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ACKNOWLEDGEMENT

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Freezing Threats: The Health Implications of Extreme Cold Weather in Pakistan

OPEN ACCESS

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Pakistan is a diverse country in terms of climate; however, some of the most extreme cold in Pakistan can be witnessed in the northern areas, such as Hunza, Skardu, Ashkomen Valley, and a section of Baltistan. During January and February, the climate in these regions can be as low as -100 °C, and glaciers like Siachin, Passu, Batura, and Baltoro make sure that the environment is as cold as it can be throughout the entire year. Cold weather is also a natural characteristic of such areas, but it presents significant health issues to the population, both physical and mental [1-3].

Extreme cold has the most direct effect on the health of human beings, especially those who are the most vulnerable. Low temperatures may cause hypothermia, which is a life-threatening condition in which the body is unable to generate heat at a rate faster than it loses it. In northern Pakistan, frostbite is also typical of hands, feet, ears, and the nose, causing tissue damage and amputation in severe cases. Specifically, children, the elderly, and individuals with chronic illnesses are more prone to it because their bodies cannot better control temperature. Unfortunately, not all houses in remote northern parts have proper heating, insulation, and proper clothes that would help people to prevent cold-related diseases [1-4].

There is also a surge of respiratory problems during winter. The cold air irritates the respiratory system, weakens immunity, and thus, makes individuals more susceptible to diseases like influenza, bronchitis, and pneumonia. The frequency of chronic respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD), also deteriorates during colder seasons as a result of indoor air pollution caused by the burning of wood, coal, or kerosene to heat the home. These indoor fuels emit toxic smoke, further complicating respiratory distress and leading to more and more hospital admissions [3, 4].

Cardiovascular health is also influenced by cold weather. Low temperatures make blood vessels narrow, resulting in a rise in blood pressure and heart rate. This increases the chances of heart attacks and strokes, especially among the aged. Research has revealed that there is a seasonal trend in mortality whereby more mortality is registered in winter months owing to cardiac-related complications. Unanticipated cold waves in cities where individuals might be exposed to cold air following the indoor heating also led to cardiovascular crises [5].

The other critical health issue is the increase in winter injuries. Falls and fractures are more likely in the northern areas where roads are slippery and icy. Only inaccessible emergency services in the mountains can postpone the treatment, which deteriorates results. Moreover, cold weather in most cases compels individuals to be at home in a congested area, thus contributing to the transmission of communicable diseases, including tuberculosis, influenza, and even COVID-19 [6].

Mental health is another area impacted by prolonged cold. Reduced daylight hours and extended indoor time may cause seasonal affective disorder (SAD) and depression and anxiety, especially in susceptible groups. Social isolation in remote areas during the winter season increases these mental health issues, and it is highly important to offer community support and mental health services [7].

Cold health impacts in Pakistan should be prevented. Heating homes and other public shelters, supplying warm clothes and

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blankets, and educating people on how to take care of themselves on winter days can save lives. Influenza and pneumonia vaccines are to be given priority, particularly to the high-risk groups. Avoidable deaths can be prevented through better access to healthcare in remote northern regions, as well as the emergency response system in severe cold waves. Health risks caused during winter seasons can be further mitigated by fortifying nutrition and educating people regarding healthy indoor heating habits.

Cold weather in Pakistan is not merely a state of the environment, but it is a major issue of public health. Hypothermia and frostbite are not the only consequences of winter on human health, since respiratory and cardiovascular issues can also be significant, especially in the highlands of the north. The solution to these problems is a complex intervention of health, community awareness, and governmental assistance to make sure that the cold is not a threat to death. Focusing on winter health strategies, Pakistan will be able to secure the most vulnerable groups and minimize the impact of cold-related diseases.

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Original Article

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Comparison of Outcomes of Transbuccal Approach Versus Transoral Fixation in Open Reduction and Internal Fixation of Mandibular Angle Fracture

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ABSTRACT

Fractures of the mandibular angle pose surgical challenges due to limited access and complex anatomy. The transbuccal approach improves access but requires a small skin incision, while the transoral approach avoids external scars but may limit visualization. **Objectives:** To compare transbuccal and transoral approaches for open reduction and internal fixation (ORIF) of mandibular angle fractures with respect to surgical time, intraoperative access, and postoperative occlusion. **Methods:** Eighty patients with isolated unilateral mandibular angle fractures were prospectively assigned to transoral (n=40) or transbuccal (n=40) fixation. Surgical time, intraoperative accessibility (scored 1–3), and postoperative occlusion were recorded. Data normality was assessed using the Shapiro-Wilk test, and comparisons were made using the Mann–Whitney U test ($p<0.05$). **Results:** The transoral approach significantly reduced median surgical time compared to transbuccal fixation (41 (15) vs. 69 (4) minutes; $U=4.000$, $p<0.001$). Conversely, intraoperative accessibility was superior with the transbuccal approach (1 [1] vs. 2 (0); $U=314.000$, $p<0.001$). Postoperative occlusion was comparable between groups (0 (0) vs. 0 (0); $U=783.000$, $p=0.765$). **Conclusions:** Both approaches provide similar postoperative occlusal outcomes. The transbuccal method offers enhanced intraoperative access, whereas the transoral technique reduces operative time and avoids external scars. Surgical technique should be selected based on case complexity, access requirements, and cosmetic considerations.

INTRODUCTION

About two-thirds of all fractures of the maxillofacial region are mandibular. Angle fractures make up 26-35% of the mandibular fractures [1]. Mandibular, zygomatic, along midface fracture occurrence has been estimated by Haug et al. to be 6:2:1 [2]. Mandibular angle fractures continue to present uncertain outcomes and management challenges in comparison with fractures in other mandibular anatomical regions, despite advancements in internal fixation employed for such fractures [3]. Numerous studies confirm that no single strategy has consistently shown to be the best. Angle fractures were traditionally mostly treated with closed reduction. However, the extraoral technique was initially used when the open reduction was thought to be necessary. With the introduction of mini plates, the transoral method became widely used. The key challenge in these methods was customising and placing the plate along the appropriate osteosynthetic line [4]. The surgical access required to insert the posterior screws is typically subpar. Consequently, compared to other sites of mandibular fracture, the rate of plate exposures and screw unlocking is higher [5]. With the advent of new techniques and the creation of miniplates, as shown by Champy, the procedure can be carried out using a transbuccal access in an anatomically optimal position [6]. Transbuccal approaches are still largely unappealing due to the potential risk of damaging the affected nerve and unsightly

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scarring as they include the introduction of a trocar via stab incision from skin into the oral cavity [7]. Since it results in minimal or no formation of scars and allows direct visualisation and evaluation of adequate occlusion throughout plate fixation, the transbuccal technique is typically supported [8]. Another strategy, known as the "transoral or intraoral technique," was put out to address these drawbacks. This method, which is commonly employed, entails operating solely via an incision created in the vestibular or oral mucosa [9]. Comparing and identifying the most effective method for just one adaptational monocortical superior border plating for mandibular angle fracture is the rationale of our investigation. Based on the relative advantages and disadvantