although modest in effect size, supports previous work by Jujo *et al.* who advocated that integrated teaching encourages deeper cognitive processing and long-term clinical reasoning development [10]. Similarly, McMains *et al.* and Al-Badri *et al.* argued that integrated approaches improve the meaningful application of knowledge rather than just factual recall [11, 12]. The OSCE scores, although slightly better in the integrated group, did not reach statistical significance, which was consistent with Rafiq-uz-Zaman *et al.* and Shahrezaei *et al.* who found that improvements in procedural skills often require repeated, hands-on reinforcement over time, regardless of curriculum format [13, 14]. The modest within-group decline in interpretation scores over time (p=0.052) without refresher training mirrors the trend reported by Shahrezaei *et al.* where skills decayed even in high-performing students unless periodic reinforcement was applied [14]. This supports Yin *et al.* that deliberate practice and spaced learning are critical for long-term retention [15]. Our results also align with Offiah *et al.* who found that integrated curricula facilitate the transfer of knowledge into clinical reasoning by blending basic sciences with clinical contexts [16]. Likewise, a systematic review by Albert *et al.* concluded that students under integrated curricula were better at diagnostic interpretation and clinical application [17]. Moreover, a multicenter longitudinal analysis by Chaou *et al.* showed that students from integrated programs sustained higher performance in licensing exams and clinical competencies

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[18]. These findings collectively suggest that while the integrated curriculum's advantage in interpretation scores is statistically significant, it should be viewed as one component of broader curriculum reform efforts rather than a sole determinant of long-term clinical competence. Despite these advantages, the lack of significant within-group improvement or maintenance in OSCE scores over time signals a potential weakness in experiential consolidation, as emphasized by Natesan *et al.* and Menard *et al.* [19, 20]. Future curriculum reforms should, therefore, pair integration with structured, repeated practical exposure to sustain psychomotor and procedural skills alongside reasoning ability.

This study has several limitations. The quasi-experimental design and purposive sampling may introduce selection bias and limit causal inference. The single-institution setting and relatively short six-month follow-up period may also restrict generalizability and the assessment of sustained long-term outcomes. Additionally, unmeasured institutional or teaching variations could have influenced performance differences. Future multicenter longitudinal studies with randomized allocation, extended follow-up periods, and incorporation of qualitative feedback are recommended to better understand the long-term educational impact of curriculum integration and its practical significance in diverse medical training environments.

## CONCLUSIONS

It was concluded that integrated curriculum models were associated with a small but statistically significant advantage in preserving interpretation-based clinical skills over a 6-month interval, despite similar trends in knowledge retention and OSCE performance. While the effect size is modest, the finding remains relevant for curriculum reform, especially in resource-constrained and transitioning medical education systems. The results reinforce global calls for curriculum integration in medical education and emphasize the need for targeted reinforcement strategies to optimize long-term clinical competence.

## Authors' Contribution

Conceptualization: SFJ
Methodology: HA, SA[1]
Formal analysis: SFJ, HA, FP, SA[1] FMK, SA[2]
Writing and Drafting: FJ, HA, FP, SA[1], FMK, SA[2]
Review and Editing: SFJ, HA, FP, SA[1], FMK, SA[2]

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Evaluation of Student Feedback on Integrated vs. Traditional Curriculum in Dental Education: A Comparative Study

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## ABSTRACT

Dental education benefits a lot from a well-designed curriculum. Integrated curricula now replace traditional teaching models by adding early practical learning, connecting different subjects in training, and making students a priority. The research investigates dental students' opinions on integrated and traditional ways of presenting the curriculum in Pakistan. **Objectives:** To compare dental students' perceptions of the learning environment and curriculum structure in integrated versus traditional curricula at a dental college in Mardan, Pakistan. **Methods:** This cross-sectional study was carried out at Bacha Khan College for the duration of 3 months. There were 182 undergraduate students in the study who were selected using stratified sampling. The study measured how students perceived the environment and curriculum with a questionnaire based on a Likert scale of 5 points. Data were analyzed in SPSS version 21.0, and $p<0.050$ were regarded as statistically significant. **Results:** Students in the integrated curriculum reported significantly higher satisfaction across all domains, including support for diversity (mean = 4.35 ± 0.65), academic discussions (4.50 ± 0.55), self-directed learning (4.45 ± 0.50), and preparedness for clinical practice (4.50 ± 0.45). Similarly, curriculum structure and delivery were better rated in the integrated group, with clearer objectives, earlier clinical exposure, and stronger subject integration ($p<0.050$). **Conclusions:** Students favored the integrated curriculum due to its inclusive environment, alignment of teaching with learning outcomes, and focus on critical competencies. These findings support curricular reform toward integrated models in dental education to enhance learning outcomes and professional readiness.

## INTRODUCTION

Developing a curriculum document is a process that involves thorough preparation, careful implementation and uninterrupted checking of results. It aids medical and dental educators in building courses that continue to address both academic and professional changes. Furthermore, the structure and approach to a curriculum have a considerable impact on how learners perceive, process, and remember knowledge [1]. The scheme of dental education curriculum has now become necessary in preparing competent oral healthcare professionals. Traditionally, dental education is organized so that basic sciences are taught in the first part of the course and clinical subjects are taught in the last year. Because of this approach, students may find it hard to translate their knowledge into practical practice of real-world scenarios [2]. The transition from traditional to integrated curricula in the dental system represents an important change in teaching approaches, aimed at bridging the gap between basic sciences and practicing dentistry [3]. Integrated curriculum focuses on horizontal and vertical integration,

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hands-on experience in the initial years, and the development of problem-solving and critical thinking skills in students. The methodology is consistent with modern educational approaches, which lay emphasis on student-centered learning and the development of abilities required for modern dental practice [4]. In Pakistan, it is recognized by the Pakistan Medical and Dental Council (PMDC) that dental education requires reform in its curriculum. The PMDC supports integrated curricula in dental schools so that graduates are set to respond to the constantly changing needs in dental practice. This initiative reflects a commitment to aligning dental education in Pakistan with international standards and best practices [2]. The modular-based curriculum has gained prominence in medical education globally, offering a dynamic and integrative approach that fosters advanced cognitive skills such as critical thinking, analytical reasoning, synthesis, evaluation, and practical application. This format enables students to actively participate in their study, developing a greater grasp of both basic and clinical sciences through collaborative and interdisciplinary approaches. This integration not only improves the educational experience but also fills the gap between academic knowledge and practical experience. [5]. Based on the fundamental value of the conventional curriculum, including early clinical experience and biological sciences into dentistry education has shown considerable results. A quasi-experimental study indicated that students in an integrated curriculum obtained clinical competency around 608 hours earlier than those in standard programs, with more confidence in applying biological knowledge to treating patients [6]. Furthermore, the integration of case-based learning (CBL) across dental curricula has been associated with positive outcomes, including improved critical thinking and problem-solving skills. CBL encourages students to apply theoretical knowledge to real-world scenarios, fostering a deeper understanding and retention of information. Such pedagogical strategies align with contemporary educational goals, preparing students for the complexities of modern dental practice [7]. Despite the many advantages of the modular method, conventional curricula are still valued because of their meticulous and well-organized foundation in the fundamental sciences [8]. Because it fosters the development of critical abilities like clinical reasoning and well-informed decision-making, this strong foundation is crucial for clinical practice. Furthermore, the ability to successfully apply information in clinical contexts depends on the long-term recall of fundamental scientific principles, confirming the enduring value of traditional educational paradigms [9].

Therefore, the purpose of this study is to assess and contrast the opinions of students on the traditional and integrated dentistry education curricula. Although integrated and modular curricula are widely discussed globally, there is a clear lack of empirical data from Pakistan that directly compares student perceptions of traditional and integrated dental education within the same institutional context. Most existing studies have focused on medical education or have not examined the combined impact on perceived learning environment and curriculum structure in dentistry. Addressing this gap will help generate context-specific evidence to inform curriculum development and policy decisions in Pakistani dental colleges. This study aimed to investigate how students perceive the learning environment, curriculum structure, and delivery to identify the benefits and drawbacks of each model.

## METHODS

This descriptive cross-sectional study was conducted at Bacha Khan College of Dentistry, a tertiary-care dental teaching institution, to assess dental students' perceptions of the transition from a traditional to an integrated curriculum at the institutional level. The study was carried out over a period of three months from August 2024 to October 2024. Approval was obtained from the Institutional Review Board of Bacha Khan College of Dentistry (Ref. No. 533/BKMC), and informed consent was secured from all participants. The target population included all undergraduate students enrolled in the Bachelor of Dental Surgery (BDS) program during the study period (N=192). As the population size was relatively small and accessible, a census approach was adopted, and all eligible students were invited to participate. To ensure proportional representation from each academic year, stratification was applied at the stage of analysis. A total of 182 students completed the questionnaire, resulting in a high response rate of 94.8%. This high participation rate minimized selection bias, strengthened internal validity, and ensured adequate power for statistical comparisons. At the time of the study, the institute was undergoing a curriculum transition in accordance with PMDC guidelines. Consequently, the older batches (third- and final-year BDS students) continued with the traditional curriculum, while newly inducted students (first- and second-year BDS) were enrolled under the integrated curriculum. This parallel implementation created a natural basis for comparison of perceptions. Inclusion criteria were all currently enrolled BDS students from first to final year, willing to participate voluntarily, and able to complete the questionnaire independently. Students on academic leave or absent during data collection were excluded. For analysis, students were grouped as: Group A (first- and second-year BDS, integrated curriculum) and Group B (third- and final-

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year BDS, traditional curriculum). Data were collected using a structured, self-administered questionnaire developed specifically for this study, with items adapted from validated instruments such as the Dundee Ready Education Environment Measure (DREEM) and relevant literature [10]. The tool was reviewed by three subject experts for face and content validity and pilot-tested with 15 students to assess clarity and comprehension. Necessary refinements were made, and the final version demonstrated good reliability (Cronbach's alpha=0.87). The questionnaire had three sections. The first section gathered demographic data (5 items: age, gender, year of study, and related background details). The second section evaluated perceptions of the learning environment (10 items) covering inclusivity, peer support, teamwork, self-directed learning, academic discussion, facilities, sense of community, professional support, and preparedness for clinical practice. The third section assessed students' perceptions of curriculum structure and delivery (6 items), including clarity of objectives, alignment of teaching with outcomes, subject integration, early clinical exposure, faculty effectiveness, and logical progression of content [11]. Responses were recorded on a 5-point Likert scale (1 = Strongly Disagree to 5 = Strongly Agree). To reduce response bias, two items in each of the learning environment and curriculum sections were negatively worded and reverse-coded during analysis, ensuring that higher scores consistently reflected more positive perceptions. Domain scores were calculated by summing the relevant items, and a combined score was computed for overall perceptions. Possible ranges were 6–30 for curriculum, 10–50 for learning environment, and 16–80 overall, with higher scores indicating more favorable perceptions. Confidentiality and anonymity were strictly maintained. Data analysis was performed using SPSS version 21.0. Descriptive statistics (frequencies, percentages, means, and standard deviations) summarized the data. The Independent Samples t-test was applied to compare mean scores between students in the integrated and traditional curricula across the two main domains (curriculum and learning environment). A p-value of <0.050 was considered statistically significant.

## RESULTS

The institution recently implemented a curriculum reform, moving from a traditional, subject-based teaching approach to an integrated curriculum. The integrated model incorporates horizontal and vertical integration of content, early clinical exposure, student-centered learning (including PBL and case-based discussions), and emphasizes professional development and ethical reasoning. The transition aimed to align dental education with international best practices and outcome-based education standards. Out of the 192 students approached, 182 responded to the survey, yielding a high response rate of 94.8%. The mean age of respondents was 19.6 ± 1.2 years (Table 1).

**Table 1:** Demographic Characteristics of the Respondents (N = 182)

| Variables | Value |
|---|---|
| Total Students Approached | 192 |
| Total Respondents | 182 (94.8%) |
| Mean Age (years) | 19.6 ± 1.2 |

Among the 182 participants, 82 (45.1%) were male and 100 (54.9%) were female (Figure 1).

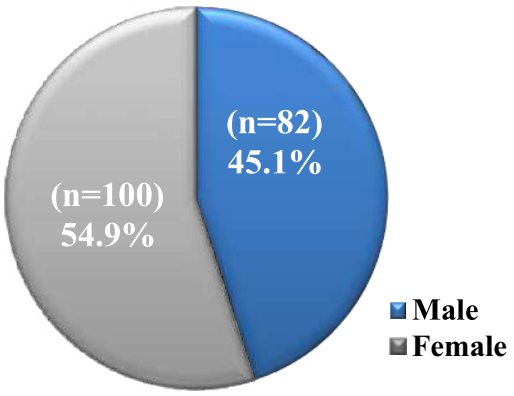


**Figure 1:** Gender Distribution of the Participants

Students following the integrated curriculum (Group A: first year and second year students) consistently reported significantly more positive perceptions across all domains compared to those in the traditional curriculum (Group B: third year and fourth year students). The integrated group rated their curriculum higher for supporting a diverse and inclusive learning environment (4.35 ± 0.65 vs. 3.40 ± 0.90, p=0.003), promoting academic discussions and problem-solving (4.50 ± 0.55 vs. 3.25 ± 0.85, p = 0.001), and encouraging teamwork and interprofessional collaboration (4.30 ± 0.60 vs. 3.60 ± 0.75, p=0.007). Similarly, self-directed learning was more effectively promoted in the integrated group (4.45 ± 0.50 vs. 3.10 ± 0.95, p<0.001). Other significantly higher scores in Group A included sense of community and peer support, adequacy of facilities and resources, overall academic environment, lifelong learning habits, professional support, and preparedness for clinical practice (all p<0.050) (Table 2).

**Table 2:** Student Perception of Learning Environment in Integrated vs. Traditional Curriculum

| S. No. | Statements (Perception Item) | Group A (Integrated Curriculum) Mean ± SD | Group B (Traditional Curriculum) Mean ± SD | p-Value |
|---|---|---|---|---|
| 1 | The curriculum supports a diverse and inclusive learning environment. | 4.35 ± 0.65 | 3.40 ± 0.90 | 0.003 |

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| | | | | |
|---|---|---|---|---|
| 2 | Students are actively engaged in academic discussions and problem-solving. | 4.50 ± 0.55 | 3.25 ± 0.85 | 0.001 |
| 3 | Teamwork and interprofessional collaboration are encouraged. | 4.30 ± 0.60 | 3.60 ± 0.75 | 0.007 |
| 4 | Self-directed learning is effectively promoted. | 4.45 ± 0.50 | 3.10 ± 0.95 | <0.001 |
| 5 | I feel a strong sense of community and peer support in the learning environment. | 4.20 ± 0.70 | 3.50 ± 0.80 | 0.012 |
| 6 | Facilities and resources adequately support educational needs. | 4.10 ± 0.60 | 3.35 ± 0.90 | 0.009 |
| 7 | The overall environment is conducive to academic excellence. | 4.40 ± 0.50 | 3.30 ± 0.85 | 0.001 |
| 8 | Lifelong learning habits are instilled through the curriculum. | 4.25 ± 0.60 | 3.20 ± 0.80 | 0.004 |
| 9 | I feel safe, respected, and professionally supported during learning. | 4.15 ± 0.65 | 3.40 ± 0.85 | 0.018 |
| 10 | The learning environment prepares me for real-world clinical practice. | 4.50 ± 0.45 | 3.50 ± 0.70 | <0.001 |

The integrated curriculum was perceived as having a clearer structure with well-defined objectives (p=0.001), and its teaching was better aligned with learning outcomes and assessments (p=0.002). Students also reported that the integrated curriculum effectively encouraged subject integration (p=<0.001) and incorporated sufficient clinical exposure early in the program (p=0.004). Additionally, faculty in the integrated curriculum were viewed as well-prepared and effective in delivering content (p=0.009), while the curriculum itself was perceived to promote continuity and logical progression (p=0.006) (Table 3).

**Table 3:** Evaluation of Curriculum Structure and Delivery in Integrated vs. Traditional Curriculum

| S. No. | Statements (Curriculum Structure and Delivery Item) | Group A (Integrated Curriculum) Mean ± SD | Group B (Traditional Curriculum) Mean ± SD | p-Value |
|---|---|---|---|---|
| 1 | The curriculum has a clear structure with well-defined objectives. | 4.45 ± 0.50 | 3.40 ± 0.85 | 0.001 |
| 2 | Teaching is aligned with learning outcomes and assessments. | 4.40 ± 0.55 | 3.35 ± 0.80 | 0.002 |
| 3 | Curriculum delivery encourages integration across subjects. | 4.50 ± 0.45 | 3.20 ± 0.75 | <0.001 |
| 4 | Sufficient clinical exposure is incorporated early in the curriculum. | 4.35 ± 0.60 | 3.25 ± 0.85 | 0.004 |
| 5 | Faculty are well-prepared and deliver content effectively. | 4.30 ± 0.65 | 3.50 ± 0.90 | 0.009 |
| 6 | The curriculum promotes continuity and logical progression of content. | 4.25 ± 0.60 | 3.30 ± 0.80 | 0.006 |

## DISCUSSION

Curriculum design is essential in shaping the quality of education and student learning experiences, particularly in fields like dental education, where both theoretical knowledge and practical skills are needed [12]. In current study, the integrated curriculum rated their learning environment significantly higher across several dimensions compared to their counterparts in the traditional curriculum. The integrated curriculum was viewed as promoting a more inclusive and diverse educational atmosphere, receiving higher ratings for its support of a varied learning environment. These findings are consistent with earlier studies highlighting the significance of inclusive and supportive academic settings in improving student engagement and learning outcomes [13]. The students in the integrated curriculum, as mentioned, exhibited significantly higher engagement in academic discussions, problem-solving, and self-directed learning (SDL) compared to those in the traditional curriculum. This supports recent research on the benefits of integrated education in dental training. For example, Ali *et al.* found that problem-based learning (PBL) improves self-regulation and intrinsic motivation among dental students [14]. Furthermore, Çelik *et al.* demonstrated that scenario-based peer learning programs effectively increased readiness for inter-professional collaboration, emphasizing the importance of communication and teamwork in dental education [15]. The supportive learning environment ensures safety and respect, promoting innovation and creativity among students. Studies have shown that integrated learning environments are better at encouraging innovation, supporting creative and critical thinking, and providing a good supporting environment for teaching and learning [16, 17]. Among the participants, those enrolled in the integrated curriculum reported a greater sense of preparedness for clinical practice compared to those in the traditional curriculum. These findings are consistent with previous studies demonstrating that early exposure to clinical environments and the integration of theoretical knowledge with practical experience enhance students' readiness for professional practice [18]. Integrated curricula enhance students' clinical competence, confidence, and ability to apply knowledge in real patient scenarios [19]. Additionally, the use of case-based and problem-based learning further improves clinical reasoning skills [20], and also the acquisition of clinical skills and long-term knowledge retention are enhanced by eliminating the divide between basic and clinical sciences [21]. The comparative evaluation of curriculum structure and delivery between integrated and traditional curricula reveals significant advantages associated with the integrated approach. Those students learning under an integrated program reported higher levels of satisfaction regarding the curriculum, the alignment between teaching and learning outcomes, integrated subjects, early exposure to clinical

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practice, and the smooth flow of information from one semester to the next. These findings align with recent literature emphasizing the benefits of integrated curricula in medical education. For instance, a study by Miller *et al.* highlighted the successful implementation of a course integrating basic, clinical, and health systems sciences, which received positive reception from students and enhanced their clinical reasoning skills [22]. Similarly, a qualitative study at Shiraz University of Medical Sciences reported that the integration of basic and clinical sciences facilitated better understanding and application of knowledge among medical students [23]. Students participating in the present research were considerably more likely to agree that the curriculum develops the material in an organized way relative to those using the traditional curriculum. This observation shares similarities with what Wijnen-Meijer *et al.* discovered, that linking basic and clinical sciences consistently throughout the curriculum helps students better tie their foundational knowledge to practical applications and engages them in learning step by step. [24]. In order to satisfy the increasing needs of multidisciplinary clinical practice and patient-centered care, dental education is changing. An intentional attempt to improve clinical competency and student involvement is shown in the transition from traditional to integrated courses [25]. This single-institution study during a transitional phase may limit generalizability.

This study was conducted at a single institution during a transitional phase of curriculum implementation, which may limit the generalizability of the findings. The cross-sectional design captures perceptions at one point in time and does not assess long-term academic performance or clinical competence outcomes. Additionally, responses were self-reported and may be influenced by subjective bias. Future multicenter longitudinal studies incorporating objective academic and clinical performance indicators are recommended to comprehensively evaluate the sustained impact of integrated curricula in dental education.

## CONCLUSIONS

In conclusion, students generally had a more positive opinion of the integrated curriculum in terms of its organization, the way that classes relate to learning objectives, clinical skills, the necessity of independent study, and the overall learning environment. Students who used the approach had more defined goals, improved grades in their classes, and more clinical work experience, which inspired many to become more committed and self-assured. However, some said that the traditional curriculum was less cohesive and did not encourage pupils to actively collaborate. In order to assist students in adjusting to the demands of today's clinical environments and collaborating more effectively with other healthcare teams, there is justification for adding more integrated curriculum components to dental schools.

## Authors' Contribution

Conceptualization: WUN
Methodology: SMA
Formal analysis: SA, IAK, MR
Writing and Drafting: MR, RZ
Review and Editing: MR, RZ, IAK, SMA, WUN

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Association between Bronchiectasis Exacerbations and FEV1 Changes at A Tertiary Care Center

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## ABSTRACT

Bronchiectasis, a common respiratory disease, presents a healthcare challenge since its evaluations do not often include health-related quality of life assessments. **Objectives:** To determine whether there is a correlation between the number of exacerbations experienced with non-cystic fibrosis bronchiectasis at baseline and the number of exacerbations experienced throughout follow-up, and identify any time-related changes in FEV1. **Methods:** 115 bronchiectasis patients were included prospectively. Evaluation of the correlation between exacerbations during the 24-month baseline period and 0-to-24-month and 24-to-48-month follow-up periods was done. Outcomes were changes in FEV1 and percentage of predicted FEV1 after 24 months, with stratification based on frequency of initial exacerbations. SPSS version 24.0 was used to analyze data. **Results:** 78 (67.8%) were female. The mean age was 63.7 years. The mean duration of bronchiectasis was 6.5 years. Mean BMI was 23.7 kg/m$^2$. The most common comorbidities were asthma and COPD. Frequency of exacerbations was 68 (59.1%). A baseline exacerbation was substantially linked to subsequent exacerbation at 0-24 months ($p=0.006$) and 24-48 months ($p<0.002$). Baseline FEV1 was considerably lower in patients with more exacerbations, but the drop was not significant between exacerbations. With more initial exacerbations, patients had substantially poorer FEV1 % predicted at baseline ($p<0.002$), 12 ($p=0.003$), and 24 months ($p<0.002$). **Conclusions:** Patients with flaring up of bronchiectasis were more likely to experience future exacerbations and have a lower FEV1 to begin with. However, the drop in FEV1 may be unrelated to the frequency of exacerbations at baseline.

## INTRODUCTION

Bronchiectasis (BE) is a chronic structural respiratory disease that causes bronchial dilatation and, in extreme cases, hospitalization for an exacerbation [1]. Although the exact prevalence of BE is unclear, the average age-adjusted hospitalization rate in the US is 16.5 per 100,000 people and 9.4 per 100,000 in Germany [2]. There were no obvious signs of hospital need; however, the over-60 age group and women had higher hospitalization rates. The causes behind the wide difference in patients' annual average rates of exacerbations remain unknown [3]. Exacerbations can deteriorate lung function, lead to a bad prognosis, increase mortality, and increase expenditures, just like other chronic respiratory illnesses [4]. The average number of exacerbations each year is two or more for patients with advanced disease stages and high scores on the FACED or Bronchiectasis Severity Index (BSI) [5]. Additionally, these patients typically have lengthier hospital stays [6, 7]. Lung imaging shows abnormal thickening and dilating of the bronchial walls in bronchiectasis, a disorder not caused by cystic fibrosis, along with coughing and sputum production [8]. One substantial feature of the natural history of bronchiectasis

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is the worsening of symptoms with time [9, 10]. Bronchiectasis exacerbations are linked to respiratory distress in addition to deteriorating lung function, increased mortality, diminished quality of life, and hospitalization risk. Adults in the US with bronchiectasis have not had their features studied until recently. Growing evidence from the US Bronchiectasis Research Registry (BRR) suggests that the majority (60 %) of bronchiectasis patients were nonsmokers, while 89 % were white, and 79 % were female. Approximately 63% of patients had Non-Tuberculosis Mycobacteria (NTM) sickness or NTM isolated during first evaluation [11]. The median age of the patients was 64 years. Studies that depended on claims data likely exaggerated the clinical burden of bronchiectasis exacerbations since data on the severity of the ailment are difficult to collect [8, 9]. Predicted FEV1% is negatively correlated with the frequency of exacerbations in chronic obstructive pulmonary disease (COPD) patients; however, this is not necessarily the case [12]. The most prominent feature of lung sickness following tuberculosis is bronchiectasis, which can range from moderate traction bronchiectasis to clinically severe bronchial dysfunction. Regarding the association between this kind of bronchiectasis and other NCFBs, there is a lack of data in the medical literature [13]. The conventional medical terminology for these disorders includes chronic obstructive pulmonary disease (COPD), asthma, and bronchiectasis. Having said that, it is an entirely distinct species. Pulmonary function tests are used to objectively evaluate the state of the lungs. Bronchitis is the most common cause of obstructive disability [14]. If lung function declines, the disease will deteriorate, the risk of mortality will rise, and the likelihood of an exacerbation requiring hospitalization will rise. While dealing with bronchiectasis, airway hyper-responsiveness has a negative correlation with quality of life, baseline spirometric values, and exacerbation frequency [15].

Bronchiectasis is characterized by recurrent exacerbations and progressive lung function decline; however, the longitudinal relationship between baseline exacerbation frequency and subsequent changes in FEV1 remains inadequately defined. While frequent exacerbations are recognized as markers of disease severity, limited prospective data from developing countries have evaluated their predictive value for long-term lung function deterioration. Moreover, regional evidence examining the association between exacerbation burden and spirometric trends in non-cystic fibrosis bronchiectasis is scarce. This gap highlights the need for longitudinal assessment to clarify whether baseline exacerbation frequency predicts future exacerbations and FEV1 decline. This study aimed to find out how FEV1 changed over time in relation to the frequency of bronchiectasis exacerbations at baseline and secondly to evaluate the correlation between the two variables throughout the 48-month follow-up period after the 24-month baseline.

## METHODS

This prospective study using non-probability consecutive sampling was conducted at the Department of Pulmonology and Critical Care, Central Park Teaching Hospital, Lahore, during January 2023 to December 2024, after approval from the Ethical Committee Ref. No. IRB-0293-344. Following patients' informed permission, trained personnel at each research location used pre-designed standardized data collection forms of the hospital to collect patients' medical records. The sample size for the study was calculated using the Open-Epi online software for sample size calculation. Keeping the prevalence of bronchiectasis at 8 % as reported in research, the sample size came out to be 114 at a 95 % confidence level and 5 % margin of error [16]. The study only included individuals who consented to reveal bronchiectasis exacerbations. The age range was 18 to 75 years. The 24 months preceding the inclusion of patients served as the baseline period for this inquiry. The purpose of the 48-month follow-up was to determine whether or not the overall number of exacerbations was related to the number of bronchiectasis exacerbations that were present at baseline. In order to determine if there was a correlation between the frequency of bronchiectasis exacerbations and changes in FEV1, participants received both baseline and 24-month FEV1 data. Baseline data were evaluated during the 24 months before enrollment, a follow-up window from 0 to 24 months (combining visits 1 and 2), and a follow-up window from 24 to 48 months (combining visits 3 and 4). Our baseline data were collected during 24 months before enrollment, so that's why we used that interval. Patients were classified over time based on the frequency of bronchiectasis exacerbations, which may be either zero or one or more. A sub-analysis was performed at each time point to further classify patients based on whether they experienced 0, 1, or ≥2 exacerbations. For data analysis, SPSS version 24.0 was used. Using descriptive statistics, the study examined the entire research population as well as subgroups broken down by the existence and frequency of exacerbations. To compare values within the strata, continuous variables were subjected to analysis of variance (ANOVA), whereas categorical variables were tested using chi-squared tests. A significance threshold of $\alpha = 0.05$ was established.

## RESULTS

The majority of the presented cases, 78 (67.8%), were female. The mean age was 63.7 years. The mean duration of

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bronchiectasis was 6.5 years. The mean BMI of the cases was 23.7 kg/m$^2$. The most common comorbidities were asthma and COPD. There were 45 (39.1%) smokers among all cases (Table 1).

**Table 1:** Characteristics of the Cases That Were Included

| Variables | n (%) |
|---|---|
| **Sex** | |
| Female | 78 (67.8%) |
| Male | 37 (32.2%) |
| **Mean Age** | |
| Years | 63.7 |
| **BMI** | |
| Mean (kg/m$^2$) | 23.7 |
| **Duration of Bronchiectasis** | |
| Mean (Years) | 6.5 |
| **Comorbidities** | |
| Asthma | 53 (46.1%) |
| COPD | 45 (39.1%) |
| No | 17 (14.8 %) |
| **Smoking Habit** | |
| Yes | 45 (39.1%) |
| No | 70 (60.9%) |

Frequency of exacerbations was 68 (59.1%), with 44 (38.3 %) experiencing 1 exacerbation, while ≥2 in 24 (20.9 %) patients (Figure 1).

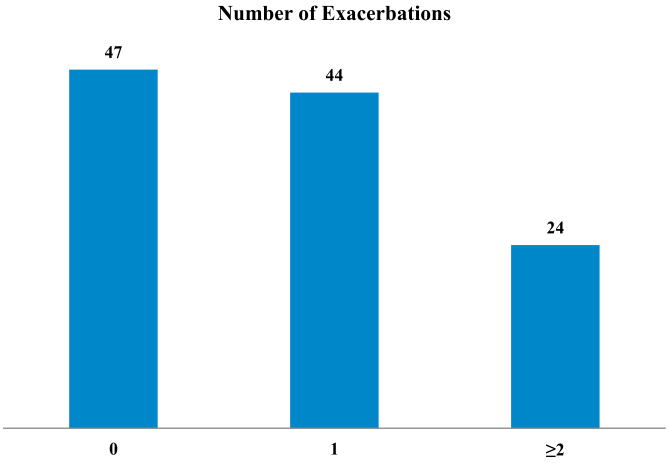


**Figure 1:** Frequency of Exacerbations in Included Patients (n=115)

At baseline, bronchiectasis exacerbation was substantially linked to a subsequent exacerbation at 0-24 months (p=0.006) and 24-48 months (p<0.002) (Table 2).

**Table 2:** Relationship Between the Number of Bronchiectasis Exacerbations (0 Or More) At Baseline and at the 0-To-24 and 24-To-48 Month Follow-Ups

| Variables | Baseline | 0-24 Months | 24-48 Months |
|---|---|---|---|
| **Bronchiectasis Exacerbation** | | | |
| 0 | 46.5 % | 41.7% | 20.6% |
| ≥1 | 32.5 % | 32.7 % | 52.5 % |
| ≥2 | 21 % | 25.6 % | 26.9 % |

The baseline FEV1 was considerably lower in patients with more exacerbations, but the drop was not significant between those with 0, 1, and ≥2 exacerbations. A lower projected FEV1 % was related to more baseline and follow-up exacerbations. There was no difference in the average change from baseline according to the number of bronchiectasis exacerbations present at baseline; however, FEV1 was lower during follow-up visits (Table 3).

**Table 3:** Overall FEV1 Change from Start, Stratified by Bronchiectasis Exacerbations

| FEV1 | Exacerbations (0) | Exacerbations (1) | Exacerbations (≥2) |
|---|---|---|---|
| At Start | 1.87 (0.51) | 1.75 (0.67) | 1.67 (0.48) |
| First Visit (1-12 Months) | -0.037 (0.021) | -0.035 (0.020) | 0.004 (0.024) |
| Second Visit (24 Months) | -0.070 (0.030) | 0.068 (0.023) | -0.052 (0.028) |

With more initial exacerbations, patients had substantially poorer FEV1 % predicted at baseline (p<0.002), 12 (p=0.003), and 24 months (p<0.002). The predicted FEV1 included a normal FEV1 in 22 (19.13 %) patients, mild obstruction in 38 (33 %), moderate obstruction in 31 (27 %), and severe obstruction in 24 (20.9 %) of patients. An FEV1 of >80 % was considered normal, between 65-79 % as mild obstruction, between 50-64 % as moderate obstruction, and <50 % as severe obstruction (Figure 2).

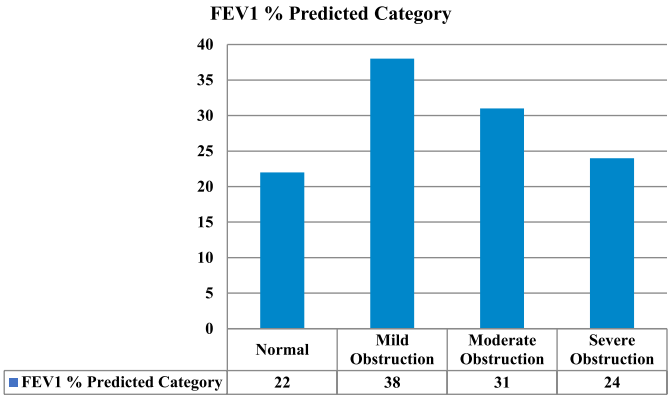


**Figure 2:** Graphical Representation of Predicted FEV1 at 24 Months (n=115)

## DISCUSSION

A lower forced expiratory volume in one second (FEV1) was associated with a higher number of bronchiectasis exacerbations at baseline, and having an elevated risk of future exacerbations was the other finding of this study. Patients with two or more exacerbations at baseline showed a significantly lower mean FEV1 at baseline and throughout time compared to patients without exacerbations at baseline. Exacerbations of bronchiectasis were much more likely to occur throughout the follow-up period if participants had a history of them at baseline, according to this study. There was a statistically significant correlation between the number of

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exacerbations a patient experienced at baseline and the number of exacerbations they experienced over the 0-to-24 months and 24-to-48 months' follow-up periods. Neither the baseline nor the post-intervention numbers of exacerbations were substantially linked to one another. Incorporating the frequency and severity of exacerbations into the E-FACED score enhanced the potential to predict future annual exacerbations, according to research that developed and externally validated the score in 1470 bronchiectasis patients [16]. A study included 2572 bronchiectasis patients from European and Israeli institutions found that a history of frequent exacerbations was the strongest predictor of future exacerbations. The incidence rate ratios rose in tandem with the number of annual exacerbations at baseline, which went from 1 to 2 to 3 or more [17]. There was an increased adjusted likelihood of bronchiectasis exacerbations occurring throughout the follow-up period in this investigation. The risk of future exacerbations was 1.5 times higher for baseline exacerbations and 2.4 times higher for subsequent exacerbations in the two years that followed. Patients who have exacerbations more frequently have a more severe condition, a worse quality of life, and a greater mortality rate [18]. The mortality rate was double for patients with bronchiectasis who experienced three or more exacerbations per year compared to those who did not, according to a prospective cohort analysis of 608 individuals [19, 20]. The current study demonstrated that the mean forced expiratory volume in one second (FEV1) was significantly lower at baseline and throughout time for people with two or more bronchiectasis exacerbations compared to those without such episodes. A robust association between the baseline exacerbation frequency and the FEV1 suggested the existence of a minor pulmonary obstruction. Previous studies have connected patient factors such as systemic inflammation and prolonged *P. aeruginosa* colonization to a worsening of symptoms, as well as decreased forced expiratory volumes in one second (FEV1) [21]. Researchers found that at least one *P. aeruginosa* isolation significantly predicted a quicker FEV1 decline in COPD patients in a post hoc analysis of an 84-month prospective cohort [22]. Reduced FEV1 has also been linked to worsened symptoms in other chronic lung disorders, including cystic fibrosis [23]. Regardless of the number of bronchiectasis exacerbations in the current trial, the rate of fall in FEV1 was not substantially different among the three groups of patients (0, 1, and ≥2 exacerbations during baseline). To have a complete understanding of the correlation between exacerbations and the decrease in FEV1 in bronchiectasis patients, future research should consider the severity of exacerbations.

This study was limited by its single-center design and relatively modest sample size, which may restrict the generalizability of the findings. The observational nature of the study precludes establishing causal relationships between exacerbation frequency and lung function decline. Additionally, factors such as microbiological profile, exacerbation severity, and treatment adherence were not comprehensively analyzed. Future multicenter longitudinal studies with larger cohorts and detailed phenotypic characterization are recommended to better elucidate the impact of exacerbation burden on long-term pulmonary function outcomes.

## CONCLUSIONS

The study found that individuals whose bronchiectasis flared up more often were more likely to experience future exacerbations and have a lower FEV1 to begin with. However, the drop in FEV1 may be unrelated to the frequency of exacerbations at baseline.

## Authors' Contribution

Conceptualization: MA
Methodology: MA, SF
Formal analysis: AI, AS
Writing and Drafting: MA, UA
Review and Editing: MA, UA, AI, AS, SF

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Original Article**

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# Etiological Factors in Patients with Lower Gastrointestinal Bleeding at a Tertiary Care Hospital of Islamabad Pakistan

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## ABSTRACT

Lower gastrointestinal bleeding (LGIB) is a significant contributor to morbidity and mortality worldwide. Its etiology varies based on age, comorbid conditions, and individual risk factors. **Objectives:** To identify the etiological factors associated with LGIB in patients treated at a tertiary care hospital in Islamabad, Pakistan. **Methods:** A retrospective analytical study was conducted on 250 patients diagnosed with LGIB at the Gastroenterology Department of Federal Government Polyclinic Hospital, Islamabad. The data included patients seen in the Outpatient Department and the Emergency Department. Data were collected from hospital records, including sociodemographic details, clinical presentations, Colonoscopy and endoscopic findings. Statistical analysis was performed using SPSS version 26.0, employing descriptive statistics and chi-square tests to evaluate associations between etiological factors and bleeding severity. **Results:** Patients with LGIB universally presented with PR bleeding (250; 100%) and a high rate of anemia (170; 68%). Constipation (132; 52.8%) and abdominal pain (82; 32.8%) were common, while weight loss (59; 23.6%), diarrhea (27; 10.8%), and melena (24; 9.6%) were less frequent. Older patients (>50 years) showed higher rates of rectal polyps (22; 27.5%), rectal masses (18; 22.5%), and colonic masses (14; 17.5%). Admitted patients had more rectal masses (16; 20.0%) and colonic masses (12; 15.0%) than outpatients, highlighting the severity of disease in hospitalized cases. **Conclusions:** The study revealed hemorrhoids as the most frequent cause of lower gastrointestinal bleeding, followed by rectal ulcers, colitis, and rectal masses. Diverticulosis was notably uncommon in this population.

## INTRODUCTION

Lower gastrointestinal bleeding (LGIB) is a clinically significant condition that ranges from benign, self-limiting episodes to severe, life-threatening hemorrhage, particularly in elderly populations [1]. Defined as bleeding originating distal to the ligament of Treitz, LGIB is most commonly attributed to colonic sources such as diverticulosis, angiodysplasia, ischemic colitis, hemorrhoids, and colorectal malignancies [2]. Globally, LGIB accounts for a substantial proportion of hospital admissions related to gastrointestinal complaints, contributing to considerable morbidity, healthcare resource utilization, and mortality [3]. Clinical presentations of LGIB vary widely, from overt hematochezia to occult blood loss, necessitating prompt and accurate evaluation. Although many cases resolve spontaneously, identifying the underlying etiology is essential for guiding treatment, stratifying risk, and preventing recurrence. Colonoscopy remains the cornerstone diagnostic modality for LGIB, offering both visualization and therapeutic capabilities [4]. Technological advancements have enhanced its diagnostic precision; however, its yield is influenced by

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factors such as timing of the procedure, adequacy of bowel preparation, and the patient's hemodynamic stability [5]. Evidence suggests that early colonoscopy may not universally improve outcomes, especially when bleeding has ceased before the procedure [6]. Nonetheless, in high-risk or unstable patients, early endoscopic intervention can facilitate hemostasis and reduce hospital stay. The diagnostic performance of colonoscopy may also differ between outpatient and inpatient settings, raising important considerations for resource allocation in emergency versus elective care environments [6, 7]. Age is a pivotal determinant in the etiology of LGIB. Younger individuals typically present with benign anorectal conditions like hemorrhoids and fissures, whereas older adults are more prone to diverticular disease, angiodysplasia, ischemic colitis, and colorectal cancer. Regional studies have highlighted age-related variability in endoscopic findings, emphasizing the need for population-specific data. In low- and middle-income countries (LMICs) such as Pakistan, disparities in access to diagnostic tools and quality care further complicate LGIB management. Early and accurate identification of bleeding sources is critical for improving both short-term clinical outcomes and long-term healthcare planning [8-10]. Despite a growing body of global literature on LGIB, there remains a paucity of data from South Asia, particularly Pakistan. Existing studies often lack age-stratified analyses and fail to differentiate between inpatient and outpatient populations. Moreover, the performance of colonoscopy across various clinical settings is underexplored, limiting insights into resource utilization and procedural efficiency. In resource-constrained hospitals, such as the Federal Government Polyclinic (FGPC) in Islamabad, these gaps have direct implications for clinical decision-making and operational planning. Colonoscopy at FGPC is inconsistently available for both emergent and elective cases, and clinicians often rely on generalized guidelines that may not reflect local realities. Without robust data on common endoscopic diagnoses and colonoscopy outcomes across patient categories, evidence-based care remains elusive. Age-specific analyses and setting-based evaluations are essential to inform diagnostic protocols and optimize gastroenterology services. By examining the spectrum of endoscopic findings across age groups and evaluating the diagnostic yield of colonoscopy in outpatient versus admitted patients, the research seeks to inform clinical prioritization, resource allocation, and policy development in both emergency and non-emergency settings.

Lower gastrointestinal bleeding (LGIB) represents a frequent clinical emergency; however, its etiological spectrum varies considerably across geographic regions, age groups, and healthcare settings. In Pakistan, limited tertiary-care data exist that stratify colonoscopic findings according to age and admission status, creating uncertainty in risk-based prioritization. Most available local studies provide generalized frequency data without evaluating differences between outpatient and hospitalized populations. This gap limits evidence-based resource allocation and age-specific diagnostic planning in public-sector hospitals. This study aims to address critical gaps in the local understanding of LGIB by providing empirical data from a tertiary care hospital in Islamabad.

## METHODS

A retrospective cohort study to analyze etiological factors in patients presenting with lower gastrointestinal bleeding (LGIB) at the Gastroenterology Department of Federal Government Polyclinic (FGPC) Hospital, Islamabad. Data collection period spanned from January 2024 to November 2024, and included patients seen in the Outpatient Department (OPD) and Emergency Department. The study was conducted from January 2025 to March 2025. A total of 250 patients were selected using a consecutive sampling technique, based on availability and completeness of medical records. Sample size was calculated using the World Health Organization (WHO) sample size formula, with expected prevalence of 20% based on prior regional studies, a 95% confidence level, and a 5% margin of error [11]. Patients aged 18 years or older, diagnosed with LGIB, who underwent colonoscopy for diagnostic evaluation, and had complete clinical documentation, including treatment and follow-up, were included in the study. Whereas, patients with upper gastrointestinal bleeding (UGIB), bleeding secondary to trauma, bleeding due to specific conditions such as hemophilia, thrombocytopenia, or anticoagulant therapy, and those with incomplete records. Patient data were extracted from hospital records and entered into a Microsoft Excel database. Variables collected included sociodemographic details (age, sex), clinical characteristics (medical history, comorbidities), endoscopic findings (lesions identified during colonoscopy), and clinical outcomes. Colonoscopy procedures were performed following standard bowel preparation protocols, which included administration of polyethene glycol (PEG) solution the evening before the procedure. All colonoscopies were conducted by board-certified gastroenterologists using the Olympus EVIS EXERA III (model: CF-HQ190L) video colonoscope. Procedures were performed under conscious sedation, with continuous vital monitoring. Lesions were described using standard terminology outlined by the American Society for Gastrointestinal Endoscopy (ASGE) [12]. Ethical approval was obtained from the hospital's Ethics and Research Committee (Reference no: FGPCI/12/2024/E-Committee). As this was a retrospective study, direct

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patient consent was not required. Data confidentiality and anonymity were maintained by removing all personally identifiable information. The study adhered to the ethical principles outlined in the Declaration of Helsinki. LGIB was defined as bleeding originating distal to the ligament of Treitz, confirmed by clinical presentation (e.g., hematochezia) and colonoscopy evidence of bleeding source. To ensure data integrity, all entries were double-checked, and cases with significant missing data were excluded from analysis; no imputation techniques were used. Inter-observer variation was not formally assessed, but all colonoscopy evaluations were performed by board-certified gastroenterologists with standardized reporting formats to minimize variability. Statistical analysis was conducted using SPSS version 26.0. Descriptive statistics were used to summarize patient characteristics, with means and standard deviations for continuous variables, and frequencies and percentages for categorical variables.

## RESULTS

The mean age of the study population was 43.77 ± 15.57 years, with a male predominance (58.4%). All patients presented with per rectal (PR) bleeding (100%), and a significant proportion exhibited anemia (68%). Other commonly reported symptoms included constipation (52.8%), abdominal pain (32.8%), and weight loss (23.6%). Less frequent presentations included diarrhea (10.8%) and melena (9.6%). These findings reflect the diverse clinical manifestations of LGIB and underscore the importance of comprehensive symptom assessment during initial evaluation (Table 1).

**Table 1:** Baseline Characteristics and Clinical Features of Patients with Lower Gastrointestinal Bleeding at a Tertiary Care Hospital (n=250)

| Variables | Sub-category | n (%) |
|---|---|---|
| Age (Mean ± SD) | – | 43.77 ± 15.57 |
| Gender | Male | 146 (58.4%) |
| | Female | 104 (41.6%) |
| **Clinical Features** | | |
| Per Rectal (PR) Bleeding | Yes | 250 (100.0%) |
| Anemia | Yes | 170 (68.0%) |
| Weight Loss | Yes | 59 (23.6%) |
| Pain Abdomen | Yes | 82 (32.8%) |
| Melena | Yes | 24 (9.6%) |
| Diarrhea | Yes | 27 (10.8%) |
| Constipation | Yes | 132 (52.8%) |

Results outline the prevalence of comorbid conditions among 250 patients presenting with lower gastrointestinal bleeding. A majority of the participants (81.2%) had no documented comorbidities. Among those with comorbid conditions, the most frequently reported were diabetes mellitus alone (6.0%) and a combination of diabetes mellitus with hypertension (6.8%). A smaller subset exhibited more complex comorbidity profiles, including combinations involving ischemic heart disease, chronic kidney disease (CKD), and osteoarthritis. Notably, only 0.4% of patients had four or more concurrent conditions, reflecting the relatively low burden of multimorbidity in this cohort (Table 2).

**Table 2:** Prevalence of Comorbid Conditions Among Study Participants (n=250)

| Comorbidity | n (%) |
|---|---|
| No Comorbidities | 203 (81.2%) |
| Diabetes Mellitus | 15 (6.0%) |
| Diabetes Mellitus and Hypertension | 17 (6.8%) |
| Diabetes Mellitus, Hypertension and Ischemic Heart Disease | 6 (2.4%) |
| Diabetes Mellitus and Ischemic Heart Disease | 3 (1.2%) |
| Ischemic Heart Disease | 3 (1.2%) |
| Diabetes Mellitus, Ischemic Heart Disease and Osteoarthritis | 1 (0.4%) |
| Ankylosing Spondylitis | 1 (0.4%) |
| CKD + DM + HTN + ischemic heart disease | 1 (0.4%) |

Hemorrhoids were the most common finding across all age groups, particularly in the 31–50 years' group (45.5%). Rectal ulcers were consistently observed across age brackets, with a slightly higher prevalence in younger patients (20.0%). Rectal polyps and masses showed a marked increase with age, especially in patients over 50 years, where rectal polyps (27.5%) and rectal masses (22.5%) were most prevalent. Colonic masses and polyps also demonstrated age-related escalation, with the highest rates in the >50 years group. Diverticula were exclusively found in patients over 30, with the highest occurrence in those above 50 (7.5%). Normal findings were rare across all age groups, indicating a high diagnostic yield of colonoscopy (Table 3).

**Table 3:** Endoscopic (Colonoscopy) Findings Stratified by Age Group (n=250)

| Endoscopic Finding | ≤30 Years (n=60) | 31–50 Years (n=110) | >50 Years (n=80) | Total n (%) |
|---|---|---|---|---|
| Hemorrhoids | 20 (33.3%) | 50 (45.5%) | 34 (42.5%) | 104 (41.6%) |
| Rectal Ulcers | 12 (20.0%) | 18 (16.4%) | 14 (17.5%) | 44 (17.6%) |
| Polyps in Rectum | 5 (8.3%) | 20 (18.2%) | 22 (27.5%) | 47 (18.8%) |
| Colitis | 8 (13.3%) | 14 (12.7%) | 11 (13.8%) | 33 (13.2%) |
| Rectal Masses | 2 (3.3%) | 10 (9.1%) | 18 (22.5%) | 30 (12.0%) |
| Proctitis | 6 (10.0%) | 12 (10.9%) | 10 (12.5%) | 28 (11.2%) |
| Polyps in the Colon | 2 (3.3%) | 10 (9.1%) | 15 (18.8%) | 27 (10.8%) |
| Colonic Masses | 1 (1.7%) | 5 (4.5%) | 14 (17.5%) | 20 (8.0%) |
| Diverticula | 0 (0.0%) | 3 (2.7%) | 6 (7.5%) | 9 (3.6%) |
| Normal Findings | 4 (6.7%) | 2 (1.8%) | 1 (1.3%) | 5 (2.0%) |

Findings compare colonoscopic findings between outpatients and admitted patients. Hemorrhoids were the most frequent finding overall, with a notably higher prevalence among outpatients (45.9%) compared to admitted patients (32.5%). Rectal ulcers and rectal polyps were similarly distributed across both groups, indicating no

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significant variation in these conditions by patient status. However, more serious pathologies such as rectal masses and colonic masses were markedly more common in admitted patients, with rectal masses found in 20.0% and colonic masses in 15.0% of this group, compared to 8.2% and 4.7% respectively in outpatients. Colitis and proctitis also showed slightly higher rates among admitted patients, suggesting a greater burden of inflammatory conditions in this cohort (Table 4).

**Table 4:** Colonoscopy Findings by Patient Type (Outpatients vs. Admitted Patients, n=250)

| Endoscopic Finding | Outpatients (n=170) | Admitted Patients (n=80) | Total n (%) |
|---|---|---|---|
| Hemorrhoids | 78 (45.9%) | 26 (32.5%) | 104 (41.6%) |
| Rectal Ulcers | 30 (17.6%) | 14 (17.5%) | 44 (17.6%) |
| Polyps in Rectum | 30 (17.6%) | 17 (21.3%) | 47 (18.8%) |
| Colitis | 20 (11.8%) | 13 (16.3%) | 33 (13.2%) |
| Rectal Masses | 14 (8.2%) | 16 (20.0%) | 30 (12.0%) |
| Proctitis | 18 (10.6%) | 10 (12.5%) | 28 (11.2%) |
| Polyps in the Colon | 18 (10.6%) | 9 (11.3%) | 27 (10.8%) |
| Colonic Masses | 8 (4.7%) | 12 (15.0%) | 20 (8.0%) |
| Diverticula | 6 (3.5%) | 3 (3.8%) | 9 (3.6%) |
| Normal Findings | 4 (2.4%) | 1 (1.3%) | 5 (2.0%) |

## DISCUSSION

This study evaluated 250 patients with lower gastrointestinal bleeding (LGIB) at a tertiary care center in Islamabad. The most common endoscopic finding was hemorrhoids (41.6%), followed by rectal polyps (18.8%), rectal ulcers (17.6%), and colitis (13.2%). Age-stratified analysis showed that rectal polyps, rectal masses, and colonic masses were more prevalent in patients aged over 50 years. Moreover, serious conditions such as rectal masses (20.0%) and colonic masses (15.0%) were observed more frequently among admitted patients compared to outpatients. Normal colonoscopy findings were rare (2.0%), indicating a high diagnostic yield. These findings highlight the utility of colonoscopy in evaluating LGIB and suggest the importance of considering age and hospitalization status when assessing patients. The predominance of hemorrhoids and rectal ulcers as leading causes of LGIB in this study aligns with regional data from South Asia, where anorectal pathology remains a common etiology. Jain *et al.* reported hemorrhoids (25.9%) and colitis (28.7%) as the most frequent findings in a large Indian cohort [13]. Similarly, Mathews *et al.* found colitis (26%) and benign anorectal disorders (19%) to be dominant in South Indian patients [14]. The age-related increase in polyps and masses is consistent with global trends. Koyuncuer observed that 86.1% of polyps occurred in adults over 50, with a significant rise in high-risk adenomas [15]. Kim *et al.* also reported a sharp increase in adenoma detection rates with age [16]. These findings reinforce the need for routine screening colonoscopy in older adults. Interestingly, diverticulosis, a major cause of LGIB in Western populations, was notably uncommon in our cohort. This contrast likely reflects geographic, dietary, and genetic differences. Western studies report diverticulosis in up to 50% of adults over 60, predominantly left-sided and symptomatic. In contrast, South Asian populations exhibit lower prevalence, often below 5%, with diverticula tending to be right-sided and less likely to bleed. Traditional South Asian diets, rich in fiber from legumes and vegetables, reduce colonic pressure and diverticula formation. Genetic factors may also influence colonic wall structure and motility, contributing to ethnic variation in disease patterns. Moreover, right-sided diverticulosis may be underdiagnosed due to lower colonoscopy visibility in non-bleeding cases. While diverticulosis rates are rising in East Asia due to dietary westernization, our Islamabad-based cohort likely reflects a population still adhering to traditional dietary habits, explaining its rarity in our findings [17, 18]. Colonoscopy's diagnostic yield in this study (88% in admitted vs. 76% in outpatients) mirrors findings from Almadi *et al.*, who reported better bowel preparation and completion rates in ambulatory settings [19]. Navaneethan *et al.* found early colonoscopy reduced hospital stay and transfusion needs, though urgent colonoscopy did not significantly impact mortality or rebleeding rates [20]. Recent guidelines emphasize risk stratification tools like the Oakland score to guide LGIB management [21]. It reviewed multiple scoring systems and found that while tools like GBS and CHAMPS are useful, none offer comprehensive predictive accuracy [22]. Saleepol *et al.* also noted poor performance of current scores in predicting rebleeding [23]. The study's findings support prioritizing colonoscopy evaluation based on age and clinical severity. Calderwood *et al.* highlighted that many older adults with limited life expectancy are still recommended for surveillance colonoscopy, despite low yield. This calls for more nuanced, individualized decision-making [24].

This study was limited by its retrospective, single-center design, which may restrict generalizability to other healthcare settings. Potential documentation bias and lack of long-term follow-up prevented assessment of recurrence rates, therapeutic outcomes, and survival trends. Additionally, risk stratification tools were not applied to predict severity or rebleeding. Future multicenter prospective studies incorporating standardized risk scores and longitudinal follow-up are recommended to better define prognostic factors and optimize management pathways for LGIB in resource-limited settings.

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## CONCLUSIONS

This retrospective identified that hemorrhoids (41.6%) were the most common cause, followed by rectal ulcers (17.6%), rectal polyps (18.8%), and colitis (13.2%). Serious pathologies such as rectal masses (12.0%) and colonic masses (8.0%) were more frequently observed in patients over 50 years and those who were admitted. The study also noted that the diagnostic yield of colonoscopy was high, with only 2.0% of cases showing normal findings. These results highlight the importance of colonoscopy in identifying the etiology of LGIB and the need for age-specific and admission-status-based evaluation strategies.

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## Authors' Contribution

Conceptualization: IZ
Methodology: IZ, NA, MN, SID, MA
Formal analysis: RT
Writing and Drafting: IZ
Review and Editing: IZ, NA, MN, SID, MA, RT

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Frequency and Clinical Risk Factors of Pneumonia among Children with Cerebral Palsy

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## ABSTRACT

Children with cerebral palsy (CP) are prone to various comorbidities, among which pneumonia is a leading cause of morbidity and hospitalization. Early identification of contributing factors is crucial to minimize respiratory complications. **Objectives:** To determine the frequency of pneumonia and identify associated clinical risk factors among children diagnosed with cerebral palsy. **Methods:** This cross-sectional study was conducted at the Pediatrics Unit, Khyber Teaching Hospital, Peshawar, for six months. Ninety-three children with confirmed CP were enrolled through consecutive sampling. Data on demographics, feeding methods, CP severity, nutritional status, immunization, and aspiration history were collected. Pneumonia was diagnosed clinically and radiologically. Statistical analysis was performed using SPSS version 26.0, and associations were tested using the Chi-square. **Results:** Among 93 children, 38 (40.9%) had pneumonia. Strong associations were observed with aspiration history ($\chi^2 = 85.14$, $p<0.001$, Cramer's V = 0.957), feeding method ($\chi^2 = 32.13$, $p<0.001$, Cramer's V = 0.588), immunization status ($\chi^2 = 74.72$, $p<0.001$, Cramer's V = 0.896), and nutritional status ($\chi^2 = 52.32$, $p<0.001$, Cramer's V = 0.750). Interestingly, no pneumonia cases occurred in children with severe CP or those who were severely malnourished. **Conclusions:** Pneumonia is highly prevalent in children with CP and is strongly linked to aspiration and oral feeding. Unexpected findings, such as the absence of pneumonia in severe CP and malnourished children, highlight the need to consider contextual exposure and monitoring factors. Targeted prevention strategies, including caregiver education, aspiration management, and individualized nutritional support, are essential to reduce respiratory complications in this vulnerable population.

## INTRODUCTION

Cerebral palsy (CP) is the most common motor disability in childhood, characterized by permanent, non-progressive damage to the developing brain [1]. Beyond motor impairment, these children often experience a wide range of medical complications, among which respiratory infections, particularly pneumonia, stand out as a leading cause of morbidity and mortality [2]. International studies have repeatedly highlighted the vulnerability of children with CP to respiratory complications. A comprehensive study by Liu *et al.* in Taiwan revealed that nearly 41% of CP children experienced recurrent pneumonia, largely due to aspiration and poor airway clearance [3]. This underscores that airway dysfunction is a universal challenge, but local factors such as malnutrition and healthcare access may modify the risk in Pakistan. Similarly, Kuo *et al.* emphasized the role of oropharyngeal dysfunction in increasing the risk of lower respiratory tract infections [4], supporting the need to assess swallowing and feeding practices in our

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population. In the United States, Stevens *et al.* reported a higher incidence of pneumonia-related hospitalizations among children with moderate to severe CP, often linked to malnutrition and poor mobility [5]. In Pakistan, limited research has explored pneumonia in children with CP despite high rates of malnutrition, incomplete immunization, and poor caregiver awareness. Understanding these associations in our setting is essential to guide context-specific preventive strategies and resource allocation. A study conducted in Islamabad by Khan *et al.* reported that 38% of CP children admitted to tertiary care centers developed pneumonia [6], while Iqbal *et al.* from Karachi emphasized aspiration and incomplete immunization as significant predictors of pneumonia in children with neurodevelopmental disorders [7].

Although pneumonia is a leading cause of morbidity and hospitalization among children with cerebral palsy, local evidence regarding its frequency and context-specific risk factors in Khyber Pakhtunkhwa remains limited. Most available studies are either international or conducted in other regions of Pakistan, with variable findings influenced by healthcare access, feeding practices, and immunization coverage. Furthermore, inconsistencies regarding the role of CP severity and nutritional status highlight the need for localized data. Therefore, assessing the burden and associated clinical risk factors in our tertiary care setting is essential to guide targeted preventive strategies. Despite these findings, there remains a substantial gap in localized data to inform clinical guidelines and prevention strategies in Pakistan. Generating local evidence to support early detection, caregiver education, and preventive interventions in Pakistan. This study aims to determine its frequency and identify clinical risk factors in a tertiary care setting in Peshawar, due to the high burden and preventable nature of pneumonia in children with CP.

## METHODS

The study was carried out in the Pediatrics Unit at Khyber Teaching Hospital (KTH), Peshawar, which is a tertiary care teaching hospital affiliated with Khyber Medical College. The hospital serves a large and diverse pediatric population from both urban and rural areas across Khyber Pakhtunkhwa. The data collection form was reviewed by three pediatric faculty members for face validity. The structured clinical assessment form was developed after an extensive literature review. Content validity was established by three senior pediatricians, and face validity was assessed through a pilot on 10 patients. Necessary modifications were incorporated before final data collection. Diagnostic consistency was maintained by ensuring that all assessments were performed by the same team using standardized clinical protocols. Data collection was conducted for six months, from 8th August 2019 to 8th Feb 2020, after obtaining ethical approval from the Institutional Research and Ethical Review Board (IREB) of Khyber Medical College (Approval No. 631/ADR/KMC). The required sample size was calculated using the single population proportion formula: $n = (Z^2 \times p \times (1-p)) / d^2$ Here, n represents the required sample size, Z is the standard normal value at a 95% confidence level (1.96), p is the anticipated population proportion (0.40), based on Whitney et al. [8] and d is the absolute precision (0.10). Substituting these values into the formula: $n = (1.96^2 \times 0.40 \times 0.60) / (0.10^2)$ = (3.8416 × 0.24) / 0.01 = 0.921984 / 0.01 = 92.2. Thus, the minimum required sample size was 93 participants, which was achieved in this study. A non-probability consecutive sampling technique was employed to recruit participants. Inclusion Criteria were children aged 6 months to 15 years with a confirmed diagnosis of cerebral palsy. Diagnosis was established through detailed clinical and neurological assessment by a pediatric neurologist, supplemented by neuroimaging (MRI or CT) findings where available. Both male and female children were included. Patients attending outpatient clinics or admitted for any reason during the study period, and parents or guardians who gave informed consent, were eligible. Exclusion Criteria were children with congenital lung malformations or primary respiratory diseases not related to CP. Patients with incomplete medical records and those who were lost to follow-up or whose caregivers declined participation. Data were collected through a structured clinical assessment form designed specifically for this study. It included demographic details (age, gender, residence, parental education); clinical classification of CP (type and severity). Severity of CP was categorized as mild, moderate, or severe based on the Gross Motor Function Classification System (GMFCS), where mild refers to independent mobility, moderate to assisted mobility, and severe to complete dependence on caregivers. Feeding method (oral, nasogastric tube, PEG); nutritional status (assessed by pediatrician and classified as normal, underweight, or severely malnourished); immunization status (complete vs. incomplete according to the Pakistan Expanded Program on Immunization (EPI) schedule, which includes BCG, OPV, pentavalent (DPT-HepB-Hib), measles, and pneumococcal vaccines); history of aspiration or recurrent choking; and diagnosis of pneumonia (based on clinical features, chest auscultation, and radiological evidence if available). All children were evaluated by a qualified pediatrician, and data were collected confidentially in accordance with ethical standards. Data were entered and analyzed using IBM SPSS Statistics version 26.0. Descriptive statistics were used to summarize frequencies and percentages for categorical variables. The primary outcome (presence or absence of pneumonia) was assessed in terms of frequency. Chi-square tests were applied to determine

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associations between pneumonia and clinical risk factors (feeding method, severity of CP, nutritional status, immunization status, and aspiration history). For statistically significant results, effect sizes were calculated using Cramer's V, and Chi-square values with degrees of freedom ($\chi^2$, df) were reported. A p-value<0.050 was considered statistically significant.

## RESULTS

The study included 93 children with cerebral palsy, with a slightly higher proportion of male, 56 (60.2%), compared to female, 37 (39.8%). The most common age group was 2–5 years, accounting for 34 (36.6%) of the participants, followed by children aged 6–10 years, 27 (29.0%), while those older than 10 years represented only 10 (10.8%). A majority of the children were from urban areas 51 (54.8%), while 42 (45.2%) resided in rural settings. In terms of parental education, 38 (40.9%) had primary-level education, whereas 29 (31.2%) were illiterate, and only 26 (28.0%) had education beyond the primary level. These figures suggest that CP in the study population was more prevalent among younger children from urban and lower-educated family backgrounds (Table 1).

**Table 1:** Demographic Characteristics of Children with CP (n=93)

| Variables | Category | Frequency (%) |
|---|---|---|
| Age Group | <2 Years | 22 (23.7%) |
| | 2–5 Years | 34 (36.6%) |
| | 6–10 Years | 27 (29.0%) |
| | >10 Years | 10 (10.8%) |
| Gender | Male | 56 (60.2%) |
| | Female | 37 (39.8%) |
| Residence | Urban | 51 (54.8%) |
| | Rural | 42 (45.2%) |
| Parental Education | Illiterate | 29 (31.2%) |
| | Primary | 38 (40.9%) |
| | Secondary or above | 26 (28.0%) |

Spastic CP was the most common subtype observed in this cohort, affecting 61 (65.6%) of the children. Mixed-type CP was noted in 14 (15.1%), followed by athetoid 11 (11.8%) and ataxic 7 (7.5%) forms. Regarding severity, nearly half the sample, 43 (46.2%), had moderate CP, while severe and mild forms were found in 31 (33.3%) and 19 (20.4%), respectively. The majority of children, 62 (66.7%), were fed orally, but a significant proportion required assisted feeding, including 20 (21.5%) via nasogastric tubes and 11 (11.8%) via PEG tubes. Nutritional assessment showed that half of the children, 47 (50.5%), were underweight and 22 (23.7%) were severely malnourished, whereas only 24 (25.8%) had a normal nutritional status (Table 2).

**Table 2:** Clinical Profile of Children with CP (n=93)

| Variables | Category | Frequency (%) |
|---|---|---|
| CP | Spastic | 61 (65.6%) |
| | Athetoid | 11 (11.8%) |
| | Ataxic | 7 (7.5%) |
| | Mixed | 14 (15.1%) |
| Severity of CP | Mild | 19 (20.4%) |
| | Moderate | 43 (46.2%) |
| | Severe | 31 (33.3%) |
| Feeding Method | Oral | 62 (66.7%) |
| | NGT | 20 (21.5%) |
| | PEG | 11 (11.8%) |
| Nutritional Status | Normal | 24 (25.8%) |
| | Underweight | 47 (50.5%) |
| | Severely Malnourished | 22 (23.7%) |

Among the 93 children, 38 (40.9%) had documented pneumonia, while 55 (59.1%) did not. This indicates a high burden of respiratory complications among children with cerebral palsy (Table 3).

**Table 3:** Frequency of Pneumonia Among Children with CP (n=93)

| Pneumonia Status | Frequency (%) |
|---|---|
| Present | 38 (40.9%) |
| Absent | 55 (59.1%) |

Significant associations were identified between pneumonia occurrence and several clinical variables. All children with mild CP had pneumonia, whereas none with severe CP were affected ($\chi^2 = 49.12$, df = 2, p<0.001, Cramer's V = 0.727). The feeding method was also significant, with all pneumonia cases occurring in orally fed children ($\chi^2 = 32.13$, df = 2, p<0.001, Cramer's V = 0.588). Nutritional status showed an unusual trend, with pneumonia present only in normally nourished and underweight children, but absent in severely malnourished children ($\chi^2 = 52.32$, df = 2, p<0.001, Cramer's V = 0.750). Immunization status was strongly associated, as all pneumonia cases occurred in children with complete immunization ($\chi^2 = 74.72$, df = 1, p<0.001, Cramer's V = 0.896). Aspiration history showed the strongest effect, with every child who had aspiration developing pneumonia ($\chi^2 = 85.14$, df = 1, p<0.001, Cramer's V = 0.957). Interestingly, no pneumonia cases were reported among children with severe CP or those who were severely malnourished. These counterintuitive findings are noted here and are further explained in the Discussion (Table 4).

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**Table 4:** Association Between Pneumonia and Clinical Risk Factors (n=93)

| Variables | Category | Pneumonia Present | Pneumonia Absent | $\chi^2$ (df) | p-Value | Cramer's V |
|---|---|---|---|---|---|---|
| Severity of CP | Mild | 19 (100%) | 0 | 49.12 (2) | <0.001* | 0.727 |
| | Moderate | 19 (44.2%) | 24 (55.8%) | | | |
| | Severe | 0 | 31 (100%) | | | |
| Feeding Method | Oral | 38 (61.3%) | 24 (38.7%) | 32.13 (2) | <0.001* | 0.588 |
| | NGT | 0 | 20 (100%) | | | |
| | PEG | 0 | 11 (100%) | | | |
| Nutritional Status | Normal | 24 (100%) | 0 | 52.32 (2) | <0.001* | 0.750 |
| | Underweight | 14 (29.8%) | 33 (70.2%) | | | |
| | Severely Malnourished | 0 | 22 (100%) | | | |
| Immunization Status | Complete | 38 (88.4%) | 5 (11.6%) | 74.72 (1) | <0.001* | 0.896 |
| | Incomplete | 0 | 50 (100%) | | | |
| Aspiration History | Yes | 38 (95.0%) | 2 (5.0%) | 85.14 (1) | <0.001* | 0.957 |
| | No | 0 | 53 (100%) | | | |

*p<0.05 considered statistically significant (Chi-square test)

As shown in the pie chart, pneumonia was present in approximately two-fifths, 38 (40.9%) of the participants, highlighting a substantial burden of respiratory complications in children with cerebral palsy. The remaining 55 (59.1%) did not have pneumonia (Figure 1).

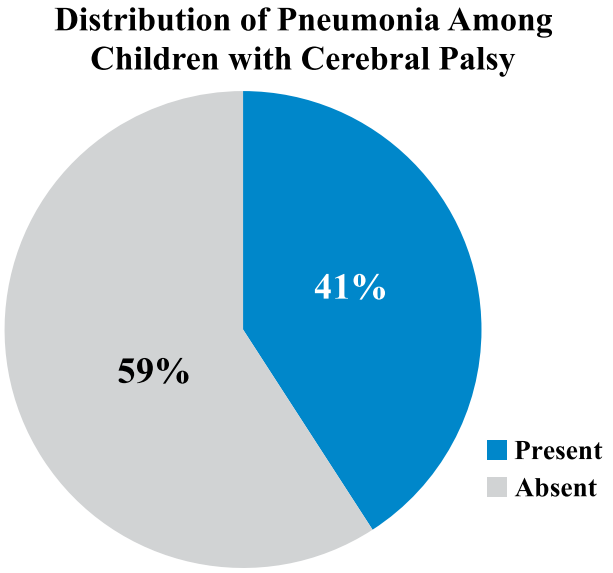


**Figure 1:** Distribution of Pneumonia among Children with CP (n=93)

## DISCUSSION

Cerebral palsy (CP) is a neurodevelopmental condition often accompanied by multiple comorbidities, with pneumonia being one of the most frequent and life-threatening complications. In our study, the prevalence of pneumonia among children with CP was 40.9%, which aligns closely with the findings of Whitney *et al.* who reported recurrent pneumonia in 41% of children with severe motor dysfunction [9]. This high burden reflects the multifactorial vulnerabilities in this population, including impaired swallowing, poor airway clearance, and limited mobility. Our study found that aspiration history had the strongest association with pneumonia (p<0.001), which is consistent with several previous studies. Mpody *et al.* demonstrated that aspiration pneumonia was a leading cause of hospitalization in children with spastic quadriplegia [10]. Similarly, a study by Kopiyka *et al.* identified oropharyngeal dysphagia as a key risk factor for respiratory infections in CP children [11]. This highlights the mechanism by which aspiration contributes to pneumonia: impaired swallowing leads to misdirection of food or saliva into the airway, while reduced cough reflex prevents clearance, resulting in recurrent lower respiratory tract infections. These findings reinforce the critical role of early identification and management of swallowing dysfunction to prevent aspiration-related complications. The feeding method was another significant predictor in our study, where all pneumonia cases occurred in orally fed children, and none in those using nasogastric or PEG feeding. This result supports the idea that assisted feeding may reduce aspiration risk by bypassing dysfunctional swallowing, although it may also reflect closer monitoring and caregiver vigilance in children who require tube feeding. Previous studies have noted both benefits and risks associated with tube feeding. Aishauova *et al.* emphasized that while PEG feeding reduces aspiration in some cases, improper technique or reflux can still pose risks [12]. Nutritional status was also significantly associated with pneumonia. Surprisingly, all pneumonia cases were seen in children with normal nutritional status, while none of the severely malnourished children developed pneumonia. This counterintuitive finding may be explained by reduced exposure of severely malnourished children, who are often less mobile and more frequently hospitalized, thereby limiting contact with community-acquired pathogens. Alternatively, detection bias may have played a role, as severely malnourished children are more closely

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monitored for nutritional complications than for respiratory illnesses. This contradicts findings by Peneva *et al.* who observed that malnourishment increases susceptibility to infections due to weakened immunity [13]. Another unusual observation was that all pneumonia cases occurred in immunized children ($p<0.001$). While this finding appears contradictory to existing evidence, it may reflect confounding factors. Immunized children in our setting may be more active, socially exposed, or better documented, which increases the likelihood of pneumonia being diagnosed and recorded. Conversely, children with incomplete immunization may have lower healthcare access, resulting in underreporting. Most prior studies, including Amer *et al.* and Strzalkowski *et al.* confirm that incomplete immunization is a major risk factor for pneumonia in CP [14, 15]. Regarding the severity of CP, children with mild CP had the highest pneumonia frequency, while those with severe CP had none. This unexpected trend might be explained by differences in exposure: children with mild CP are more mobile, attend school or social gatherings, and therefore face greater exposure to pathogens, whereas children with severe CP remain mostly indoors and under constant supervision. Previous studies, such as Spoto *et al.* where severe CP was associated with increased risk due to poor cough reflex and limited mobility [16]. But our results suggest that social and environmental exposure may play a more significant role than severity alone in this context. Comparable findings were reported by Jonsson *et al.* who observed that pneumonia risk in CP may vary more with feeding and aspiration patterns than with gross motor function alone [17]. Furthermore, a study by Gordon *et al.* concluded that caregiver education and feeding practices greatly influenced respiratory outcomes, regardless of CP subtype or severity [18]. In Pakistan, local evidence remains limited, but studies highlight similar concerns. Rafique *et al.* reported respiratory complications in 38% of CP patients at a tertiary center in Karachi, while Qureshi *et al.* emphasized aspiration and poor feeding practices as major risk factors [19, 20]. Our findings are consistent with this regional data and underline the urgent need for structured feeding assessments, aspiration prevention protocols, and caregiver training programs in Pakistani hospitals. In summary, our study reinforces existing international and local evidence that pneumonia is a significant clinical concern in children with cerebral palsy, particularly in relation to aspiration, feeding method, and immunization. Unexpected findings such as the absence of pneumonia in severe CP and severely malnourished children highlight the importance of considering contextual factors like exposure risk, caregiver behavior, and healthcare access. These insights underscore the need for tailored preventive strategies.

This study was limited by its single-center, cross-sectional design and relatively small sample size, which may restrict generalizability and prevent causal inference. The reliance on clinical diagnosis and hospital-based sampling may also introduce detection bias. Future multicenter, longitudinal studies with larger cohorts and standardized diagnostic criteria are recommended to better clarify causal relationships and evaluate long-term respiratory outcomes. Incorporating objective swallowing assessments and follow-up data would further strengthen evidence for preventive interventions in children with cerebral palsy.

## CONCLUSIONS

The present study identified a high frequency of pneumonia (40.9%) among children with cerebral palsy. Aspiration history, oral feeding, and immunization status were found to be strongly associated with the presence of pneumonia. Contrary to expectations, severe CP and malnutrition were not linked with increased pneumonia risk, which may point to confounding protective factors or limited exposure. These findings highlight the need for structured feeding assessments, aspiration prevention protocols, and continued caregiver education to mitigate respiratory complications in children with CP.

## Authors' Contribution

Conceptualization: BH
Methodology: SP, SA, AF, AMK, AAQ
Formal analysis: BH, SP, SA, AF, AMK, AAQ
Writing and Drafting: BH, AAQ
Review and Editing: BH, AAQ, SP, SA, AF, AMK

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Early Detection of Sepsis and NEC Using Serial Vital Sign Trends (HR, $SpO_2$, RR) on Standard NICU Monitors in Preterm Neonates

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## ABSTRACT

Preterm neonates are at high risk for sepsis and necrotizing enterocolitis (NEC), but early signs are often subtle, delaying diagnosis and worsening outcomes. **Objectives:** To evaluate whether trends in routinely monitored heart rate (HR), respiratory rate (RR), and oxygen saturation ($SpO_2$) predict sepsis and NEC and to examine their association with NICU stay, mortality, and discharge outcomes. **Methods:** A prospective observational cohort study was conducted among 103 preterm infants (<37 weeks' gestation) admitted to a tertiary NICU with continuous multi-parameter monitoring. HR, RR, and $SpO_2$ trends were compared between infants with sepsis/NEC and those who remained stable. Outcomes were analyzed using t-tests, Mann–Whitney U tests, Chi-square tests, and logistic regression. Cox regression identified mortality predictors, and Kaplan–Meier curves compared survival between groups. **Results:** Sepsis occurred in 22.3% and NEC in 7.8% of neonates. Female infants had lower odds of sepsis/NEC (adjusted OR = 0.23, 95% CI: 0.07–0.74, p=0.013). Sepsis/NEC was linked to longer NICU stay (21.6 ± 6.8 vs 11.9 ± 4.4 days, p<0.001) and higher mortality (30.4% vs 10.0%, p=0.014). Cox regression confirmed sepsis/NEC as an independent predictor of mortality (HR = 0.084, p=0.005). **Conclusions:** Routine vital sign trends alone were insufficient for early detection, but their association with adverse outcomes underscores the potential of enhanced monitoring and predictive modeling to enable earlier recognition and improved survival.

## INTRODUCTION

Neonatal sepsis continues to be a major contributor to infant mortality worldwide, particularly among preterm and low-birth-weight infants [1]. In Pakistan, reported incidence rates of neonatal sepsis range from 20–40%, with mortality rates reaching up to 30% in high-risk NICU populations [2]. These figures highlight the significant burden of disease and the need for robust surveillance systems in local NICU settings [2, 3]. Similarly, necrotizing enterocolitis (NEC) remains a formidable gastrointestinal emergency in the neonatal period, with profound morbidity and limited early detection capabilities [4]. Accurate and timely diagnosis remains elusive. Traditional reliance on clinical signs and intermittent assessments often fails to anticipate rapid deterioration [5]. Risk stratification tools and biomarkers have been explored, but their applicability remains limited in low-resource environments [6, 7].

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Advancements in continuous vital sign monitoring offer new promise. Machine learning approaches applying heart rate variability and other physiologic signals have demonstrated potential in early detection of neonatal sepsis and NEC [8, 9], while near-infrared spectroscopy (NIRS) has been leveraged to predict NEC with high accuracy in preterm infants [10]. Early warning scores and physio-marker analysis are being adopted in critical care to detect early deterioration (Vital signs as physio-markers review, 2025) [11]. Locally, however, evidence remains sparse. Although there are emerging practices in Pakistani NICUs regarding vital sign surveillance, data-driven strategies for early detection of sepsis and NEC using routine monitoring are not well established. Despite the high burden of neonatal sepsis and NEC in Pakistan, there is limited published research evaluating whether serial trends of routinely monitored HR, RR, and $SpO_2$ can serve as reliable early predictors of these conditions. Establishing such evidence in the local context can support the development of cost-effective early warning protocols and potentially improve survival outcomes in resource-limited settings.

Neonatal sepsis and necrotizing enterocolitis (NEC) remain major contributors to morbidity and mortality among preterm infants, particularly in resource-limited NICU settings. Although continuous monitoring of heart rate (HR), respiratory rate (RR), and oxygen saturation ($SpO_2$) is routinely performed, their serial trends are rarely analyzed systematically for early disease prediction in local clinical practice. Most available evidence relies on advanced machine learning models or high-resolution physiological data, which may not be feasible in many Pakistani NICUs. Consequently, there is limited region-specific evidence evaluating whether routinely available vital sign trends alone can serve as early predictive markers for sepsis and NEC in preterm neonates. This study aims to investigate the predictive value of these vital sign trends for early detection of sepsis and NEC in preterm neonates admitted to a tertiary-level NICU.

## METHODS

This study was designed as a prospective observational cohort study conducted in a tertiary-level neonatal intensive care unit (NICU). The objective was to determine whether serial trends in vital signs, specifically heart rate (HR), oxygen saturation ($SpO_2$), and respiratory rate (RR) monitored through standard NICU bedside monitors, could aid in the early detection of sepsis and necrotizing enterocolitis (NEC) in preterm neonates. The study was conducted over 12 months, from April 2024 to April 2025, allowing capture of seasonal variations in neonatal admissions and infections. The study was carried out in the Department of Pediatrics, Northwest General Hospital and Research Centre, Peshawar, which is a referral center equipped with a Level III NICU and advanced neonatal monitoring facilities. Before initiation, the study protocol was reviewed and approved by the Institutional Review Board and Ethical Committee of Alliance Healthcare Pvt. Ltd. (Approval Ref: IRB&EC/2024-GH/0280). The principal investigator was responsible for ensuring compliance with all ethical conditions, and written informed consent was obtained from parents or guardians before enrolling neonates. The sample size was calculated using OpenEpi version 4.0 with the formula: $n = DEFF \times Np(1-p)] / ((d^2/Z^2_{1-}\alpha/2 \times (N-1) + p(1-p))$, where p = 20–25 % expected prevalence of sepsis based on previously published regional studies [2], d = 5 % margin of error, Z = 1.96 for 95 % CI, and power = 80 %. These assumptions were applied uniformly for both sepsis and NEC outcomes. The minimum required sample size was 96. To account for a 5–7 % attrition rate due to incomplete monitoring records, the final sample size was increased to 103 neonates. All preterm neonates admitted to the NICU during the study period who fulfilled the eligibility criteria were considered for inclusion. Inclusion criteria include preterm neonates with gestational age <37 weeks, admitted within 72 hours of birth, placed on continuous multi-parameter monitoring (HR, $SpO_2$, RR), and whose parents or guardians provided informed consent. Exclusion criteria were neonates with major congenital anomalies of the heart, lungs, or gastrointestinal tract, severe birth asphyxia with an Apgar score <3 at five minutes, or those transferred from outside facilities without complete baseline data. Neonates with <90 % completeness of monitoring data were excluded rather than imputed to avoid selection bias. Upon admission, demographic and baseline clinical details (gestational age, birth weight, sex, and mode of delivery) were recorded. Each neonate was continuously monitored using standard NICU multi-parameter monitors, which automatically log HR, $SpO_2$, and RR trends. Data on clinical episodes such as apnea, bradycardia, and desaturation events were also captured. All enrolled neonates were followed prospectively daily until discharge or death. Sepsis was diagnosed through a combination of clinical findings and laboratory evidence, including positive blood culture, elevated C-reactive protein (CRP), or abnormal white blood cell (WBC) counts. NEC was staged according to Bell's criteria, with Stage II and above considered diagnostic [8]. Early detection was defined as abnormal vital-sign patterns appearing ≥24 hours before the clinical confirmation of sepsis or NEC, based on chart review. Serial trends in HR, $SpO_2$, and RR were compared between neonates with confirmed sepsis/NEC and those who remained clinically stable. The main outcomes assessed included duration of NICU stay, mortality, and discharge status. All NICU monitors used for data collection were

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regularly calibrated and standardized by hospital biomedical engineers. To minimize errors, data entry was cross-checked by two independent researchers. A pilot run of 10 neonates was conducted to validate data collection tools and assess feasibility; no major protocol modifications were required. Data from these pilot participants were not included in the final analysis, leaving a final study sample size of 103. Diagnostic definitions strictly followed internationally accepted criteria, thereby enhancing diagnostic accuracy. Structured training sessions were provided for NICU staff to reduce inter-observer variability in data collection. Data were entered and analyzed using IBM SPSS Statistics (version 26.0). Continuous variables were summarized as mean ± standard deviation (SD) for normally distributed data, and as median with interquartile range (IQR) for non-normally distributed data. Categorical variables were presented as frequency (%). Normality of continuous data (HR, RR, $SpO_2$, NICU stay) was assessed using histograms, Q-Q plots, and the Shapiro–Wilk test. Variables with p>0.05 were considered normally distributed. For normally distributed variables, comparisons between groups (sepsis vs. no sepsis; stable vs. sepsis/NEC) used the independent samples t-test; for skewed variables, the Mann–Whitney U test was applied. Categorical variables (sex, gestational age category, birth weight group, delivery mode, bradycardia, apnea, desaturation, mortality, discharge) were analyzed using the Chi-square test or Fisher's exact test when expected counts were <5. Multivariable logistic regression was used to adjust for confounders, including gestational age, birth weight, and delivery mode, when analyzing predictors of sepsis and NEC. Cox proportional hazards modeling was applied for mortality outcomes to account for time-to-event effects. Effect sizes were reported alongside p-values: Cohen's d for continuous data, Cramér's V for categorical data, and odds ratios (OR) with 95 % confidence intervals for regression models. A p-value <0.050 was considered statistically significant. To adjust for potential confounders, binary logistic regression was performed to identify independent predictors of sepsis/NEC, with gestational age, birth weight, sex, delivery mode, and bradycardia episodes included as covariates. Adjusted odds ratios with 95% confidence intervals were reported, and model fit was evaluated using the Hosmer–Lemeshow test and Nagelkerke $R^2$. For mortality outcomes, Cox proportional hazards regression was used with NICU stay as the time variable and mortality as the event, reporting hazard ratios with 95% confidence intervals. The proportional hazards assumption was verified using log-minus-log plots. Kaplan–Meier survival analysis with the log-rank test was also conducted to compare survival curves between neonates with and without sepsis/NEC. A p-value <0.050 was considered statistically significant.

## RESULTS

Prior to the main study, a pilot was conducted on 10 preterm neonates to test feasibility of continuous vital sign monitoring and data collection procedures. The pilot confirmed that NICU monitors successfully captured heart rate, respiratory rate, and $SpO_2$ trends without major technical interruptions. No protocol modifications were required, and the pilot data were not included in the final analysis. In this cohort of 103 preterm neonates, the majority (43.7%) were born between 28–32 weeks of gestation, followed by 36.9% between 33–36 weeks. Sepsis occurred across all gestational age and birth weight categories with no statistically significant differences (p>0.050). A nearly equal sex distribution was observed, but female neonates had significantly higher rates of sepsis compared to males (32.7% vs 11.8%, p=0.011, Cramér's V = 0.251, small-to-moderate association). Mode of delivery showed no significant association with sepsis (Table 1).

**Table 1:** Demographic Characteristics of Preterm Neonates (n=103)

| Variables | Total n, (%) | Sepsis, n (%) | No Sepsis, n (%) | p-Value | Cramér's V |
|---|---|---|---|---|---|
| **Gestational Age** | | | | | |
| <28 weeks | 20 (19.4%) | 6 (30.0) | 14 (70.0%) | 0.602 | – |
| 28–32 weeks | 45 (43.7%) | 10 (22.2) | 35 (77.8%) | | |
| 33–36 weeks | 38 (36.9%) | 7 (18.4) | 31 (81.6%) | | |
| **Birth Weight** | | | | | |
| <1000 g | 13 (12.6%) | 2 (15.4) | 11 (84.6%) | 0.775 | – |
| 1000–1500 g | 36 (35.0%) | 9 (25.0) | 27 (75.0%) | | |
| 1501–2500 g | 54 (52.4%) | 12 (22.2) | 42 (77.8%) | | |
| **Sex** | | | | | |
| Male | 51 (49.5%) | 6 (11.8) | 45 (88.2%) | 0.011* | 0.251 |
| Female | 52 (50.5%) | 17 (32.7) | 35 (67.3%) | | |
| **Delivery Mode** | | | | | |
| Cesarean | 67 (65.0%) | 13 (19.4%) | 54 (80.6%) | 0.330 | – |
| Vaginal | 36 (35.0%) | 10 (27.8%) | 26 (72.2%) | | |

*Significant at p<0.050

No statistically significant differences were found in mean HR, RR, or $SpO_2$ between neonates with and without sepsis (p>0.05). Heart rate showed a small but non-significant effect size (Cohen's d = 0.29). Similarly, bradycardia, apnea, and desaturation episodes were not significantly associated with sepsis (Table 2).

**Table 2:** Vital Sign Trends in Preterm Neonates with and without Sepsis (n=103)

| Parameters | No Sepsis (n=80) | Sepsis (n=23) | p-Value | Effect Size |
|---|---|---|---|---|
| Heart Rate (Beats/Min) | 147.8 ± 9.5 | 145.1 ± 9.3 | 0.228 | Cohen's d = 0.29 |
| Respiratory Rate (Breaths/Min) | 48 (44–52) | 49 (45–53) | 0.924 | – (Mann–Whitney) |
| $SpO_2$ (%) | 92.6 ± 2.9 | 92.7 ± 3.2 | 0.955 | Cohen's d = 0.01 |
| Bradycardia ≥1/Day | 16 (20.0%) | 1 (4.3%) | 0.075 | Cramér's V = 0.176 |

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| | | | | |
|---|---|---|---|---|
| Apnea ≥1/Day | 17 (21.3%) | 3 (13.0%) | 0.381 | Cramér's V = 0.086 |
| Desaturation <90% | 29 (36.3%) | 7 (30.4%) | 0.606 | Cramér's V = 0.051 |

Sepsis was diagnosed in 22.3% of neonates, whereas NEC occurred in 7.8%. No significant predictors were found for NEC, though a trend toward higher incidence was observed among vaginal deliveries (p=0.089) (Table 3).

**Table 3:** Frequency of Sepsis and NEC in Study Population (n=103)

| Outcomes | n (%) | Significant Association |
|---|---|---|
| Sepsis | 23 (22.3%) | Sex (p=0.011, V = 0.251) |
| NEC | 8 (7.8%) | None (Borderline: Delivery Mode p=0.089) |
| No Sepsis/NEC | 72 (69.9%) | – |

Neonates with sepsis or NEC had significantly longer NICU stays (21.6 ± 6.8 days) compared to stable infants (11.9 ± 4.4 days, p<0.001, large effect size). Mortality was also significantly higher in the sepsis/NEC group (30.4% vs 10.0%, p=0.014), while survival to discharge was significantly lower (Table 4).

**Table 4:** Clinical Outcomes of Preterm Neonates (n=103)

| Outcomes | Stable (n = 80) | Sepsis/ NEC (n = 23) | p-Value | Effect Size |
|---|---|---|---|---|
| NICU Stay (Days) | 11.9 ± 4.4 | 21.6 ± 6.8 | <0.001 | Cohen's d ≈ 1.7 |
| Mortality | 8 (10.0%) | 7 (30.4%) | 0.014 | Cramér's V = 0.241 |
| Discharged Alive | 72 (90.0%) | 16 (69.6%) | 0.014 | Cramér's V = 0.241 |

After adjusting for gestational age, birth weight, delivery mode, and bradycardia episodes, female sex remained a statistically significant predictor of sepsis/NEC (adjusted OR 0.23, 95% CI: 0.07–0.74, p=0.013), indicating that female infants had significantly lower odds of developing sepsis/NEC compared to males. Gestational age and birth weight showed no significant independent association with sepsis/NEC after adjustment. Delivery mode and bradycardia episodes also did not retain significance in the multivariable model, although vaginal delivery showed a trend toward reduced odds (p=0.100). The model explained approximately 18.9% of the variance in sepsis/NEC occurrence (Nagelkerke $R^2$ = 0.189) and had acceptable goodness of fit (Hosmer–Lemeshow p=0.328) (Table 5).

**Table 5:** Multivariable Logistic Regression for Predictors of Sepsis/NEC (n=103)

| Predictors | Adjusted OR (Exp (B)) | 95% CI | p-Value |
|---|---|---|---|
| **Gestational Age** | | | |
| <28 Weeks vs 33–36 Weeks | 2.26 | 0.57 – 8.96 | 0.248 |
| 28–32 Weeks vs 33–36 Weeks | 1.06 | 0.33 – 3.45 | 0.918 |
| **Birth Weight** | | | |
| <1000 g vs 1501–2500 g | 0.30 | 0.05 – 1.88 | 0.201 |
| 1000–1500 g vs 1501–2500 g | 1.09 | 0.37 – 3.21 | 0.867 |
| **Sex** | | | |
| Male vs Female | 0.23 | 0.07 – 0.74 | 0.013* |
| **Delivery Mode** | | | |
| Vaginal vs Cesarean | 0.40 | 0.13 – 1.19 | 0.100 |
| **Bradycardia** | | | |
| ≥1/Day | 0.33 | 0.04 – 2.90 | 0.318 |

Reference categories: gestational age 33–36 weeks, birth weight 1501–2500 g, male sex, cesarean delivery, and no bradycardia episode. *Significant at p<0.050

Cox regression revealed that sepsis/NEC was a strong independent predictor of mortality, with a hazard ratio of 0.084 (95% CI: 0.015–0.470, p=0.005), The HR of 0.084 for sepsis/NEC indicates a markedly increased mortality risk in affected neonates (inverse HR interpretation: ≈ 12-fold higher hazard of death). Gestational age <28 weeks demonstrated a trend toward increased mortality risk (HR = 4.21, p=0.081), though this did not reach statistical significance. Vaginal delivery showed a borderline association with reduced hazard of death (HR = 0.29, p=0.061). Birth weight, sex, and bradycardia episodes were not statistically significant predictors after adjustment. The survival plot generated from the Cox model showed a distinct separation between curves, with survival probability consistently lower in the sepsis/NEC group throughout the NICU stay, particularly during the first two weeks (Table 6).

**Table 6:** Cox Regression Analysis for Predictors of Mortality (n=103)

| Predictors | Adjusted HR (Exp (B)) | 95% CI | p-Value |
|---|---|---|---|
| **Gestational Age** | | | |
| <28 Weeks vs 33–36 Weeks | 4.21 | 0.84 – 21.11 | 0.081 |
| 28–32 Weeks vs 33–36 Weeks | 2.55 | 0.47 – 13.82 | 0.277 |
| **Birth Weight** | | | |
| <1000 g vs 1501–2500 g | 0.57 | 0.09 – 3.42 | 0.536 |
| 1000–1500 g vs 1501–2500 g | 1.83 | 0.45 – 7.42 | 0.395 |
| **Sex** | | | |
| Male vs Female | 0.96 | 0.23 – 3.97 | 0.952 |
| **Delivery Mode** | | | |
| Vaginal vs Cesarean | 0.29 | 0.08 – 1.06 | 0.061 |
| **Bradycardia** | | | |
| ≥1/Day | 2.32 | 0.41 – 13.20 | 0.341 |
| **Sepsis/NEC** | | | |
| Yes vs No | 0.084 | 0.015 – 0.470 | 0.005* |

HR = Hazard Ratio. Reference categories: gestational age 33–36 weeks, birth weight 1501–2500 g, female sex, cesarean delivery, no bradycardia episode, no sepsis/NEC. Significant associations are bolded.

The study illustrates marked differences in clinical outcomes between groups. Neonates with sepsis or NEC had a prolonged NICU stay (21.6 vs 11.9 days) compared to stable infants. Mortality was also notably higher in the Sepsis/NEC group (30.4% vs 10.0%), while the proportion discharged alive was significantly lower (69.6% vs 90.0%). These findings emphasize the adverse impact of sepsis and NEC on both survival and hospitalization burden. The graph compares mean NICU stay (days), mortality

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percentage, and discharge rate between the Stable group (n=80) and the Sepsis/NEC group (n=23) (Figure 1).

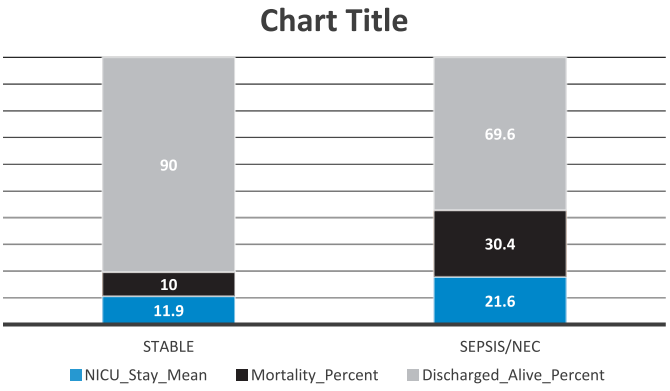


**Figure 1:** Clinical Outcomes of Preterm Neonates with and without Sepsis/NEC

The sepsis/NEC group showed significantly lower survival probability (log-rank p<0.050), with most deaths occurring within the first 20 days of NICU stay (Figure 2).

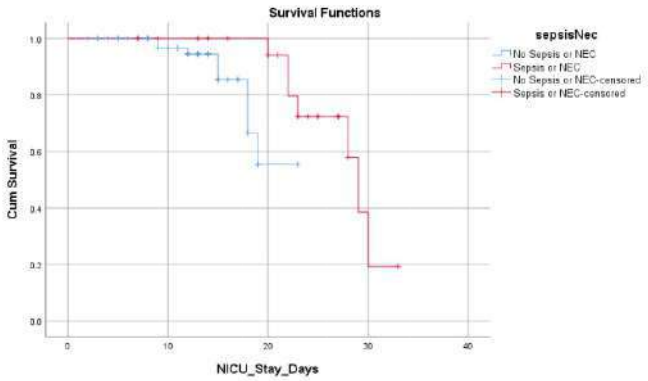


**Figure 2:** Kaplan–Meier Survival Curves Comparing Neonates with Sepsis/NEC (Red Line) and Those Without (Blue Line)

## DISCUSSION

In this prospective cohort study, we explored whether trends in vital signs, heart rate (HR), respiratory rate (RR), and oxygen saturation ($SpO_2$) could serve as early indicators of sepsis and necrotizing enterocolitis (NEC) among preterm neonates. Although our results did not show significant differences in these vital sign trends between stable infants and those who developed sepsis, our findings align with several recent studies emphasizing both the potential and challenges of this approach. First, Honoré *et al.* highlighted the clinical difficulty in diagnosing neonatal sepsis early due to nonspecific signs; researchers underscored the potential of vital sign–based models for improved detection [12]. Similarly, Garstman *et al.* reported that decreased heart rate variability (HRV), which often precedes sepsis, can be a subtle yet reliable early marker in preterm infants [13]. These studies reinforce our decision to explore nuanced HR features, even though our mean HR differences were not significant.

Recent advances also suggest that more complex monitoring modalities may be superior. For instance, Verhoeven *et al.* demonstrated that combining cerebral and splanchnic regional oxygen measurements via near-infrared spectroscopy greatly enhanced NEC prediction using advanced algorithms [14]. Likewise, Yang *et al.* achieved high predictive performance (F1 scores up to 0.82) by applying ML models to early postnatal vital sign trends, emphasizing sophisticated analysis beyond simple trend comparison [15]. Broad reviews support the promise of advanced analytics: Narasimha *et al.* identified machine learning and predictive modeling as transformative tools for early sepsis detection in neonates [16], and Rahman *et al.* pointed out the importance of robust preprocessing in physiological signal analysis to ensure reproducibility and reliability [17]. At the same time, technological innovations are enhancing vital sign capture. Williams *et al.* discussed future NICU monitoring technologies, such as wearable sensors and sophisticated HRV analysis that promise improved early warning detection [18]. Krbec *et al.* emphasized the emerging role of non-contact monitoring devices in reducing harm and enhancing comfort, an important consideration in fragile preterm populations [19]. Current findings diverge somewhat from these advanced approaches, likely due to methodological differences. We relied on mean and median comparisons of standard vital signs, whereas many of the referenced studies utilized high-frequency data, variability metrics, or cerebral/splanchnic oxygenation measures, offering greater sensitivity to early disease markers. Notably, despite no significant early vital sign differences, our study revealed significant clinical outcomes. Neonates with sepsis or NEC experienced longer NICU stays and higher mortality, echoing findings from experimental work by Sullivan and Fairchild, which showed that endotoxemia produced notable increases in heart rate and reductions in HRV [20]. These physiological patterns underscore the systemic disruption caused by sepsis, even if the mean vital sign differences were subtle. Future research should address these limitations through larger, multicenter studies to improve generalizability and statistical power, particularly for less common outcomes such as NEC. Incorporating high-resolution physiological data and advanced analytic approaches, including heart rate variability, multivariate signal processing, and machine learning models, could significantly enhance predictive accuracy. The integration of novel monitoring technologies, such as wearable, non-contact, or multimodal sensors, may also provide more reliable early warning systems while reducing discomfort in fragile preterm infants. Moreover, future work should explore the combined role of clinical, laboratory, and monitoring

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parameters, rather than relying on vital signs alone, to build robust risk stratification models. Longitudinal follow-up of neonates beyond NICU discharge would also be valuable to assess whether early detection strategies influence not only short-term outcomes but also neurodevelopmental trajectories and long-term survival.

This study was limited by its single-center design and relatively small sample size, which may restrict generalizability and reduce statistical power, particularly for NEC outcomes. Additionally, only mean and median vital sign trends were analyzed, without incorporating high-frequency variability metrics or advanced predictive algorithms. Future multicenter studies with larger cohorts should integrate high-resolution physiological data, heart rate variability analysis, and machine learning approaches to enhance early detection accuracy. Combining continuous monitoring data with laboratory and clinical parameters may further improve risk stratification and survival outcomes in preterm neonates.

## CONCLUSIONS

This study demonstrates that preterm neonates who develop sepsis or NEC experience significantly prolonged NICU stays and higher mortality rates, emphasizing the clinical burden of these conditions. While trends in HR, RR, and $SpO_2$ provide useful contextual information, they were not sufficient as standalone early predictors of sepsis or NEC. These findings highlight the need for integrating continuous vital sign monitoring with advanced signal analysis and predictive modeling to enable earlier recognition and timely intervention, ultimately improving outcomes in preterm populations.

## Authors' Contribution

Conceptualization: DH
Methodology: DH, JI, MS, TT, AJ, KK
Formal analysis: DH
Writing and Drafting: DH, MS, TT, AJ, KK
Review and Editing: DH, MS, TT, AJ, KK

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Improvement in Stereoacuity After Refractive Correction in Astigmatic Children: A Cross-Sectional Study

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## ABSTRACT

Uncorrected astigmatism in children is a major cause of visual impairment, often associated with reduced stereopsis and visual symptoms, which may be further exacerbated by prolonged screen exposure. **Objectives:** This study aimed to evaluate the effect of full refractive correction on stereopsis in children with moderate-to-high astigmatism and to examine the association between cylindrical error, screen time, and stereoacuity. **Methods:** A cross-sectional study was conducted among 273 children aged 4–8 years attending the ophthalmology department of KRL hospital, Islamabad. Consecutive sampling was employed. After ethical approval and informed consent, each participant underwent a comprehensive ocular examination, including visual acuity testing with ETDRS charts and stereopsis assessment using vectograph circles. Demographic data, refractive status, screen exposure, and outdoor activity were recorded. Statistical analysis included Spearman's correlation and the Wilcoxon Signed-Rank Test. **Results:** The mean uncorrected stereopsis was 141.5 ± 108.1 arc seconds, improving significantly to 66.8 ± 36.6 arc seconds after optical correction ($Z=-14.031$, $p<0.001$). A significant positive correlation was found between cylindrical error in the right eye and baseline stereopsis (Spearman's rho=0.465, $p<0.001$). Screen time averaged 4.9 ± 1.5 hours/day. Asthenopic symptoms, including frequent blinking (82.4%) and blurred vision (81.0%), were highly prevalent. **Conclusion:** Full refractive correction significantly improves stereopsis in children with high astigmatism. Excessive screen exposure may further compromise binocular function, underscoring the importance of early detection, timely correction, and lifestyle modifications in pediatric populations.

## INTRODUCTION

Stereopsis is a key aspect of pediatric vision. It develops postnatally and relies on well-aligned eyes with clear retinal images [1]. Even a slight optical blur or unequal refractive error between the eyes can substantially degrade stereoacuity [1, 2]. In recent years, lifestyle changes, especially increased near work and screen exposure, have been implicated in pediatric refractive problems. Prolonged digital screen time has been linked to various ocular issues, including asthenopic symptoms such as eyestrain, blinking, and blurred vision, and refractive errors in children [3, 4]. Notably, large population studies have shown that extensive early-life screen exposure is associated with a higher risk of developing astigmatism, and the COVID-19 pandemic, with its related lockdowns and screen-centered activities, was accompanied by a marked rise in astigmatism prevalence among schoolchildren [5, 6]. Astigmatism, especially when unequal between eyes, anisometropia, is a potent risk factor for poor stereopsis [7, 8]. However, how optical correction affects stereopsis in astigmatic children with excessive screen use remains

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understudied. Understanding this impact is important because early optical correction can potentially reverse sensory deficits during the critical period of neural plasticity. Despite the high prevalence of refractive errors, particularly astigmatism, there is limited exploration of how cylindrical errors influence depth perception, especially in the context of increased screen time. Given the growing reliance on digital devices from an early age and the lack of emphasis on outdoor activities, this research is crucial for understanding how these factors compound visual impairments. Current study addresses the significant gap in research regarding the impact of uncorrected astigmatism on binocular vision, specifically stereopsis, in children in Pakistan.

Despite increasing recognition of astigmatism as a significant cause of visual impairment in children, its specific impact on binocular vision and stereopsis remains insufficiently explored in the Pakistani pediatric population. While previous studies have linked excessive screen time with refractive errors, limited data exist on how cylindrical error magnitude interacts with digital exposure to influence stereoacuity. Moreover, the extent to which full optical correction can reverse stereopsis deficits in young children during the critical period of visual development is not well documented locally. Therefore, evidence-based evaluation of stereopsis improvement following refractive correction is needed to guide early screening and intervention strategies. This study aims to provide valuable insights into the role of timely visual correction in preventing amblyopia, enhancing binocular function, and mitigating the long-term risk of visual disabilities, particularly in the face of modern digital lifestyles, by focusing on the effects of full refractive correction on stereopsis in children with moderate-to-high astigmatism.

## METHODS

This cross-sectional study was conducted on 273 children aged 4–8 years who attended the tertiary pediatric ophthalmology clinic. Ethical approval was obtained from the institutional review board, KRL Hospital, Islamabad (Ref. No. KRL-HI-PUB-ERC/March 23/24), and written informed consent was secured from the parents or guardians of all participants. The study lasted for one year from April 2023 to March 2024. The sample size was estimated using the single proportion formula, based on a presumed prevalence of 14.9%, with a 95% confidence level and a 5% margin of error [9]. This yielded a minimum required sample size of approximately 195 participants. However, it is important to note that this calculation did not account for the design effect (DE), which could be introduced due to factors such as clustering or sampling complexities. To address this, we applied a design effect of 1.5, resulting in an adjusted sample size of 271 children. This adjustment ensures that the sample size is adequate to account for potential bias and variability in the study's design. Consecutive non-probability sampling was applied for participant selection. Children aged 4–8 years with moderate-to-high astigmatism, ≥1.50 D cylinder in at least one eye, who could reliably complete ETDRS visual acuity and vectograph stereopsis testing were included. Exclusion criteria were manifest strabismus, other ocular or systemic diseases affecting vision, history of ocular surgery, severe amblyopia, ongoing occlusion/orthoptic therapy, developmental delay, or incomplete clinical data. Children were referred from the pediatric department with complaints of headaches, after thorough evaluation and exclusion of other medical causes by the pediatrician. Each child subsequently underwent a comprehensive ophthalmic examination. Best-corrected visual acuity (BCVA) was measured with standard ETDRS logMAR charts. Refractive error (spherical and cylindrical) was determined by cycloplegic refraction and refined by subjective methods. Stereoacuity was tested binocularly using vectographic stereograms (Vectograph circles) with appropriate polarizing glasses, yielding results in seconds of arc. History of ocular symptoms, blurring, excessive blinking, family ocular history, daily screen time, and outdoor activity were recorded via the questionnaire. Uncorrected and corrected stereoacuity were both measured. Anisometropia was defined as ≥1.00 D interocular difference in spherical equivalent or cylinder. Data were analyzed using descriptive statistics (mean±SD), Spearman rank correlation for refractive error vs. uncorrected stereo, and the Wilcoxon signed-rank test to compare uncorrected vs. corrected stereopsis (since stereo values are non-normally distributed). A p-value <0.050 was considered significant.

## RESULTS

The current study participants (n=273) had a mean age of 5.95 ± 1.26 years, born predominantly at term with normal birth weights. Average daily screen exposure was high (4.94±1.92 hours), and the mean outdoor activity time was less than the recommended time (35.1±21.3 minutes). Common visual symptoms were noted: 82.4% reported frequent blinking, and 81.0% had blurring of vision, symptoms consistent with digital eyestrain. Anisometropia was prevalent in 89.0% of children (CI=1.0727, 1.1471), whereas only 11.0% had essentially equal refraction isoametropia. Astigmatism was most often mixed type (56.4%), followed by compound hyperopic (17.2%) and simple myopic (13.9%) patterns (Table 1).

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**Table 1:** Frequency Distribution of Ocular Symptoms, Family History, and Refractive Characteristics (N=273)

| Variables | Category | Frequency (%) |
|---|---|---|
| Unhabitual blinking | Yes | 225 (82.4) |
| | No | 48 (17.6) |
| Blurring of vision | Yes | 221 (81.0) |
| | No | 52 (19.0) |
| Family history of ocular disease | Yes | 71 (26.0) |
| | No | 202 (74.0) |
| Refractive type | Anisometropia | 243 (89.0) |
| | Isoametropia | 30 (11.0) |
| Type of astigmatism (right eye) | SMA | 38 (13.9) |
| | CMA | 25 (9.2) |
| | SHA | 9 (3.3) |
| | CHA | 47 (17.2) |
| | MA | 154 (56.4) |

Refractive errors revealed significant astigmatism: mean cylindrical error was -2.88±1.00 D (RE) and -2.89±0.99 D (LE), with spherical equivalent hyperopia around +1.7 D in each eye. Visual acuity improved markedly with correction. The mean uncorrected logMAR VA was 0.65±0.14 (approx. 20/90), improving to 0.24±0.12 (20/35) with glasses. This confirms a clinically meaningful gain in clarity after refraction. Screen exposure averaged 4.91 ± 1.45 hours per day, with some children reporting up to 13 hours of daily use. Outdoor activity time was relatively low, with a mean of only 35.1 ± 21.3 minutes per day. Depth perception, measured as stereopsis, showed marked improvement after correction. The median uncorrected stereopsis was 120 ± 40 (IQR: 80-120) arc seconds, which improved to 60 ± 30 (IQR range 50 to 80) arc seconds following optical correction. This highlights the positive effect of refractive correction on binocular visual function (Table 2).

**Table 2:** Descriptive Statistics of Demographic, Clinical, and Visual Parameters (N = 273)

| Variables | Minimum | Maximum | Mean/Median ± SD/IQR) |
|---|---|---|---|
| Age (years) | 4.0 | 8.0 | 5.95 ± 1.26 |
| Birth weight (kg) | 2.0 | 4.5 | 3.04 ± 0.36 |
| Gestational period (weeks) | 34.0 | 42.0 | 37.83 ± 1.36 |
| Visual acuity RE uncorrected (logMAR) | 0.30 | 1.20 | 0.65 ± 0.14 |
| Visual acuity RE corrected (logMAR) | 0.00 | 0.46 | 0.24 ± 0.12 |
| Spherical error RE (D) | -4.25 | 6.00 | 1.71 ± 1.70 |
| Wet cylinder RE (D) | 1.50 | 6.50 | 2.88 ± 1.0 |
| Spherical error LE (D) | -4.75 | 6.50 | 1.72 ± 1.67 |
| Cylindrical error LE (D) | -6.00 | -1.50 | -2.89 ± 0.99 |
| Screen time exposure (hours/day) | 2.5 | 13.0 | 4.91 ± 1.45 |
| Outdoor activity (minutes/day) | 15.0 | 120.0 | 35.15 ± 21.26 |
| Stereopsis uncorrected (arc sec) | 40 | 800 | 120 ± 40 (IQR: 80-120) |
| Stereopsis corrected (arc sec) | 40 | 400 | 60 ± 30 (IQR range 50 to 80) |

In statistical terms, the Wilcoxon test showed a highly significant improvement in stereopsis post-correction (Z=–14.031, <0.001). Out of 273 children, 258 (94.5%) had better stereoacuity with glasses, 14 (5.1%) were unchanged, and only 1 child (0.4%) had slightly worse measured stereo with correction (Table 3).

**Table 3:** Wilcoxon Signed-Rank Test for Stereopsis Before and After Optical Correction (N=273)

| Comparison | Frequency (%) | p-Value | Confidence Interval |
|---|---|---|---|
| Improved stereopsis (Corrected < Uncorrected) | 258 (94.5%) | <0.001 | CI= 15.9-276.9 |
| No change (Ties) | 14 (5.1%) | – | – |
| Worsened stereopsis (Corrected > Uncorrected) | 1 (0.4%) | – | – |

Z=–14.031, p<0.001

Spearman correlation confirmed a moderate positive relationship between cylindrical magnitude and baseline stereo threshold (ρ=0.465, p<0.001). The effect size for the Spearman's rho correlation of 0.465 is 0.216, indicating that 21.6% of the variance in stereopsis uncorrected can be explained by the Wet Cylinder. This represents a moderate effect size. In other words, higher uncorrected astigmatism was associated with poorer depth perception before correction. This echoes prior evidence that all forms of refractive error introduce blur that degrades stereoacuity, and that anisometropia/aniseikonia further exacerbate binocular fusion difficulties (Table 4).

**Table 4:** Correlation Between Wet Cylinder and Uncorrected Stereopsis (Spearman's Rho)

| Variables | Wet Cylinder | Stereopsis Uncorrected | Confidence Interval |
|---|---|---|---|
| Wet Cylinder RE | 1.000 | 0.465** | CI=(0.346-0.584) |
| Stereopsis Uncorrected | 0.465** | 1.000 | - |
| p-Value (2-tailed) | — | <0.001 | - |
| N | 273 | 273 | - |

## DISCUSSION

The findings of the current study revealed that optical correction produces substantial gains in binocular function in astigmatic children. The high prevalence of astigmatism and anisometropia in this symptomatic cohort, 89% anisometropia, mostly mixed or hyperopic astigmatism, reflects recent trends linking near-focused lifestyles to refractive anomalies [9]. For example, large cohort studies have reported that early and prolonged screen time exposure significantly raises astigmatism risk, and global data now show a post-pandemic surge in astigmatism among children [10, 11]. In our patients, average daily screen time was well above recommended limits, which likely contributed to visual strain, evidenced by high rates of blinking and blur. A study showed similar

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findings that blurred vision and eyestrain are hallmark symptoms of digital eye strain, which increases dramatically in schoolchildren exposed to prolonged screen hours [12]. The current study demonstrated that all children experienced an improvement in stereo acuity after refraction. This aligns with studies showing that providing clear retinal images restores the cues needed for depth perception [13, 14]. It also extends findings from other pediatric studies: for instance, Xiao et al. identified greater astigmatism and anisometropia as independent risk factors for subnormal stereoacuity [8]. The correlation analysis mirrors this, confirming that children with higher magnitude uncorrected cylindrical prescriptions had worse baseline stereo. The dramatic improvement we observed implies that these children had adequate neural plasticity to benefit from correction. Similar findings were shown in studies that highlighted that early intervention can recapture binocular function [15, 16]. The current study highlighted that mixed astigmatism is the common refractive error, followed by hyperopic astigmatism. Mixed astigmatism blurs images along one meridian more than the other, which can induce meridional amblyopia if uncorrected [17, 8]. Although we did not specifically measure amblyopia, the large improvements in visual acuity and stereopsis suggested that even mild binocular suppression was alleviated by symmetric correction. Our results underscore the importance of early refractive screening. Since stereopsis matures in early childhood, prolonged uncorrected blur can have lasting developmental consequences. Given that anisometropia and astigmatism compromise stereopsis, as our data and others showed, routine pediatric eye exams should include stereopsis testing and refraction [19, 20]. Lastly, the limited outdoor time meant 35 minutes/day in our patients was concerning, as lack of sunlight was a known myopia risk factor and may indirectly promote near work [21]. Encouraging outdoor activity and limiting screens could help curb the epidemic of pediatric refractive errors seen globally.

This study has certain limitations, including its cross-sectional design, which precludes causal inference between screen exposure and astigmatism-related stereopsis changes. The use of consecutive non-probability sampling from a single tertiary center may also limit the generalizability of the findings. Additionally, screen time and outdoor activity data were parent-reported and may be subject to recall bias. Future longitudinal and interventional studies are recommended to evaluate long-term stereopsis outcomes after correction and to investigate whether reducing screen time and increasing outdoor exposure can prevent or mitigate astigmatism-related binocular dysfunction in children.

## CONCLUSIONS

In conclusion, 4–8-year-old children with significant astigmatism and screen exposure, full spectacle correction produced robust improvement in both visual acuity and stereoacuity. Nearly all patients achieved better depth perception once astigmatic blur was removed. These findings highlight that uncorrected astigmatism is a major impediment to binocular vision, but one that can be largely reversed with timely refractive correction. They reinforce current recommendations for early visual screening in children, especially those with prolonged digital device use, to prevent straining symptoms and preserve stereo function. Future longitudinal studies should explore whether reducing screen time and increasing outdoor play can lessen the development of high astigmatism and its stereopsis consequences.

## Authors' Contribution

Conceptualization: AK, NA
Methodology: SAK, MS, AK, MQ
Formal analysis: MS, AV, NA
Writing and Drafting: SAK, MS, AK, AV, MQ, NA
Review and Editing: SAK, MS, AK, AV, MQ, NA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Radiological and Functional Outcomes of External Fixation in Osteoporotic Proximal Humerus Fractures at a Tertiary Care Hospital

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## ABSTRACT

Treatment of humeral shaft fractures typically involves conservative methods or surgical options like plating and intramedullary nailing, each with limitations. External fixation, allowing for adjustable reduction and early mobilization, has emerged as a promising alternative. **Objectives:** To assess external fixators' functional and radiological outcomes in patients with humeral shaft fractures at a tertiary care hospital. **Methods:** This quasi-experimental study included 60 patients meeting the inclusion criteria enrolled from the Department of Orthopedic Surgery, Ghurki Hospital, Lahore. External fixators were applied under fluoroscopic guidance, with two half-pins inserted proximally and distally to stabilize the fracture. Patients were followed up at 4, 6, and 12 weeks post-surgery, with functional outcomes evaluated at 12 weeks using the University of California, Los Angeles (UCLA) rating scale. **Results:** The patient cohort was predominantly male (83.3%), with a mean age of 40.25 ± 11.54 years. The mean duration of fracture before treatment was 4.4 ± 2.38 days. Fractures were nearly evenly distributed between the left (48.3%) and right (51.7%) sides. Road traffic accidents were the primary cause of injury (66.7%). The mean UCLA score at 12 weeks was 30.30 ± 3.32, with 52 patients (86.7%) achieving satisfactory outcomes and 8 (13.3%) experiencing unsatisfactory results. The patients reached radiological union at an average of 10.5 ± 1.9 weeks. **Conclusions:** The results of our study demonstrate that external fixation is a feasible option for treating proximal humerus fractures, improving both functional and radiological outcomes. While reducing surgical difficulties, the suggested method increases fixation stability.

## INTRODUCTION

Humeral shaft fractures commonly appear as trauma cases at services where they occur at a rate of 13 per 100000 per year. The frequency of these fractures shows a double peak pattern based on gender and age groups, where male patients between 20 and 30 years old experience the first peak, while female patients between 60 and 70 years old experience the second peak [1, 2]. The aging population may substantially increase incidence projections for the upcoming years, affecting healthcare delivery significantly. Future trauma management will increasingly focus on these fractures because adequate knowledge of research evidence and gaps will help improve patient outcomes. The accepted treatment standard remains conservative management. The high morbidity rates, together with surgery-related complications and reduced acceptance among patients and surgeons regarding treatment outcomes, have increased the surgical indications for these fractures [3]. Research

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confirms that plate and screw fixation with open reduction and minimally invasive procedures, along with intramedullary nails and external fixation achieve successful consolidation rates according to the literature. [4-6] The literature already provides information about intramedullary fixation for humeral diaphyseal fractures, compression plating, and external fixation for open fractures. Current opinion does not agree on the best method to repair proximal humerus fractures. Our recent experience with external fixation devices enabled research into how the fixators delivered similar outcomes as traditional invasive procedures while providing fast recovery times and minimal surgical invasiveness [7]. Egyptian research reported satisfactory outcomes in 83 % of cases (UCLA score more than 27), with 17 % of patients demonstrating unsatisfactory results [8]. Treatment of humeral shaft fractures is usually done by conservative methods or surgery, like plating and intramedullary nailing, each with drawbacks like infection or prolonged immobilization. External fixator, with adjustable reduction and early mobilization, has been a promising new alternative, especially for osteoporotic proximal humerus fractures where bone quality makes fixation stability difficult. Nonetheless, limited local data are available regarding the effectiveness of external fixation in osteoporotic patients. Thus, there is a lack of knowledge about its functional and radiological results in such populations.

Although multiple surgical options exist for proximal humerus fractures, optimal management in osteoporotic patients remains controversial due to poor bone quality and fixation instability. Most comparative literature focuses on plating or intramedullary nailing, while external fixation is primarily discussed in the context of open fractures or temporary stabilization. Limited local data are available evaluating external fixation as a definitive treatment modality in osteoporotic proximal humerus fractures, particularly regarding functional recovery and radiological union. This lack of region-specific evidence highlights the need to systematically assess its clinical effectiveness. This study aimed to assess the radiological (union time) and functional (UCLA score) outcomes of external fixation in patients with osteoporotic proximal humerus fractures at a tertiary care hospital.

## METHODS

This quasi-experimental study was conducted in the Department of Orthopedic Surgery at Ghurki Trust Teaching Hospital, Lahore, after taking ethical approval from the Hospital Ethical Committee (Ref. No. 2022/10/R-15). The study spanned from March 2023 to September 2023. A total of 60 patients were included in the study, with the sample size calculated based on an anticipated frequency of satisfactory functional outcomes (P=83%), a 95% confidence interval, and a 10% margin of error using formula $n = z^2 \cdot p \cdot (1-p) / E^2$ [8]. A non-probability consecutive sampling technique was employed for patient selection Patients aged ≥50 years, both genders, with osteoporotic proximal humerus fractures (diagnosed via DEXA scan), presenting within 15 days of injury were included Patients were excluded if they had a history of previous humeral shaft fractures, neurovascular compromise, or prior maltreatment by bone setters, as reported by the patient and confirmed through clinical records. Patients with healthy bone (non-osteoporotic bone) or those unwilling to provide consent were also excluded from the study. The demographic details, including age, gender, residential status, side-affected comorbid status, etiology as well as the determinants of BMI, were recorded on the enrolment of the individual patients. Relevant functional and radiologic outcome components were regularly assessed and recorded on a preformed data collection proforma. Baseline investigations were performed before proceeding with the external fixator application, which was conducted under fluoroscopic control. The procedure involved inserting two half-pins proximally and distally. The pins are placed so that the ones near the fractures are at least 2cm away from the fracture line and the farther pins are placed as far as possible; ensuring appropriate spacing between the pin and the nail. The distal half-pin cluster was positioned precisely to minimize the risk of ulnar nerve injury, utilizing fluoroscopic guidance to maintain alignment and achieve optimal fixation. This study used two external fixators: the unilateral external fixator, including the limb reconstruction system and dynamic axial fixator (LRS and DAF), and the modified Ilizarov fixator. The unilateral fixator was preferred for obese and female patients to avoid discomfort due to the chest wall and breast abutment. The rest of the patients underwent modified Ilizarov fixation. The modified Ilizarov fixator was composed of half-rings divided into quarters assembled into proximal and distal blocks. Postoperative compression commenced 3 to 5 days after surgery at a rate of 0.25 mm twice weekly until early radiological signs of healing were visible. Patients were followed up at 4, 6, and 12 weeks postoperatively, with the outcome assessment conducted at 12 weeks based on functional outcomes and radiological outcomes categorized as satisfactory or unsatisfactory, and radiological outcomes in terms of union time. Functional Outcome was evaluated using the University of California, Los Angeles (UCLA) rating scale, which assesses pain, function, motion, and strength (maximum score: 35). The scoring system evaluates multiple aspects of patient outcomes. Pain is rated as 10 for no pain, 6 for pain during heavy activity, and 2 for constant but tolerable pain.

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Function is assessed with 10 points for normal activities, 6 for performing housework and driving, and 2 for being able to complete only light tasks. Flexion receives 5 points for a range of motion of 150° or more, 3 points for 90°–120°, and 0 points for 30° or less. Strength is scored as 5 for normal muscle power (Grade 5), 3 for fair strength (Grade 3), and 0 for no contraction (Grade 0). Patient satisfaction contributes 5 points if the patient feels improved, and 0 if dissatisfied or worsened. When these scores are totaled, a score below 21 is considered poor, 22 to 27 is fair, 28 to 33 is good, and 34 to 35 is excellent. Scores of 27 and above are classified as satisfactory, while those below 27 are considered unsatisfactory. Radiological Outcome is Defined as the time to achieve union, confirmed by radiographic evidence of bridging callus across at least three cortices on anteroposterior and lateral views. All collected data were entered and analyzed using SPSS version 27. Mean and standard deviation were calculated for continuous variables such as age, body mass index (BMI), and fracture duration. Frequencies and percentages were determined for categorical variables, including gender, age groups, affected arm side (left or right), residential status, etiology, presence of diabetes, hypertension, obesity, and functional outcome classification (satisfactory vs. unsatisfactory). Effect modifiers such as age, BMI, diabetes, hypertension, etiology, side of arm involvement, fracture duration, residential status, and gender were controlled by creating stratified tables. A post-stratification chi-square test with a p-value of ≤ 0.050 is statistically significant.

## RESULTS

The study analyzed the demographic and clinical characteristics of 60 patients who underwent external fixator treatment for proximal humerus fractures. Most patients were male (83.3%), with a mean age of 62.60. Most fractures were treated within an average of 4.4 days from injury. A slight majority of the patients were from rural areas (55.0%), and the distribution of fracture sides was nearly equal between the left (48.3%) and right (51.7%) humerus. Road traffic accidents were the most common cause of injury (66.7%), followed by falls from height and assault (both 16.7%). Regarding health status, 38.3% of patients were obese (BMI ≥ 25), while 23.3% had diabetes and 18.3% had hypertension. Functional outcomes were assessed using the UCLA score, with a mean of 30.33, and radiological union was achieved on average at 10.5 weeks (Table 1).

**Table 1:** Characteristics of Humerus Shaft Fracture Patients Who Underwent External Fixator(N=60)

| Variables | Mean ± SD / Frequency (%) | Min | Max |
|---|---|---|---|
| Gender | Male: 50 (83.3%) | – | – |
| | Female: 10 (16.7%) | – | – |
| Age (years) | 62.6 ± 11.54 | 50.0 | 75.0 |
| Fracture Duration (days) | 4.40 ± 2.38 | 1.00 | 8.00 |
| Residence | Rural: 33 (55.0%) | – | – |
| | Urban: 27 (45.0%) | – | – |
| Side Affected | Left: 29 (48.3%) | – | – |
| | Right: 31 (51.7%) | – | – |
| Etiology | Fall: 10 (16.7%) | – | – |
| | Assault: 10 (16.7%) | – | – |
| | Road Traffic Accident: 40 (66.7%) | – | – |
| Obesity | Yes: 23 (38.3%) | – | – |
| | No: 37 (61.7%) | – | – |
| Diabetes | Yes: 14 (23.3%) | – | – |
| | No: 46 (76.7%) | – | – |
| Hypertension | Yes: 11 (18.3%) | – | – |
| | No: 49 (81.7%) | – | – |
| Height (cm) | 169.37 ± 11.43 | 150.0 | 190.0 |
| Weight (kg) | 81.38 ± 19.87 | 43.0 | 119.0 |
| BMI | 29.07 ± 9.37 | 13.15 | 49.35 |
| UCLA Score | 30.33 ± 3.32 | 21 | 35 |
| Union (weeks) | 10.5 ± 6.2 | – | – |

Results showed that 52(86.7%) cases were observed to have satisfactory outcomes, while unsatisfactory outcomes were found in 8(13.3%) cases (Figure 1).

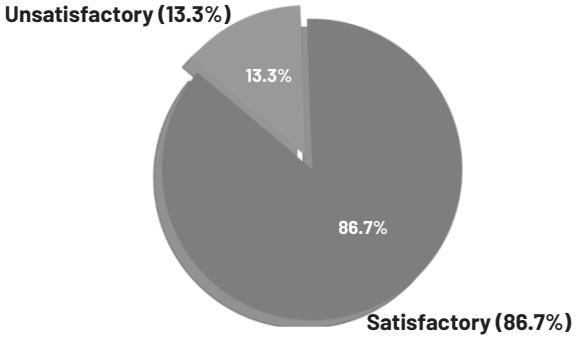


**Figure 1:** Functional Outcome of Patients

When stratifying functional outcomes, 86.7% of patients had satisfactory results, while 13.3% had unsatisfactory outcomes. Gender, age, side of injury, residence, etiology, and obesity were not significantly associated with functional outcomes. However, diabetes and hypertension showed statistically significant associations with poorer outcomes. Half of the patients with diabetes and 37.5% of those with hypertension had unsatisfactory results (p=0.030 and p=0.040, respectively). Additionally, patients with a lower BMI (<25 kg/m$^2$) were more likely to have unsatisfactory outcomes compared to those with a higher BMI (p=0.025) (Table 2).

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**Table 2:** Stratification of Functional Outcomes Among Patients Based on Various Factors

| Variables | Satisfactory (N=52) | Unsatisfactory (N=8) | p-Value |
|---|---|---|---|
| **Gender** | | | |
| Male | 45 (86.5%) | 5 (62.5%) | 0.120 |
| Female | 7 (13.5%) | 3 (37.5%) | |
| **Age (years)** | | | |
| 50–65 | 26 (50.0%) | 3 (37.5%) | 0.708 |
| 66–70 | 26 (50.0%) | 5 (62.5%) | |
| **Side** | | | |
| Left | 24 (46.2%) | 5 (62.5%) | 0.465 |
| Right | 28 (53.8%) | 3 (37.5%) | |

## DISCUSSION

External fixation has a role in treating humeral shaft fractures, even though it is seldom advised due to the danger of deep infection. In the context of war or polytrauma patients, it is becoming more commonly used for short-term stabilization [9]. External fixation may also be necessary in cases of severe soft tissue injuries, serious exposed bone fractures (Gustilo type II-III), unstable elbow joint following bony fixation, vascular injuries that require immediate stabilization before repair, and severe soft tissue injuries (Tscherne grade II-III) [10, 11]. In addition, it is a physiologically "friendly" treatment that maximizes the clearance of the fracture hematoma and reduces the risk of developing pseudoarthrosis. Moreover, it helps expeditiously stabilize a fracture in polytrauma patients, for whom prioritizing other therapeutic and diagnostic treatments (e.g., treating head injuries and abdominal trauma) is necessary. In our study, the mean UCLA score was 30.30 ± 3.32, showing that 52 (86.7%) cases were observed with satisfactory outcome, while the unsatisfactory outcome was found in 8 (13.3%) cases. An Egyptian study has documented 83% satisfactory outcomes (UCLA score more than 27), while 17% of patients were observed with unsatisfactory functional outcomes [8]. Due to the greater mobility at the fracture site, patients who already have stiffness in their shoulders or elbows are more prone to develop delayed nonunion [12]. This emphasizes how crucial it is to have a solid fixation to restore joint range of motion as quickly as possible with postoperative physical therapy. The status of the soft tissues before treatment determines the level of functional success; excellent bone union, alignment, and length results do not guarantee high functional success. Elbow and shoulder pain were the leading causes of the dismal results, regardless of the bone results. This finding should not preclude attempts at bone restoration; however, it should be discussed with the patient during preoperative counseling. A retrospective study of 84 instances of diaphyseal humeral fractures treated with external fixation was conducted [13]. Radial nerve palsy complicated six of these fractures. Excellent shoulder function was noted in 54.6% of the cases, good outcomes in 25%, fair results in 13.6%, and poor results in 6.8%. Per the Mayo Elbow Performance Index, the elbow function was deemed outstanding in 81.8% of instances, good in 13.6%, fair in 2.3%, and poor in 2.3% of cases. According to the case series, external fixation of humeral diaphyseal fractures offers a management option that enables simple fracture reduction and sufficient stability, with a brief surgical period, a high consolidation rate, and good functional outcomes without significant postoperative complications. The most significant findings documented in the literature are equal to the satisfactory functional outcomes of 79.6% and 95.3% of this cohort of humeral shaft cases, regarding the elbow and shoulder joints, respectively, and the documented consolidation of 100% of these instances [14-18]. Another study reported a mean time to achieve union of 14.5 ± 2.4 weeks, significantly longer than the union time observed in our study. In contrast, our findings align more closely with those of Dheenadhayalan *et al.*, who reported a mean union time of 14 ± 2 weeks in a cohort of 127 patients [19, 20]. Alternative fixation approaches allow for a more comprehensive evaluation when used for comparison. Previous researchers conducted a meta-analysis to evaluate the functional results between intramedullary nailing and compression plating methods for humeral shaft fractures and discovered no substantial differences in outcomes [8]. The researchers omitted external fixation from their study, thus demonstrating a lack of direct evidence comparison. Earlier studies found that humeral shaft fracture treatment methods have different non-union and infection rates, while external fixation remains primarily used for patients with severe soft tissue injuries [5]. Results from our study demonstrate a satisfactory outcome rate, which supports the wider application of external fixation in clinical practice. Previous studies reported that external fixation treatment for severe open humeral fractures, which provided stable results combined with minimal adverse effects, similar to our patient population affected mainly by road traffic accidents (66.7%) [11]. Previous studies examined surgical interventions for humeral shaft fractures while documenting high bone consolidation rates across the treatment methods. Our investigation still contains various shortcomings despite achieving positive outcomes. The small sample of 60 patients hinders the widespread applicability of our results because of the diverse group characteristics and different types of fractures involved. The 12-week follow-up duration might not reveal extended outcomes from the delayed union or persistent pain, which influence the recovery of

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functionality. Our ability to evaluate external fixation effectiveness against plating or intramedullary nailing is restricted because we lack direct method comparisons. Future research requires a clear direction based on these findings. Extended multicenter research focusing on external fixation treatment of humeral shaft fractures must be conducted to validate its long-term effectiveness. This study is limited by its single-center, quasi-experimental design and relatively small sample size, which may restrict generalizability. The absence of a comparative control group (e.g., plating or intramedullary nailing) limits direct evaluation of relative effectiveness. Additionally, the short 12-week follow-up period may not fully capture long-term functional outcomes, delayed union, or complications. Future multicenter randomized controlled trials with larger cohorts and extended follow-up are recommended to validate long-term outcomes and establish standardized treatment protocols for osteoporotic proximal humerus fractures.

## CONCLUSIONS

External fixation for osteoporotic proximal humerus fractures yields high rates of functional recovery (86.7% satisfactory UCLA scores) and radiological union (96.7% by 12 weeks), offering a stable and minimally invasive treatment option. So external fixation is an excellent fixation technique for osteoporotic proximal humerus fractures to improve functional and radiological outcomes.

## Authors' Contribution

Conceptualization: KS
Methodology: ZD, ZN, SS, ZK
Formal analysis: MI, SS
Writing and Drafting: FUH, WA, A
Review and Editing: FUH, WA, A, MI, SS, ZD, ZN, ZK, KS

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

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**Original Article**

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# Comparison of Biliary Leakage between Laparoscopic Versus Open Surgery of Liver Hydatid Cyst: A Randomized Controlled Trial

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## ABSTRACT

Hydatid cyst disease is challenging to treat, and surgery remains curative in the majority of cases. There has been more working done recently on laparoscopic Hydatid cyst disease surgery and comparing the outcomes with the open method. **Objectives:** To compare the frequency of post-operative outcomes vis. Biliary leakage, post-operative pain, wound infection rate, recurrence of Hydatid cyst disease, and length of hospital stay between open versus laparoscopic surgery in patients with liver Hydatid cyst disease. **Methods:** This randomized controlled trial was conducted in the Surgical Department of Nishtar Hospital, Multan. 84 patients were enrolled and underwent either laparoscopic or open conservative surgery with external drainage. Outcomes between the two groups in terms of biliary leakage, length of stay, pain, wound infection, and recurrence were compared. Statistical analysis was done using SPSS-25.0. **Results:** There was no significant difference present between groups in terms of biliary leakage (p=0.330), biliary leak output (p=0.210), and days till leak resolution (p=0.320). Biliary leaks occurred in 16.7% of cases in the open group. Pain scores were significantly lower in the laparoscopic group as compared to the open group (p=0.001). Wound infections occurred in 19% of cases in the open group and 4.8% cases in the laparoscopic group, and were significantly different (p=0.040). 2.4% cases had recurrences in both groups. **Conclusions:** Biliary leak rates between open and laparoscopic surgery for Hydatid cyst disease are comparable. Open surgery may have greater high-output biliary leaks. Advantages conferred by laparoscopic surgery are shorter length of hospital stay, fewer wound infections, and better pain control.

## INTRODUCTION

Hydatid disease (HD) is a zoonotic disease caused by the Echinococcus species of tapeworm worldwide [1]. It is endemic in different countries such as Central Asia, South America, North Africa, the Mediterranean, Turkey, Australia, and New Zealand. The incidence of Hydatid disease in endemic areas ranges from 1 to 220 per 100,000 populations annually. Because of human migration, surgeons in developed countries are encountering patients with hepatic Hydatid disease more frequently, but may be unfamiliar with the treatment options for this condition [2]. It can affect any part of the body, although the most common 50% to 70% site of occurrence is the right lobe of the liver, and finally cause a hydatid cyst, lower in the Lungs, 10%-15% and 5%- 10% respectively in other organs of the human body [3]. Hydatid liver disease affects all age groups and both sexes equally. Most commonly involved age group is the third and fourth decade of life in endemic areas [4]. Without treatment, the cysts grow in size and eventually cause complications, leading to disability or even death. Only in exceptional circumstances

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can spontaneous healing occur through the parasite's death and calcification [5]. First, in the 1600s, surgical procedure was tried for the treatment of hydatid cyst, and still now it is followed as the gold standard treatment and performed by conventional method [3, 6]. Therefore, the primary treatment option for hydatid cyst was only surgery, such as liver resection, cystectomy, pericystectomy, and deroofing with omentoplasty were practiced throughout the years [7], despite the increased interest in nonsurgical techniques. Because open procedures were reported as significant morbidity, especially in terms of wound infection and other complications [8]. The laparoscopic approach has become increasingly popular, although controversies regarding the role of laparoscopy in the management of hydatid disease have not been resolved to date. Laparoscopic approach has the advantages of smaller incision with better cosmetic results, and recent studies reveal the safety and effectiveness of the laparoscopic approach in hepatic Hydatid cyst. Laparoscopic techniques for drainage and unroofing of Hydatid cyst have been reported in a number of series with encouraging results [9]. Local literature on the optimum management of Hydatid disease is lacking, and no consensus guidelines are available. The result of the current study will help to compare the frequency of biliary leakage, pain, wound infection, recurrence, and hospital stay with open versus laparoscopic surgery in patients with liver Hydatid cyst. This will decrease disease-related morbidity in these patients and improve their quality of life.

Hydatid liver disease remains a significant surgical challenge in endemic regions, with postoperative biliary leakage being one of the most concerning complications. Although laparoscopic surgery is increasingly adopted due to its minimally invasive advantages, its safety in terms of biliary leakage compared to open surgery remains debated. Most available studies are retrospective or observational, with limited randomized controlled trials directly comparing biliary leak rates and related outcomes. Additionally, local evidence from Pakistani tertiary care settings is scarce. Therefore, a randomized comparison was necessary to clarify whether laparoscopic surgery offers comparable safety with improved postoperative recovery. This study aims to compare the frequency of post-operative outcomes vis. Biliary leakage, post-operative pain, wound infection rate, recurrence of hydatid cyst disease, and length of hospital stay between open versus laparoscopic surgery in patients with liver hydatid cyst disease.

## METHODS

This Randomized Controlled Trial (IRCT20240503061640 N3) was conducted at Surgical Unit-I, Nishtar Medical University/Hospital, Multan, from 17th June 2022 to 15th January 2023. Sampling was done using the Random Allocation Software 2.0. Patients were allocated to either group using a computer-generated set of random allocation to group A or B. The group allocation was done in advance and sealed in consecutively numbered opaque envelopes. A sample size of 42 patients in each group was calculated by 5% level of significance with 80% power of the study and by taking the expected percentage of complications = 32% with open surgery (group A) and 08% with the laparoscopic method (group B) [10]. The statistician was blinded in the study analysis, i.e. single single-blinded RCT. Both male and female patients of 18-60 years of age with a Hydatid cyst with a size >3cm were included in this study. Patients with recurrent disease, cysts in liver segment 1 and 7, concomitant cyst in other organs, cysto-biliary communication and patients with ruptured cyst (confirmed from patient record file and any suspected communication was confirmed on CT), Severely anemic patients (Hb levels less than 8 g/dl), pregnant ladies and patients with chronic liver disease (confirmed from patient record file). And Alcoholic abuse (patient's history, alcohol consumption for > 1 year was excluded. The eighty-four patients (84) were enrolled from the Surgical Department of Nishtar Medical University, Multan, after ethical approval (Ref no: 9652) and informed consent of the patients. Baseline demographic data, and comorbid like, hypertension, diabetes, and disease duration, were recorded. Senior Surgeon with five years' post-fellowship experience conducted the laparoscopic or open surgical intervention, with the researcher assisting. The procedures involved cyst aspiration, instillation of scolicidal agent, respiration, cyst content removal, deroofing, and omentoplasty with a drain placement. Standard post-operative care, including analgesics, antibiotics, and albendazole administration, was provided. Diagnosis of hydatid cysts was based on patients' history, physical examination, and confirmed on ultrasound (US) and CT reports. Biliary Leakage was labelled if it was present grossly (brownish yellow) or bilirubin concentration (on lab report) in the drain fluid at least 3 times the serum bilirubin (on lab report) concentration, and detection of biliary leak on abdominal ultrasound after 72 hours of surgery. It was classified as high output or low output based on the fluid in the drain greater than or less than 100ml every 24 hours. Wound infection was assessed clinically, such as redness, swelling, and discharge of pus from the surgical area. It was confirmed on a positive culture report of the wound swab. Pain score zero on the visual pain analogue scale means no pain, and a pain score of 10 means severe pain. After 3 days of procedure, each patient has their pain level based on the visual analog scale (VAS). Early recurrence was assessed based on the presence of signs

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on sonography within one month of surgery, of residual cyst size increasing, or the presence of new cysts in previous or new locations. Patients were categorized into group A (open surgery) and group B (laparoscopic surgery) and followed up for 72 hours' post-surgery for Biliary leakage, hospital stay, wound infection, pain, and early recurrence, and on follow-up visits at 1, 2, and 4 weeks post-surgery. All the information was recorded on a proforma (attached). If any complication occurred, such as biliary leakage, wound infection, or recurrence, patients were promptly treated by the department, and no cost was borne by the patient. Patients were facilitated if the need for an ERCP arose for post-operative biliary leaks. All the data were entered and analyzed using SPSS-25. Mean and standard deviation for the age, duration of disease, and hospital stay were calculated. Frequency and percentages were calculated for categorical variables like gender, biliary leak, pain, wound infection, and recurrence. The frequency of biliary leak, pain, wound infection, and recurrence was compared by the chi-square test. Confounding variables like age, gender, hypertension, diabetes, and duration of disease were controlled by making stratified tables. Chi-square was applied for qualitative variables, and a post-stratification independent sample t-test will be applied for quantitative results. A p-value ≤0.050 was taken as significant.

## RESULTS

Eighty-four patients were enrolled in the study with a mean age of 31.1 ± 7.32 years. There were 33 (39.3%) female and 51 (60.7%) male enrolled. 8 (9.5%) were hypertensive and 5 (6.0%) were diabetic. The mean duration since symptoms were present or diagnosis was established for Hydatid cyst disease was 30.8 ± 16.6 days (Table 1).

**Table 1:** Comparison of the Patients' Demographics Between the Two Groups

| Variables | Open, Mean ± SD / n (%) | Lap, Mean ± SD / n (%) | p-value |
|---|---|---|---|
| Age | 30.8 ± 6.84 | 31.33 ± 7.85 | 0.770 |
| **Duration** | | | |
| Till Treatment | 31.7 ± 16.9 | 29.8 ± 16.5 | 0.600 |
| **Gender** | | | |
| Male | 28 (66.6%) | 23 (54.7%) | 0.260 |
| Female | 14 (33.3%) | 19 (45.2%) | |
| **Diabetes** | | | |
| Yes | 2 (4.76%) | 3 (7.14%) | 0.640 |
| No | 40 (95.2%) | 39 (92.8%) | |
| **Hypertension** | | | |
| Yes | 3 (7.14%) (3) | 5 (11.9%) | 0.450 |
| No | 39 (92.9%) | 37 (88.1%) | |

The mean length of hospital stay was 5.11 ± 4.57 days. 11 (13.1%) cases presented with a biliary leak. The mean biliary drainage in 24 hours was 138.1 ± 114.5. The mean number of days till biliary leak resolved was 9.27 ± 4.92. The mean VAS score 72 hours post-operatively was 5.62 ± 1.64. This decreased to 3.21 ± 1.04 at 1-week follow-up and 1.40 ± 0.69 at 2-week follow-up. 10 (11.9%) patients experienced a wound infection within 72 hours, and 1 (1.2%) presented with a wound infection after 1 week. 2 (2.4%) recurrences were identified at the 4-week follow up and none were identified at the 1 and 2-week follow-up. Differences in both groups were analyzed using a Student's t-test for length of stay, and a significant difference was found (p=0.001). The mean length of stay in the open group was 7.21 ± 5.76 days, while in the laparoscopic group it was 3.43 ± 1.59 days. In the open group, biliary leak was present in 7 (16.7%) patients, and 35 (83.3%) did not leak. In the laparoscopic group, biliary leak was present in 4 (9.5%) patients, and 38 (90.5%) were spared. Chi-square analysis showed no difference with a p-value of 0.330. The group had 80.0 ± 21.6ml per 24 hours. An independent Student's test showed no significant difference in biliary leak output among open and laparoscopic groups, with a p-value of 0.21. It was noted that all the leaks in the laparoscopic group had an output of less than 100ml/24 hours. In the open surgery group, 1 out of 7 leaks was in the range of 100-250ml/24hours, and 2 leaks had an output of greater than 250ml/24hours. Four leaks had an output of less than 100ml/24 hours. The mean VAS score was significantly lower for the laparoscopic group at each follow-up as reflected by the p-value (p=0.001) of the laparoscopic and open group (p=0.020), respectively. Mean VAS pain scores decreased from 5.62 ± 1.64 at 72 hours' post-op to 3.21 ± 1.04 at one week, and 1.40 ± 0.69 at two weeks (Table 2).

**Table 2:** Biliary Leak Outcomes for Open Vs Laparoscopic Group

| Variables | Open, Mean ± SD / n (%) | Lap, Mean ± SD / n (%) | p-value |
|---|---|---|---|
| Biliary Output (ml/24hours) | 171.4 ± 134.4 | 80.0 ± 21.6 | 0.210 |
| **Days** | | | |
| Till the Resolution of the Leak | 10.4 ± 5.94 | 7.25 ± 1.25 | 0.320 |
| **Biliary Leak** | | | |
| Yes | 7 (16.7%) | 4 (9.5%) | 0.330 |
| No | 35 (83.3%) | 38 (90.5%) | |
| **Pain** | | | |
| VAS at 72 Hours | 6.90 ± 1.07 | 4.33 ± 0.95 | 0.001 |
| VAS at 1 Week Follow-Up | 4.02 ± 0.56 | 2.40 ± 0.73 | 0.001 |
| VAS at 2 Week Follow-Up | 1.57 ± 0.85 | 1.24 ± 0.43 | 0.020 |

The mean age of patients with a biliary leak was 33±9.27 years and without a biliary leak was 31.1±7.81 years in the laparoscopic group, and no difference was observed (p=0.66). In the open group, patients had a mean age of 30.5±3.40 years in the biliary leak group vs 30.9 ± 7.37 years in the no leak group, with no difference between the groups (p=0.890). Age did not affect recurrence in the laparoscopic group (p=0.580) and had no effect in the open group

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(p=0.370). VAS score was stratified as higher than or equal to 5 or less than 5, and an independent Student's t-test was used to assess whether there was a difference in the mean age for higher pain scores and for lower pain scores. No difference was found with a p-value of 0.84. Age did not affect wound infections in the laparoscopic group (p=0.300) or in the open group (0.19). The mean duration of symptoms was 40.5±33.3 days for those with a biliary leak and 28.7±14.2 days for those without a biliary leak in the laparoscopic group, and no difference between the groups was observed (p=0.180). In the open group mean duration of symptoms was 26±10.9 days in the biliary leak group, and it was 32.9 ± 17.7 days in the no leak group, with no difference observed (p=0.320). Duration of symptoms did not affect recurrence in the laparoscopic group (0.18) and had no effect in the open group (p=0.500). Chi-square test was used to assess the effect of gender on outcomes. For the laparoscopic group, gender did not affect biliary leak (p=0.840), wound infection (p=0.890), recurrence (p=0.350), or pain scores (p=0.610). For the open group, gender did not affect biliary leak (p=0.240), wound infection (p=0.780), recurrence (p=0.470), and pain score (0.82) (Table 3).

**Table 3:** Outcome of Recurrence and Wound Infection in Both Groups Assessed by Chi-Square Analysis

| Variable SSI | Open | Lap | p-value |
|---|---|---|---|
| SSI at 72 Hours | 8 (19.0%) | 2 (4.8%) | 0.040 |
| SSI at 1 Week | 1 (2.4%) | 0 (0%) | 0.310 |
| Recurrence at 4 Weeks | 1 (2.4%) | 1 (2.4%) | 1.000 |

Length of stay was assessed in terms of wound infection and pain for each group. For patients with a wound infection length of stay was found to be significantly higher than those without an infection in the laparoscopic group (p=0.01) and in the open group (p=0.05). Pain score had a significant effect on length of stay, where patients with pain scores higher than 5 had lengthier stays (p=0.001). There were no recurrences at the 1 and 2 week follow up with 1 recurrence in each group at the 4 week follow up which was analyzed as statistically insignificant. Wound infection rate was lower in the laparoscopic group at 72 hrs. Follow up, i.e, 4.8% (n=2) and none at one week (Table 4).

**Table 4:** Effect of Pain and Wound Infection on Length of Stay

| Variables | | Mean ± SD | p-value |
|---|---|---|---|
| Pain | >/=5 | 6.65 ± 5.39 | 0.001 |
| | <5 | 3.16 ± 1.16 | |
| Wound Infection (Laparoscopic) | Yes | 6.00 ± 4.24 | 0.008 |
| | No | 3.30 ± 1.36 | |
| Wound Infection (Open) | Yes | 10.75 ± 8.94 | 0.010 |
| | No | 6.38 ± 4.53 | |

## DISCUSSION

The postoperative course of laparoscopic Hydatid disease surgery is not fully evaluated, but still, there is an increased tendency of laparoscopic intervention in Hydatid disease of the liver. The literature has mixed data about this notion [11]. Moreover, even though surgery remains the Gold standard for Hydatid disease of the liver but still optimal choice of conventional versus laparoscopic needs to be addressed. Both approaches include removal of cyst contents, avoidance of spillage of contents, sterilization, and obliteration of the cavity [12]. A meta-analysis performed by Sokouti *et al.* depicted the advantages of the minimally invasive puncture, aspiration, injection, and respiration technique in simple, uncomplicated cysts that are accessible [13]. It offers a less invasive, cost-effective, and low-morbidity solution to a complex problem. It is mainly reserved for the surgically unfit patients or in case of contraindications to surgery, which includes biliary communication with a subsequent high recurrence rate [14]. Our study confirms that the laparoscopic approach to Hydatid cyst disease (HCD) surgery is safe and effective, consistent with most literature. Laparoscopy offers significant advantages over open surgery, including fewer wound infections, better post-operative pain control, and shorter hospital stays with similar results to open surgery in terms of biliary leak and recurrence [15]. Though statistically not significant, our data did show that biliary leaks were nearly 7% fewer in the laparoscopic group and resolved in fewer days with lesser output and fewer high-output fistulas than the open surgery group. This may be the first time a study has reported on the difference between biliary outputs between the two groups, keeping in mind high and low output fistulae. Biliary complications, however, were not statistically significant between the two groups and were comparable; thus, both procedures are equally effective and safe in terms of the occurrence of this outcome. Previous studies support our findings, noting that laparoscopic techniques can mitigate biliary leaks. A study used magnification to check for biliary communications in the cystic cavity, and this was hypothesized to decrease the rates of biliary leaks occurring with laparoscopic surgery. The laparoscopic group in our study experienced only minor leaks of ≤100ml/24 hours, unlike the open group, which had some major leaks [16]. Wang *et al.* have commented that leaks may occur and complicate up to 30% of all HCD surgical procedures, thus our leak rates of less than 20% in both open and laparoscopic surgery are acceptable by the established norms in the literature [17]. Masood *et al.* conducted a randomized trial comparing the two techniques in HCD surgery in children. Study had a VAS score of 6.3 in the lap group and 7.16 in the open group post-

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operatively, and this was significant even after 72 hours, where the laparoscopic group had a VAS of 1.3 and the open group had a VAS of 4.26. This was not comparable to our study, where at 72 hours our patients had a pain score of 4.33 in the laparoscopic group and 6.9 in the open group, and this was higher than that experienced in this study cohort but still lower in the laparoscopic group [18]. Biliary complications, though not statistically significant, were fewer and less severe in the laparoscopic group [19]. There is no standard time for biliary leak resolution. Most leaks in our study subsides in one month, with a predilection for early resolution with post-laparoscopic leaks. Abbasi *et al.* in their study found that biliary leakage occurred in higher percentages in the case of radical surgery, like pericystectomy, as compared to endocystectomy [20]. In our study, all patients underwent conservative surgery, and this may be the reason for a slightly lower biliary leak percentage in our cohort of patients. Contrarily, some authors hypothesized that conservative surgery is more likely to result in leaks [21]. In their series, they identified that patients with outputs of greater than 250ml were less likely to spontaneously resolve, and the time till resolution ranged from three weeks to three months. Most of our patients' leaks resolved within a month, the longest requiring 21 days. It is clear from the literature that definitions of minor and major leaks are not consistent across the board, and this leaves gray areas, and outcome reporting is affected [22]. Open surgery may have a higher propensity for post-operative biliary leaks than laparoscopic surgery. But this difference was statistically insignificant in our study. This may simply be due to the advantage of magnification that laparoscopy offers in closing larger biliary communications intra-operatively, resulting in a greater percentage of minor biliary leaks post-operatively that are amenable to conservative treatment [23]. Different studies reiterate the fact that wound infections and length of stay are considerably better in the laparoscopic cohort as compared to open intervention [24]. Hospital stay was shorter in the laparoscopic group at a mean of 6 days; in our cohort, the laparoscopic group had a mean stay of 3.41 days. Zaharie *et al.* did their study a decade earlier than ours, and with enhanced recovery protocols, patients after laparoscopic surgery are discharged in shorter durations than before [5]. On the other hand, Hospital stay was similar between the groups, with only a difference of a mean of 1 day; however, this was not the case in our study, and there were no factors identifiable in their study findings to appreciate why this occurred.

This study was limited by its single-center design and relatively small sample size, which may restrict the generalizability of the findings. The short follow-up duration primarily assessed early recurrence and did not evaluate long-term recurrence or late biliary complications. Furthermore, advanced intraoperative imaging techniques to detect occult cysto-biliary communications were not utilized. Future multicenter randomized trials with larger cohorts and extended follow-up are recommended to assess long-term outcomes, refine patient selection criteria, and establish standardized management guidelines for hepatic hydatid cyst surgery.

## CONCLUSIONS

Biliary leak rates between open and laparoscopic surgery for Hydatid cyst disease are comparable. Open surgery may have greater high-output biliary leaks. Advantages conferred by laparoscopic surgery are shorter length of hospital stay, fewer wound infections, and better pain control.

## Authors' Contribution

Conceptualization: MFA
Methodology: MFA, KN, HA, MHU, KJ, LA
Formal analysis: MFA
Writing and Drafting: MFA, KN
Review and Editing: MFA, KN, HA, MHU, KJ, LA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Systematic Review**

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# Impact of Problem-Based Learning (PBL) on Knowledge Retention and Clinical Reasoning: A Systematic Review

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## ABSTRACT

Problem-Based Learning (PBL) is a learner-centered educational approach widely adopted in health professions education to enhance critical thinking, self-directed learning, and long-term knowledge retention. However, results from individual studies vary, warranting a synthesis of recent evidence. **Objectives:** To evaluate studies published between 2019 and 2024 to determine the impact of PBL on knowledge retention and clinical reasoning among medical, nursing, dental, and allied health students. **Methods:** This systematic review followed PRISMA 2020 guidelines. PubMed, ScienceDirect, ERIC, and Google Scholar were searched (January 2019–December 2024) using MeSH terms and Boolean operators. Eligible studies included quasi-experimental, cross-sectional, survey-based, and observational designs measuring knowledge retention or clinical reasoning. Two reviewers independently screened and extracted data, resolving disagreements by consensus. Due to heterogeneity, a narrative synthesis was performed, summarizing p-values, effect sizes, and confidence intervals. Risk of bias was assessed across six domains. **Results:** Fourteen studies met the inclusion criteria. Most reported significant improvements in knowledge retention ($t(76) = 3.93$, $p=0.00$, $\beta=9.40$, $p=0.03$) and clinical reasoning ($t=-4.599$, $p<0.001$) with PBL compared to lectures. A few studies showed no significant difference, though student preference favored PBL. Performance and reporting biases were low, with some studies showing unclear selection and detection bias. **Conclusions:** PBL consistently improves knowledge retention and clinical reasoning across health professions education. Despite methodological variability, the evidence supports integrating PBL into curricula. Future research should adopt standardized outcome measures and rigorous study designs to strengthen the evidence base.

## INTRODUCTION

Problem-Based Learning (PBL) is an active, student-centered approach that uses real-world clinical problems as a stimulus for learning. It is widely adopted in medical, dental, nursing, and allied health curricula to enhance critical thinking, promote self-directed learning, and improve long-term retention of knowledge [1, 2]. Globally, health professions education is shifting from teacher-centered lectures to learner-centered approaches that foster problem-solving skills and deeper understanding [3]. Evidence suggests that PBL not only improves immediate comprehension but also promotes better long-term knowledge retention and clinical reasoning compared to traditional lecture-based methods. Trullàs *et al.* showed in a comprehensive scoping review that PBL methodology enhances learning and retention of knowledge in undergraduate medical education [4], while Lin *et al.* reported that a lecture PBL clinical sequence produced superior knowledge acquisition [5]. Similarly, Pakhmode *et*

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*al.* found PBL more effective for fostering critical thinking [6], and Towfik *et al.* reported improved clinical reasoning and communication skills in nursing students. These outcomes are critical for preparing graduates to integrate knowledge into clinical decision-making and patient care [7]. However, some studies have reported no significant difference in knowledge retention between PBL and traditional methods, raising questions about its universal benefit [8, 9]. This heterogeneity in study design, participant populations, and outcome measures complicates interpretation and highlights the need for a recent, structured synthesis of the evidence. Given the variability in findings and the absence of a comprehensive review synthesizing studies published after 2019, this review was undertaken to systematically evaluate original research examining the effect of PBL on two primary outcomes: knowledge retention and clinical reasoning among medical, nursing, dental, and allied health students.

Although Problem-Based Learning (PBL) is widely implemented in health professions education, evidence regarding its sustained impact on knowledge retention and clinical reasoning remains heterogeneous. Individual studies report varying outcomes due to differences in study design, participant populations, intervention formats, and assessment tools. Moreover, few recent reviews have synthesized post-2019 evidence across multiple health disciplines to provide an updated and comprehensive evaluation. This gap necessitates a structured synthesis of contemporary research to clarify PBL's effectiveness and guide curriculum development. This study aims to summarize and critically appraise the current evidence to guide curriculum developers and educators in making evidence-informed decisions regarding the adoption and optimization of PBL in health professions education.

## METHODS

This systematic review was conducted in alignment with the PRISMA 2020 guidelines to ensure transparency and reproducibility. A comprehensive search was performed across PubMed, ScienceDirect, ERIC, and Google Scholar, covering publications from January 2019 to December 2024. The search strategy combined MeSH terms and free-text keywords such as "problem-based learning", "PBL", "knowledge retention", "clinical reasoning", "nursing education", and "medical education". Boolean operators (AND, OR) were used to optimize the search results. Manual searches of reference lists and grey literature were also performed to capture additional records. Studies were included if they were original research evaluating PBL interventions, conducted among medical, nursing, dental, or allied health students, measured knowledge retention and/or clinical reasoning, and were published in English between 2019 and 2024. Eligible designs included quasi-experimental, cross-sectional, survey-based, and descriptive observational studies to capture a broad range of PBL interventions, as randomized controlled trials are often limited in educational settings. Studies were excluded if they were systematic reviews, meta-analyses, case reports, editorials, or purely qualitative studies without measurable outcomes. Longitudinal studies assessing only professional practice outcomes without academic performance measures were also excluded. Two independent reviewers screened titles, abstracts, and full texts. Disagreements were resolved through discussion or adjudication by a third reviewer. Data were extracted using a structured proforma that included the following fields: author(s), year of publication, country, study design, sample size, participant characteristics, details of the PBL intervention, comparison groups (if any), outcome measures (knowledge retention, clinical reasoning), statistical tests used, effect sizes or p-values, and main findings. Because of heterogeneity in study designs and outcome measures, no meta-analysis was performed. Instead, a narrative synthesis approach was adopted, summarizing p-values, effect sizes, and confidence intervals where reported. Each included study underwent an independent risk of bias evaluation by two reviewers across six predefined domains. Selection bias was assessed by determining whether participants were recruited using random or clearly defined inclusion criteria and whether baseline equivalence between groups was reported. Performance bias was evaluated by reviewing how consistently the PBL intervention was implemented and whether control or comparison groups received similar teaching resources. Detection bias was judged by examining whether outcome assessors were blinded and whether validated or objective measures were used to evaluate knowledge retention and clinical reasoning. Attrition bias was assessed by reviewing the completeness of follow-up, documentation of dropout rates, and handling of missing data. Reporting bias was checked by comparing reported outcomes with study objectives to ensure selective reporting did not occur. Other potential sources of bias, such as small sample sizes, confounding variables, or inappropriate statistical analysis, were also considered. Ratings for each domain were classified as low, high, or unclear risk, and any discrepancies between reviewers were resolved through discussion and, when necessary, arbitration by a third reviewer. A total of 350 records were initially identified through database searches (PubMed, Science Direct, ERIC, and Google Scholar) and manual reference list screening. After removing 45 duplicates, 305 records remained for title and abstract screening. Of these, 251 were excluded for the following reasons: studies not related to PBL (n=130), not measuring knowledge retention or clinical reasoning outcomes (n=65), duplicate or overlapping data from the same study population (n=25), and conference abstracts or editorials with insufficient data for inclusion (n=31). The remaining 54 full-text articles

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were retrieved and assessed for eligibility. Among these, 40 were excluded for being review articles (n=17), not reporting measurable outcomes (n=10), having inaccessible full texts (n=8), or being published in non-English languages (n=5). Finally, 13 studies met all the inclusion criteria and were included in the qualitative synthesis (Figure 1).

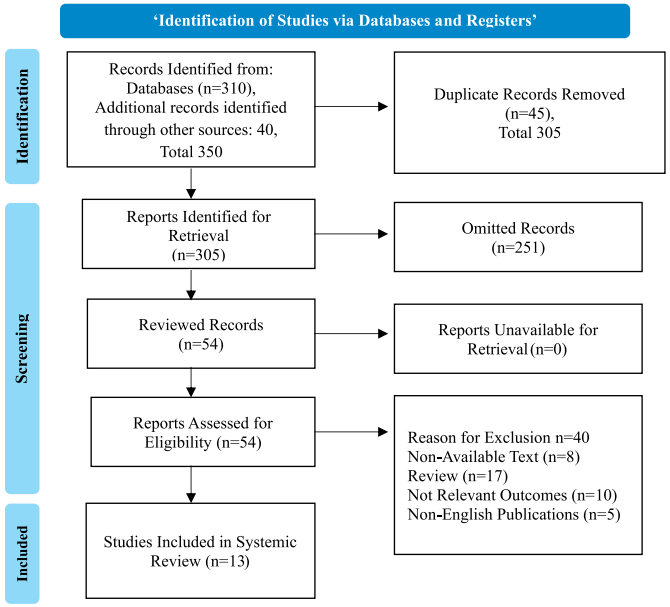


**Figure 1:** Process of Study Identification, Screening, and Inclusion

## RESULTS

A total of 14 original and quasi-experimental studies conducted between 2019 and 2024 were included in the final synthesis. These studies represented diverse geographic regions including Indonesia, Brazil, Nepal, India, Morocco, Kazakhstan, South Korea, Taiwan, Egypt, Pakistan, and the UK, and spanned disciplines such as medical, nursing, and dental education. 10 studies reported statistically significant improvements in knowledge retention with PBL compared to traditional lecture-based learning. Amin *et al.* reported higher 7-day post-test knowledge scores in the PBL group (mean 24.28 vs 19.36; t (48) = 2.71, p=0.050) [10], while Lin *et al.* showed that a lecture-PBL-clinical sequence produced greater knowledge retention (β=9.40, p=0.030)[5]. Pakhmode *et al.* observed that although team-based learning achieved higher immediate knowledge gain (p<0.001) [6], PBL was superior for promoting critical thinking (p<0.001). Eight studies reported enhanced clinical reasoning, communication, or decision-making skills with PBL. Yang *et al.* [11] observed significant gains in clinical reasoning (t=-4.599, p<0.001) and communication skills (t=-1.848, p=0.033)among nursing students in the PBL group. Survey-based studies reported improved questioning ability, confidence, and cognitive engagement, even when no formal statistical testing was applied [12, 13]. Three studies, including Yadav *et al.* found no statistically significant difference in knowledge retention between PBL and traditional lectures [14], but students strongly preferred PBL or hybrid approaches due to higher engagement and satisfaction. Overall, the narrative synthesis indicates that PBL consistently improves knowledge retention and clinical reasoning across multiple health professions education contexts, though variability exists in study design and assessment methods (Table 1).

**Table 1:** Included Studies on the Impact of PBL (2019–2024)

| Sr. No. | References | Country | Discipline | Sample Size | Study Design | Key Outcome/Finding | Statistical Result |
|---|---|---|---|---|---|---|---|
| 1 | [5] | Egypt | Medical Education | 56 | Quasi-experimental | The lecture-PBL-clinical sequence produced better retention | β=9.40, p=0.030 |
| 2 | [10] | India | Nursing | 50 | Quasi-experimental (parallel groups, post-test at 7 days) | PBL produced higher knowledge scores/short-term retention vs lecture | t (48)=2.71, p=0.050; Mean (PBL)=24.28 vs 19.36 |
| 3 | [12] | Brazil | Medical Education | 21 | Comparative Descriptive | PBL promoted exploratory questioning and deeper interaction | Qualitative ↑ in exploratory questions |
| 4 | [13] | South Korea | Nursing | Not stated | Survey-based | Improved critical thinking and reasoning in the embryology course | Likert feedback only |
| 5 | [14] | India | Dental Education | 107 | Cross-sectional | Equal retention scores, but students preferred the hybrid model | Median PBL=17, Lecture=16 |
| 6 | [15] | Nepal | Medical Education | 374 | Cross-sectional | Positive student perceptions of PBL sessions | Cronbach's α=0.92 |
| 7 | [16] | Morocco | Dental Education | 18 | Qualitative | PBL improved reasoning and skill development | Thematic coding (no p-value) |
| 8 | [17] | Kazakhstan | Dental Education | 91 | Survey-based | High student satisfaction with PBL | Mean score 3.4/4 |
| 9 | [18] | Pakistan | Medical Education | Not stated | Survey-based | Tutor facilitation improved engagement in PBL groups | Descriptive (no test stats) |

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| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 10 | [19] | Taiwan | Nursing | Not stated | Experimental (Pre-Post) | The PBL group scored higher in diabetes knowledge and reasoning | p<0.050 |
| 11 | [20] | India | Nursing | 156 | Quasi-experimental | Higher clinical reasoning and communication skills with PBL | t=-4.599, p<0.001; t=-1.848, p=0.033 |
| 12 | [21] | Nepal | Nursing | Not reported | Quasi-experimental (Pre-Post) | Improved self-directed learning and reasoning post-intervention | All skills improved (no p-values) |
| 13 | [22] | UK | Medical Education | Not specified | Descriptive Observational | PBL promoted knowledge and skill development | Mean score 3.4/4 |

Most included studies demonstrated a low risk of bias in performance and reporting domains, indicating that PBL interventions were implemented consistently and outcomes were transparently reported. Selection bias was generally low in controlled or quasi-experimental studies such as Amin *et al.* [10], Nasim *et al.* [19], Lin *et al.* [5] and Pakhmode *et al.* [6], where participant recruitment and group comparability were clearly described. In contrast, survey-based and qualitative studies, including Nerali and Chakravarthy [16], Elhijazi and Benyahya [17], Khamchiyev *et al.* [18], and Ittycheria *et al.* [22] had unclear selection bias due to a lack of randomization or baseline equivalence reporting. Detection bias was also frequently unclear in perception-based studies such as Carroll and Tomova [13] and Nerali and Chakravarthy [16], where self-reported outcomes were not validated with objective assessments. Studies using standardized measures like Yadav *et al.* [14], Nasim *et al.* [19], and Lee and Son [20] were judged low risk for detection bias. Attrition bias was low for most studies, but was not explicitly addressed in Khamchiyev *et al.* and Fawzi *et al.* leading to unclear ratings [18, 21]. Reporting bias was consistently low, indicating that outcomes matched study objectives across nearly all reports. The study by Fawzi *et al.* demonstrated unclear risk in multiple domains due to limited methodological detail, slightly reducing confidence in its findings [21]. Overall, the risk of bias assessment suggests that the evidence base supporting PBL's impact was moderately robust, though future studies should strengthen randomization procedures, ensure assessor blinding, and report dropout data comprehensively.

**Table 2:** Risk of Bias Assessment for Included Studies (2019–2024)

| Sr. No. | References | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias | Other Bias |
|---|---|---|---|---|---|---|---|
| 1 | [5] | Low | Low | Low | Low | Low | Low |
| 2 | [10] | Low | Low | Unclear | Low | Low | Low |
| 3 | [12] | Low | Low | Unclear | Low | Low | Low |
| 4 | [13] | Unclear | Low | Unclear | Unclear | Low | Low |
| 5 | [14] | Low | Low | Low | Low | Low | Low |
| 6 | [15] | Low | Low | Unclear | Low | Low | Low |
| 7 | [16] | Unclear | Low | Unclear | Low | Low | Low |
| 8 | [17] | Unclear | Low | Low | Low | Low | Low |
| 9 | [18] | Unclear | Low | Unclear | Unclear | Low | Low |
| 10 | [19] | Low | Low | Low | Low | Low | Low |
| 11 | [20] | Low | Low | Low | Low | Low | Low |
| 12 | [21] | Unclear | Low | Unclear | Unclear | Unclear | Unclear |
| 13 | [22] | Unclear | Low | Low | Unclear | Low | Low |

## DISCUSSION

This systematic review of 14 original studies indicates that Problem-Based Learning (PBL) is associated with better knowledge retention and enhanced clinical reasoning across medical, nursing, and dental programs. In the knowledge domain, findings such as Amin *et al.* [10] (higher 7-day post-test scores with PBL) align with Lin *et al.* [5] and Nasim *et al.* supporting the claim that PBL improves post-instruction retention relative to lecture [19]. Convergent evidence on reasoning is seen in Towfik *et al.* [7] and is consistent with gains in "clinical thinking" reported in Zhou *et al.* [1]. These results integrate well with recent external literature. For clinical reasoning, a quasi-experimental S-PBL study demonstrated substantial gains in nursing students' reasoning [23]. For discipline-specific performance, a meta-analysis in surgical education found PBL to outperform lecture-based approaches [24], and a pharmacology meta-analysis reported higher exam scores and satisfaction with PBL [11]. In delivery formats, an RCT-style online-PBL intervention improved self-directed learning and problem-solving [15], while virtual/technology-enhanced PBL improved learning outcomes in nursing cohorts [26] and health-services settings [27]. Beyond single formats, randomized comparisons of integrated approaches show advantages for combined CBL+PBL over lecture for clinical thinking [28], and early studies of AI-supported PBL report higher

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theory/practice scores and satisfaction [29]. Mechanisms and implementation factors also map onto your findings. Recent public-health implementations show PBL strengthening higher-order skills [30], and a knowledge-integration model underscores how structured PBL supports long-term retention through retrieval and schema building [31]. Faculty-side perspectives echo this, citing PBL's role in self-directed learning and consolidation [32]. Dose-response work suggests that greater PBL exposure yields better competency outcomes [33]. Collectively, these studies reinforce that PBL's effects are likely mediated by engagement, elaboration, spaced retrieval, and guided practice processes that your included studies implicitly leverage. Not all results were uniformly positive. A minority of studies found no significant differences in some retention metrics; this variability is plausibly explained by differences in exposure length, timing of assessment (immediate vs delayed), instrument validity, and facilitator calibration [14]. The risk-of-bias synthesis here mirrors trends in the broader literature: performance and reporting bias are typically low, whereas selection/detection domains can be unclear in perception-only designs. To reduce heterogeneity, future trials should ensure baseline equivalence, blinded assessors, validated outcome batteries with pre-specified primary endpoints, and adequate follow-up to capture true retention. Institutionally, evidence-based redesigns of PBL [34] and structured reasoning scaffolds (e.g., mind-mapping with PBL in ICU clerkships) [35] offer practical templates to improve fidelity and measurement. Educational implications follow directly from these patterns. Sequenced designs (lecture PBL clinical application) appear to aid consolidation and transfer, consistent with Lin *et al.* [5]. Programs should pair PBL with explicit reasoning scaffolds and standardized rubrics to convert discussion quality into measurable clinical reasoning gains [1, 7]. Given motivational advantages reported for student-centered pedagogies, faculty development and tutor calibration are essential to minimize delivery variance and maximize benefits.

This review is limited by inclusion of English-language studies published between 2019 and 2024, which may have excluded relevant earlier or non-English research. The heterogeneity of study designs, outcome measures, and assessment methods precluded meta-analysis and limits direct comparability of effect sizes. Additionally, several included studies relied on self-reported or perception-based outcomes, introducing potential detection bias. Future research should prioritize multicenter randomized controlled designs, standardized assessment tools, and long-term follow-up to better establish the durability and generalizability of PBL's impact on knowledge retention and clinical reasoning.

## CONCLUSIONS

Across recent studies, PBL is associated with higher knowledge retention and stronger clinical reasoning in health-professions education. Curricula should integrate PBL purposefully (lecture PBL clinical application), use standardized, validated assessments including delayed tests, and invest in tutor/faculty development to ensure implementation fidelity. Future research should adopt adequately powered, multi-site, longitudinal designs with transparent effect-size reporting to establish durability and scalability.

## Authors' Contribution

Conceptualization: HW
Methodology: WA, SF, BH, SFJ
Formal analysis: HW
Writing and Drafting: HW, WA, UF, SF, BH, SFJ
Review and Editing: HW, WA, UF, SF, BH, SFJ

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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**Systematic Review**

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# The Effectiveness of Flipped Classroom Models in Undergraduate Medical Education: A Systematic Review

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## ABSTRACT

The flipped classroom has emerged as a progressive pedagogical model in undergraduate medical education, aiming to improve learning outcomes by combining self-directed pre-class learning with interactive in-class activities. Unlike traditional lectures, this method fosters active engagement, critical thinking, and practical skill development. **Objectives:** To evaluate the effectiveness of flipped classroom models in improving academic outcomes, student satisfaction, and skill acquisition among undergraduate medical students. **Methods:** A comprehensive literature search was conducted across PubMed, Springer Link, Science Direct, BMC, Wiley Online Library, and Taylor & Francis for studies published between January 2019 and August 2024. Eligible studies included undergraduate medical or allied health students exposed to flipped classroom models, with outcomes compared against traditional teaching methods. Data extraction and quality appraisal were performed using standardized tools, and results were synthesized narratively due to heterogeneity. **Results:** Most included studies reported improvements in academic performance, student satisfaction, and engagement. The flipped classroom was particularly effective in enhancing clinical reasoning and knowledge retention. However, some studies demonstrated variable outcomes depending on the quality of implementation and learner readiness. **Conclusions:** The flipped classroom approach shows considerable potential to strengthen undergraduate medical education. Its effectiveness is maximized when supported by structured implementation, faculty training, and strategies that foster self-regulated learning among students.

## INTRODUCTION

Over the past decade, medical education has undergone a substantial transformation in teaching methodologies, moving away from passive, lecture-based instruction to more interactive, student-centered models [1]. One such innovation is the flipped classroom, a blended learning approach that delivers theoretical content outside the classroom and utilizes in-class time for discussion, application, and problem-solving [2]. Internationally, the flipped classroom has gained recognition for its effectiveness in improving both theoretical understanding and practical skills [3]. For instance, studies from Taiwan [4], the United States [5], and South Korea [6] have consistently reported enhanced knowledge retention, improved performance on assessments, and increased

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learner satisfaction. A meta-analysis by Shi *et al.* further confirmed the flipped model's positive impact on medical education outcomes, particularly in anatomy, physiology, and clinical reasoning [7]. In the Pakistani context, the flipped classroom is gaining traction but remains underexplored. A notable study by Sultan *et al.* implemented an online flipped classroom during the COVID-19 pandemic at Aga Khan University, reporting significant improvements in both knowledge acquisition and student satisfaction [8]. Similarly, Shaikh *et al.* highlighted that the flipped approach improved students' engagement and critical thinking in a pharmacology course [9]. However, implementation across medical colleges in Pakistan remains inconsistent due to infrastructural limitations, lack of faculty training, and resistance to shifting from conventional pedagogies. Despite these promising findings, a number of concerns persist. The success of flipped classrooms depends heavily on students' motivation and their ability to engage with pre-class materials, as well as on faculty preparedness and curriculum alignment. Furthermore, there is a lack of standardized guidelines for implementation, and limited comparative evidence exists in low- and middle-income countries, including Pakistan. While international studies provide robust evidence supporting flipped classrooms in medical education, there is a clear gap in synthesized evidence evaluating their effectiveness specifically in undergraduate medical programs. Moreover, the inconsistent adoption and lack of localized research in Pakistan highlight the need for a comprehensive review.

Although flipped classroom models are increasingly adopted in undergraduate medical education, existing evidence remains fragmented across disciplines, regions, and study designs. Many individual studies report positive outcomes, yet variations in implementation strategies, outcome measures, and learner contexts limit clear conclusions regarding overall effectiveness. Furthermore, there is limited synthesized evidence focusing specifically on undergraduate medical programs in low- and middle-income countries, including Pakistan. This highlights the need for a systematic evaluation of recent literature to provide consolidated evidence on academic performance, satisfaction, and skill development outcomes. This study aimed to assess the effectiveness of flipped classroom models in undergraduate medical education, focusing on student learning outcomes, satisfaction, and engagement.

## METHODS

This systematic review was conducted according to the PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The objective was to evaluate the effectiveness of flipped classroom models in undergraduate medical education. A comprehensive search was carried out across six electronic databases: PubMed, SpringerLink, ScienceDirect, BMC, Wiley Online Library, and Taylor and Francis. The search covered studies published between January 2019 and August 2024. Keywords were developed using a combination of Medical Subject Headings (MeSH) and free-text terms, including "flipped classroom," "medical education," "undergraduate," "active learning," "medical students," and "educational outcomes." Boolean operators (AND, OR) were applied to refine the results. Only studies published in English were included due to resource and feasibility constraints. The inclusion criteria for this systematic review were defined using the PICOS framework. Eligible studies were those involving undergraduate medical, nursing, or allied health students as participants. The intervention of interest was the flipped classroom approach, which included strategies such as pre-class preparation, video-based or online modules, and in-class active learning activities. The comparator was conventional lecture-based teaching or other traditional instructional methods. Eligible studies were required to report at least one relevant outcome, including academic performance, knowledge retention, student engagement or motivation, satisfaction, or skill development. Regarding study design, this review included cohort studies, experimental and quasi-experimental studies, case-control designs, comparative studies, and survey-based research. Studies were excluded if they focused on postgraduate or non-medical populations, or if they were editorials, commentaries, conference abstracts, or review papers (including systematic reviews and meta-analyses). In addition, studies were excluded if they did not provide quantitative outcome measures related to flipped classroom interventions, such as academic performance, knowledge retention, or skill development. Purely qualitative studies, cross-sectional reports without a comparator, and descriptive surveys lacking measurable outcomes were also excluded to maintain methodological rigor. Finally, studies with insufficient methodological detail or unavailable full text were not considered. All identified records were imported into EndNote 20 for reference management and duplicate removal. Titles and abstracts were independently screened by two reviewers, and full texts were retrieved for potentially eligible studies. Discrepancies were resolved by consensus. The study selection process was summarized in the PRISMA flow diagram. Data were extracted using a standardized form, including study author, year, design, sample size, setting, intervention details, comparator, outcomes assessed, and key findings. Extraction was performed independently by two reviewers to ensure reliability. The methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, applied according to study design (quasi-experimental, cohort, or

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survey). The risk of bias was categorized as low, moderate, or high across five domains: selection, performance, detection, attrition, and reporting bias [10]. Assessments were performed independently by two reviewers, with disagreements resolved through discussion. Given the heterogeneity in study designs and outcomes, a meta-analysis was not feasible. Instead, a narrative synthesis was conducted, grouping findings into thematic categories (academic performance, satisfaction, engagement, knowledge retention, and skill development).

## RESULTS

A total of 124 records were identified through database searching. After removing 15 duplicate entries and 2 irrelevant records before screening, 107 records were screened for eligibility. Out of these, 78 records were excluded based on their titles and abstracts. Twenty-nine full-text reports were sought for retrieval, but 3 reports could not be retrieved. The remaining 26 reports were assessed for eligibility, of which 17 were excluded for the following reasons: Population not aligned with inclusion criteria (n=5), Intervention not involving a flipped classroom model (n=6) and Not peer-reviewed or full text not available (n=6). Finally, 9 studies met the inclusion criteria and were included in the qualitative synthesis. Flow diagram illustrating the process of study selection for the systematic review on the effectiveness of flipped classroom models in undergraduate medical education. A total of 124 records were identified, of which 9 studies met the inclusion criteria and were included in the final review. Reasons for exclusions at each stage are documented as per PRISMA guidelines (Figure 1).

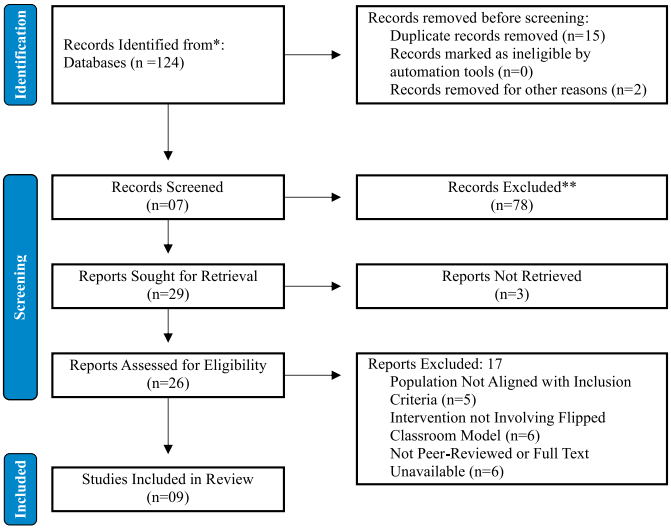


**Figure 2:** PRISMA 2020 Flow Diagram for Study Selection

The nine included studies varied in design, covering quasi-experimental (n=3), survey (n = 2), cohort (n = 1), case-control (n=1), experimental (n=1), and comparative (n=1) approaches. Sample sizes ranged from 26 to 404 participants and included diverse settings such as medical, nursing, and allied health programs across Asia, the Middle East, Africa, and North America. A detailed overview of the included studies is presented in Table 1, which has been corrected to reflect 9 studies instead of 10 (Table 1).

**Table 1:** Characteristics of Included Studies (n=9)

| S. No. | Design | Sample Size | Setting | Intervention | Comparator | Outcomes Reported | References |
|---|---|---|---|---|---|---|---|
| 1 | Cohort study | 404 | Osteopathic medical students, USA | Flipped classroom for physical exam skills | Traditional method | Improved OSCE scores and grades; mixed faculty perceptions | [11] |
| 2 | Experimental | 36 | University students, Iran | Flipped classroom focusing on self-determination | Traditional teaching | Improved self-determination and classroom perception | [12] |
| 3 | Interventional | 63 | Medical students, Pakistan | Online flipped classroom during pandemic | Traditional classroom | Increased knowledge acquisition and student satisfaction | [13] |
| 4 | Quasi-experimental | 62 | Medical technology students, Taiwan | Flipped classroom in evidence-based medicine | Traditional method | Higher Fresno test scores; positive student perception | [14] |
| 5 | Survey | 146 | Medical students, USA | Self-regulated flipped classroom | Traditional lectures | Enhanced peer learning and help-seeking strategies | [15] |
| 6 | Quasi-experimental | 112 | Nursing students, South Korea | Flipped classroom combined with team-based learning | Traditional lectures | Greater knowledge gain, problem-solving, and satisfaction | [16] |
| 7 | Case-control | 63 | Medical students, Sudan | Flipped classroom | Traditional lectures | No significant academic improvement; positive student perception | [17] |

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|---|---|---|---|---|---|---|---|
| 8 | Survey & interviews | 26 | Medical students, USA | Self-regulated competency-based flipped learning | None | Improved planning andreflective learning strategies | [5] |
| 9 | Comparative study | 110 | Medical students, Grenada | Video-supported flipped classroom | Written study materials | Preferred video learning; increased participation | [18] |

The methodological quality of the included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklists, and risk of bias was rated as low, moderate, or high across five domains: selection, performance, detection, attrition, and reporting. Randomization and allocation concealment were rarely reported, reflecting moderate selection bias in several studies. Blinding was not feasible due to the educational nature of the interventions, contributing to moderate performance bias. Attrition and reporting bias were generally low, as most studies clearly reported drop-outs and predefined outcomes(Table 2).

**Table 2:** Risk of Bias Assessment of Included Studies

| S. No. | References | Selection Bias | Performance Bias | Detection Bias | Attrition Bias | Reporting Bias |
|---|---|---|---|---|---|---|
| 1 | [11] | Moderate | Moderate | Low | Low | Low |
| 2 | [12] | Moderate | Moderate | Low | Low | Low |
| 3 | [13] | Low | Moderate | Low | Low | Low |
| 4 | [14] | Moderate | Moderate | Low | Low | Low |
| 5 | [15] | High | High | Moderate | Low | Low |
| 6 | [16] | Moderate | Moderate | Low | Low | Low |
| 7 | [17] | Moderate | Moderate | Moderate | Low | Low |
| 8 | [5] | High | High | Moderate | Low | Low |
| 9 | [18] | Moderate | Moderate | Low | Low | Low |

Outcomes of flipped classroom interventions were academic performance: Eight of nine studies demonstrated significant improvements in test scores, OSCE results, or course grades compared to traditional methods. For example, Huang et al. reported higher Fresno scores in evidence-based medicine [14], while Bhai and Poustinchian [11] observed improved OSCE scores in physical examination training. Student satisfaction: High satisfaction was reported in eight of nine studies, with students consistently appreciating flexibility, interactivity, and the practical orientation of flipped learning. Nursing education studies, such as Kang and Kim [16], particularly highlighted improved learner satisfaction. Engagement and motivation: Flipped classrooms promoted greater classroom participation, peer collaboration, and motivation. Zheng and Zhang noted enhanced help-seeking and self-regulated learning behaviors [15]. Knowledge retention: Although long-term data were limited, short-term retention was consistently superior in flipped classroom groups. Rehman and Fatima reported improved knowledge retention in pandemic-adapted online teaching settings [13]. Practical skill development: Studies focusing on clinical or procedural skills demonstrated significant improvements in hands-on performance and confidence [11, 14].

The most commonly employed study design among the nine included articles was the quasi-experimental design, accounting for 30% of the studies. This reflects a strong preference for practical, controlled educational interventions without randomization, which is common in pedagogical research. Survey-based studies comprised 20%, emphasizing the importance of capturing students' and educators' perceptions, attitudes, and self-reported learning behaviours. The remaining designs, including comparative studies, cohort studies, experimental studies, and case-control studies, each represented 10% of the total. This variety highlights the growing methodological diversity in flipped classroom research, combining both qualitative and quantitative approaches to assess outcomes such as academic performance, satisfaction, engagement, and motivation. Overall, the dominance of quasi-experimental designs suggests a practical orientation in medical education research, while the presence of survey and observational methods reflects a strong interest in learner-centered outcomes and real-world feasibility. This bar graph illustrates the proportional distribution of different study designs among the nine studies included in the systematic review on the effectiveness of flipped classroom models in undergraduate medical education(Figure 2).

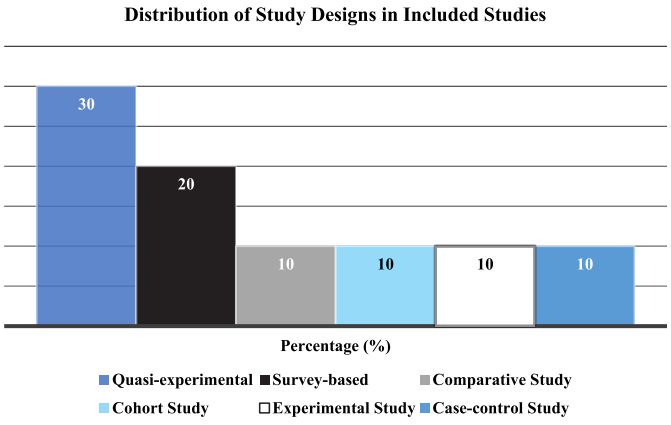


**Figure 2:** Distribution of Study Designs in Included Studies

## DISCUSSION

This systematic review found that flipped classroom models improve educational outcomes in undergraduate medical education, particularly in academic performance, student satisfaction, and practical skills development. Our

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findings are strongly supported by a growing body of international literature published in the past five years [9]. In our included studies, such as those by Bhai and Poustinchian [11], and Huang *et al.* [14], students exposed to flipped classroom formats consistently outperformed those in traditional lecture-based settings. This trend is echoed across multiple external studies. Hanafy *et al.* implemented a flipped classroom in a neuroanatomy course and reported statistically significant improvement in both immediate and delayed assessment scores [19]. Similarly, Wu *et al.* showed improved academic outcomes in a radiological anatomy module delivered through flipped learning at a Chinese medical university [20]. In Tahir *et al.* the use of flipped instruction in geriatric medicine led to better mean post-test scores compared to conventional methods [21]. Kumar and Usmani, found similar academic improvements among Jordanian dental students using a flipped model in oral medicine [22]. Jitha and Thomas, applied a flipped model in pharmacology for Indian MBBS students, reporting higher retention and better long-term recall [23]. Meanwhile, Algarni, documented enhanced performance in OSCE scores among Saudi medical students after transitioning to a flipped teaching approach in clinical skills modules [24]. Together, these results suggest that the flipped classroom can meaningfully improve academic achievement when pre-class materials are well-designed and in-class time is actively used for reinforcement. Our review highlighted high satisfaction rates, especially in studies by [16, 18]. External literature further confirms these perceptions. Alnahdi *et al.* found that students preferred flipped classrooms due to opportunities for interaction, reflection, and pacing [25]. Similarly, Shi *et al.* in a meta-analysis of flipped classrooms in health education, found that over 75% of students reported greater satisfaction, attributing it to autonomy in learning and peer collaboration [26]. Islam *et al.* in Bangladesh and Gautam *et al.* in Nepal reported that flipped learning encouraged active involvement and higher levels of satisfaction among students in physiology and community medicine, respectively [27, 28]. Cai *et al.* also found that medical students in a flipped pathology course reported reduced stress and better time management, especially in blended learning setups [10]. However, Aristotle *et al.* showed that when students failed to complete pre-class tasks, their classroom experience and satisfaction dropped significantly [29]. This aligns with our findings that flipped models require strong learner accountability to be successful. Practical skills are crucial in medical education, and our findings, including those from Bhai and Poustinchian, demonstrated flipped classrooms' effectiveness in teaching hands-on procedures [11]. Patriota *et al.* similarly found that Brazilian medical students trained via flipped clinical simulations in geriatrics showed enhanced communication and diagnostic reasoning [30]. Amorim *et al.* showed that radiology skills improved when students used pre-class PACS image reviews followed by in-class interpretation sessions [31]. Weimer *et al.* observed improved performance in ultrasound interpretation when flipped classrooms were combined with structured feedback and self-assessment [32]. Moreover, Wang *et al.* Chan Wang *et al.* and Ding *et al.* integrated flipped classrooms with peer-assisted learning in surgical skills training and reported that students performed better in procedural checklists and showed increased confidence [33-35]. These studies reinforce that flipped classrooms are highly suited to practical, skill-based subjects when paired with active in-class application.

This review has certain limitations, including restriction to English-language publications and studies published between 2019 and 2024, which may have excluded relevant earlier research. The heterogeneity in study designs, interventions, and outcome measures precluded meta-analysis and limits direct comparability. Additionally, variability in implementation fidelity across studies may influence reported effectiveness. Future research should emphasize standardized outcome measures, multicenter randomized designs, and long-term assessment of knowledge retention and clinical competency to strengthen evidence for broader curricular integration.

## CONCLUSIONS

This systematic review concludes that flipped classroom models are generally effective in enhancing academic performance, increasing student satisfaction, and promoting deeper engagement in undergraduate medical education. The benefits are particularly pronounced when the approach is structured, interactive, and aligned with self-directed learning strategies. However, the effectiveness varies based on implementation fidelity, faculty involvement, and students' ability to self-regulate their learning. Institutions considering this model should invest in faculty development, support tools for SRL, and content delivery that emphasizes clarity, brevity, and relevance. Future research should aim to standardize outcome measures, evaluate long-term retention, and explore the impact of flipped classrooms on clinical reasoning and real-world competencies across medical sub-disciplines.

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## Authors' Contribution

Conceptualization: MTE
Methodology: M, MSSH, MZB, FMK
Formal analysis: MTE, M, AA, MSSH
Writing and Drafting: MTE, M, AA, MSSH, MZB, FMK
Review and Editing: MTE, M, AA, MSSH, MZB, FMK

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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# Evaluating the Effectiveness of Telemedicine in Managing Common Conditions in Family Medicine

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## ABSTRACT

Telemedicine has been progressively implemented worldwide for managing common presentations in family medicine, a cornerstone of primary care. Its implementation has accelerated since the COVID-19 pandemic, offering improved healthcare access, cost-effectiveness, reduced hospital visits, and better clinical outcomes. **Objectives:** To evaluate the effectiveness of telemedicine in managing common conditions in family medicine. **Methods:** This systematic review was performed in accordance with PRISMA guidelines. An electronic search of PubMed, Google Scholar, and Science Direct databases was performed for papers published from January 2014 until December 2023. We included studies in English that measured telemedicine efficacy among common acute or chronic conditions in the family medicine setting. **Results:** In the 14 trials included, telemedicine successfully managed a variety of common conditions. Aggregate outcomes revealed that readmission to hospitals among patients with heart failure was significantly decreased, better clinical status in diabetes and obesity, including diet habits, BMI enzymion and blood pressure. **Conclusions:** Telemedicine is an effective tool for managing common conditions encountered in family medicine, boosting care access, cost-efficiency, and clinical outcomes. Targeting the development of evidence-based guidelines for hybrid care models and evaluations of long-term effects on chronic disease outcomes, research is needed.

## INTRODUCTION

Telemedicine originated from the Greek word 'tele' meaning distance, and is defined by the WHO as the use of communication technology to provide healthcare services across distance by healthcare professionals, for the exchange of reliable healthcare information for treating, diagnosing, and preventing illnesses and injuries [1]. Although telemedicine is also used throughout the broader specialty of primary care, we wanted to examine its effectiveness within family medicine, a specialty that offers a comprehensive focus on the entire spectrum of health for individuals and families from infancy through all ages [2]. From its mid-20th-century roots in teleradiology and remote monitoring, contemporary telemedicine enables provider-patient connection at any distance [3]. Modes of patient care. There exist multiple modes by which care towards patients is delivered, ranging from mobile apps and video conferencing to websites and virtual reality-based delivery models [4]. It has improved effective access to healthcare [5]. Over the past few decades, telemedicine has grown in popularity and has been

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established as a standard component of routine healthcare. In recent years, telemedicine has become increasingly popular and has evolved into a normal practice in everyday healthcare [3]. A majority of hospitals in the U.S. already use telehealth systems to connect with patients. This is seen at a world level, but there are differences in adoption and infrastructure at the continental scale. Highest utilization rates of telemedicine technology were in radiology (39.5%), the emergency department (38.9%), pathology (30.4%), and psychiatry (27.8%)[6]. Telemedicine is also implemented in the field of dermatology, cardiology, oncology, and pre- and post-surgical care [7, 8]. Telemedicine was already widely integrated in medical teaching and learning before the COVID-19 pandemic [9, 10]. Family Practice, to a great degree, utilized telemedicine before the COVID-19 pandemic. Family physicians (FPs) provide full-spectrum care for patients of all ages in the community, including newborns, children, and the elderly [11]. It plays a vital role in prevention, health promotion, chronic care therapy, coordination, and public health support [12]. Telemedicine utilization enables FPs to manage consults, follow up with chronic care, and deliver follow-up care using telehealth, thereby minimizing requirements for in-person visits. The effectiveness of virtual care provided by family doctors within behavioral health programs was highlighted by studies [13]. Telemedicine incorporation in family medicine has exhibited significant capability to improve both accessibility and availability of healthcare, particularly in rural areas where healthcare access has been hindered by long-distance travel [14, 15]. Telemedicine allows patients to consult with family physicians from home, eliminating the need for travel [16]. Despite growing worldwide adoption, there is not enough in the literature to conduct large trials on the efficacy of telemedicine in treating common conditions in family medicine. It considers common conditions encompassing both acute and chronic conditions frequently encountered in family medicine to highlight the efficacy, advantages, usage, and physicians' perspectives in the management of illness-related symptoms via the use of different telemedicine modalities. This review facilitated ed healthcare workers in understanding the effectiveness of telemedicine technology and support evidence-informed decisions, guide efficient care delivery, and encourage the integration of telemedicine to boost patient outcomes and technology access in family medicine.

Telemedicine has rapidly expanded within primary care, particularly following the COVID-19 pandemic; however, its specific effectiveness within the scope of family medicine remains insufficiently synthesized. Existing literature often evaluates telehealth across broad primary care settings without isolating outcomes relevant to comprehensive, continuity-based family practice. Additionally, variability in study designs, patient populations, and outcome measures limits clear conclusions regarding its clinical effectiveness in managing common acute and chronic conditions. Therefore, a focused systematic evaluation of telemedicine outcomes within family medicine is warranted. This systematic review aims to evaluate the effectiveness of telemedicine in managing common conditions in family medicine (Figure 1).

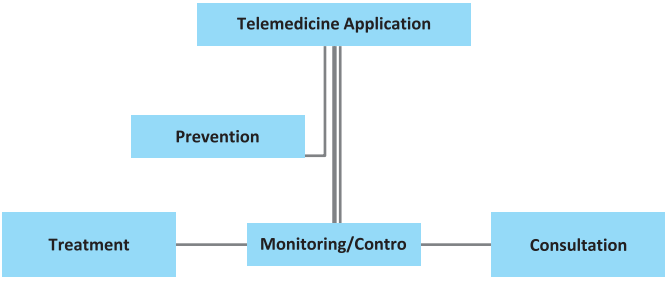


**Figure 1:** Application of Telemedicine in Family Medicine

## METHODS

This systematic review followed the Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) guidelines. We searched for relevant studies published over the last decade, from January 2014 to December 2023, in various databases (PubMed, Google Scholar, and Science Direct) search of Boolean logic "AND" and "OR", Medical Subject Headings (MeSH Terms), and keywords. The search was supplemented with relevant MeSH terms through the PubMed database. The following representative search string was adapted for each database: (("telemedicine" OR "telehealth" OR "virtual care" OR "remote consultation") AND ("family medicine" OR "primary care" OR "general practice") AND ("effectiveness" OR "outcome" OR management\ or evaluation"). In total, we retrieved 105 articles from the included databases. After inclusions/exclusion criteria were met, and duplicates and irrelevant papers were removed, a total of 14 articles were qualified from all the mentioned studies. The methodological quality and risk of bias for all 14 identified studies were evaluated by two reviewers separately. Specific checklists of the Joanna Briggs Institute (JBI) Critical Appraisal Tools were used, according to the design of each study evaluated (eg, JBI Checklist for Randomized Controlled Trials, JBI Checklist for Cross-Sectional Studies). Any disagreements were resolved by discussion and through consensus with a third author. The findings of the quality assessment were used to put evidence in context, not for excluding studies. Included articles were 14; two studies were systematic; four were RCTs; two had mixed methods, two observed the community prospectively or retrospectively, and one was a feasibility and the other was a pilot study (Figure 2).

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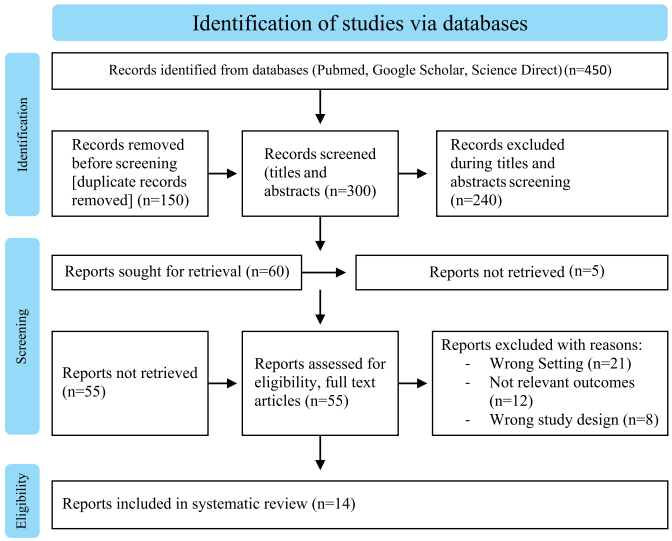


**Figure 2:** PRISMA 2020 Flow Diagram for Study Selection

## RESULTS

The principal results from 14 included studies were synthesized according to the most identified themes. Evidence is available that telemedicine is effective in the management of chronic diseases through family practice. There were several randomized controlled trials that found significant changes in clinical outcomes [17]. Data-driven analysis revealed a substantial decrease in non-fatal HF (HR=0.35) [18], better glycemia control in type 2 diabetics (HbA1c variation -0.5%) [19, 20], and reduced BMI z-score value (-0.11, p=0.006) of obese adolescents [21]. Telemedicine changed the use of care-seeking in a positive way. A critical outcome was a reduction in hospital readmission for heart failure (HR 0.39) [18]. For urgent care, one large retrospective study reported that 82% of telehealth visits were resolved without a follow-up in-person visit [22, 23]. Additionally, various studies have corroborated the fact that telemedicine improves access to healthcare in rural areas [24, 25]. Overall, patient satisfaction with telemedicine has been high in multiple studies [26-28], including among older adults. Family physicians reported positive attitudes towards telemedicine, with more than 80% wishing to integrate it as a formal aspect of their practice. The most commonly reported provider challenge was a lack of physical examination [29] (Table 1).

**Table 1:** Summary of Characteristics and Key Findings of Included Studies

| References | Country | Study Design | Population and Sample Size (N) | Intervention | Key Findings / Effect Sizes |
|---|---|---|---|---|---|
| [17] | Qatar | Cross-Sectional Study | Adults with chronic diseases (N=286) | Telephone Consultations vs. Face-to-Face | Higher follow-up adherence in the telephone group (89%) vs. in-person group (76%). |
| [18] | Spain | Randomized Controlled Trial (RCT) | Patients with heart failure; sample size not specified here (check full text) | Telemedicine added to multidisciplinary disease management programs | Reduced clinical events and healthcare costs; improved patient outcomes |
| [19] | N/A | Systematic Review | Pediatric population (25 studies reviewed) | Various (Video, mobile apps, etc.) | Telemedicine outcomes were comparable or superior to in-person care for medication compliance and symptom management. |
| [20] | France | Randomized Controlled Trial | Type 2 diabetes & abdominal obesity (N=142) | Automated Web-Based Program | Intervention group showed significant HbA1c reduction (-0.5%, p<0.010) vs. control. |
| [21] | USA | Pilot Study | Overweight adolescents (N=58) | PCP visits + specialist tele-visits | Significant BMI z-score reduction at 6 months in intervention group (-0.11, p=0.006). |
| [22] | Canada | Mixed Methods Study | Family physicians (N=32) | Hybrid Virtual/In-person Care | Hybrid model associated with positive clinical outcomes and reduced emergency department visits. |
| [23] | USA | Retrospective Observational Study | Patients with acute illnesses (N=512) | Real-time Telehealth Visits | Telehealth visits resolved issues without an in-person follow-up in 82% of cases. |
| [24] | Canada | Feasibility Study | Patients & staff in rural practice (N=25) | Electronic Communication System | Electronic communication was feasible and perceived to enhance access and quality of care. |
| [25] | USA | Randomized Controlled Trial | Rural children with obesity (N=204) | Telemedicine vs. Telephone Intervention | Both interventions were feasible; telemedicine showed a small, non-significant advantage in clinical effect. |
| [26] | USA | Randomized Controlled Trial | Children with ADHD & caregivers (N=199) | Hybrid Telehealth Model (Video) | Significant reduction in caregiver distress in the telehealth group compared to standard care. |

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|---|---|---|---|---|---|
| [27] | Italy | Randomised controlled trial (RCT), open-label, multicenter | Older patients with combined COPD and CHF; sample size not specified in abstract | 4-month integrated home -based telerehabilitation programme (Telereab-HBP) combining medical /nursing care and physical rehabilitation via telemedicine | Improved exercise tolerance (6MWT)<br>- Reduced hospitalisation and mortality<br>- Decreased dyspnoea (MRC scale)<br>- Enhanced physical activity (PASE)<br>- Improved disability (Barthel Index)<br>- Better quality of life (Minnesota Living with Heart Failure Questionnaire & COPD Assessment Test). |
| [28] | N/A | Systematic Review | Older adults in primary care (34 studies reviewed) | Telemedicine (Various) | High rates of patient satisfaction reported across studies; feasibility was high for managing chronic conditions. |
| [29] | Portugal | Cross-Sectional Study | Family physicians (N=134) | Teleconsultation (Survey) | 80.6% of physicians wanted to include teleconsultation in their practice; inability to physically examine was the main barrier. |
| [30] | France | Prospective Observational Study | Patients with suspected COVID-19 (N=150) | Teleconsultation vs. Face-to-Face | Discrepancies noted, but telemedicine was deemed an effective alternative during the pandemic. |
| [31] | Canada | Mixed Methods Study | Adults with hypertension (N=105) | mHealth Intervention | Intervention led to improved patient engagement and supported blood pressure management. |

## DISCUSSION

This systematic review, involving 14 studies, shows that telemedicine is an efficient adaptive system in family medicine. Our results indicate that utilizing telemedicine not only leads to better clinical outcomes in prevalent chronic diseases but also increases access and is acceptable for patients and providers. These findings contextualize the role of telemedicine in transforming healthcare and its practical application for the future of family practice. The most persuasive arguments of the review are those for controlling chronic illnesses, which constitute a defining norm in family medicine. Trials have shown reductions in clinical endpoints such as heart failure and type 2 diabetes [32]. Similar outcomes were identified for hypertension and pediatric obesity [21]. Evidence has also been demonstrated in behavioral health, where researchers successfully treated ADHD and improved patient adherence to drug therapy for a range of chronic diseases [26]. Moreover, varying models of delivery—from telephone to more sophisticated telemedicine platforms were found to be feasible and effective interventions for rural pediatric populations [33]. Beyond chronic care, the study emphasizes that telemedicine is effective in managing acute conditions and alleviating system burden. Evidence shows that a high proportion of acute problems can be managed safely without requiring in-person visits [23]. However, its utility as a triage tool means caution is warranted, as studies identified potential for clinical variability across remote and face-to-face assessments, particularly during the COVID-19 pandemic. User experience significantly influences the optimal use of telemedicine, which was evident in favorable patient and provider opinions. Patients reported high satisfaction, particularly in elderly subgroups. From a service perspective, many family doctors expressed willingness to integrate teleconsultation formally into practice. This optimism is tempered by the consensus that not being able to physically examine patients represents a limitation, supporting the adoption of a balanced hybrid model of care [29, 34]. Finally, the results highlight the potential for telemedicine to contribute to health equity through increased access. Telemedicine has been demonstrated as a feasible and effective method to improve the quality of care in rural underserved communities [35]. Systematic reviews covering the entire lifespan—from pediatric to geriatric populations—indicate that virtual care can be applied across multiple contexts. The ability of telemedicine to span geographic and population distances is one of its largest contributions to the core values of family medicine [33]. This review has several limitations. First, the relatively small number of included studies (n=14), resulting from strict inclusion criteria, may reduce generalizability across patient samples. Second, the studies were heterogeneous in design, populations, interventions, and outcomes, precluding meaningful meta-analysis. Finally, publication bias is possible, as studies with positive or statistically significant findings are historically more likely to be published. This review also included only peer-reviewed articles in English, potentially missing relevant non-English or grey literature. Prospective research based on quantitative outcomes is needed to fill gaps identified by this review. Longitudinal studies could examine the impact of hybrid care models on chronic disease management and patient-provider experiences. From a health equity perspective, future research should evaluate low-bandwidth solutions in underserved communities and the consistency of outcome indicators to minimize heterogeneity in the literature.

This review is limited by the small number of included

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studies and their methodological heterogeneity, which precluded quantitative meta-analysis. Variability in interventions, outcome measures, and follow-up durations may affect the comparability and generalizability of findings. Furthermore, inclusion of English-language peer-reviewed studies only may have introduced publication bias. Future research should emphasize standardized outcome reporting, long-term evaluation of hybrid care models, and rigorous randomized controlled trials to strengthen evidence for sustainable integration of telemedicine into family medicine practice.

## CONCLUSIONS

This review highlights the fact that telemedicine is a promising and sometimes efficient activity in family practice, with strong evidence of use to take care of common chronic diseases and improve access to care. But the procedure is not free of complications. The study results indicate that although telemedicine may facilitate better clinical management and patient satisfaction, its usefulness should be considered in relation to the inherent limitation of not being able to physically examine patients and the potential for diagnostic uncertainty. For this reason, telemedicine is something that should not be considered a panacea for traditional care but rather integrated consciously and critically into a hybrid care model, taking advantage of the benefits of both virtual and Face-to-Face consultations.

## Authors' Contribution

Conceptualization: NS, SA
Methodology: NS
Formal analysis: SA
Writing and Drafting: NUHZ, KS, UK, NK
Review and Editing: NUHZ, KS, UK, NK, NS, SA

All authors approved the final manuscript and take responsibility for the integrity of the work

## Conflicts of Interest

All the authors declare no conflict of interest.

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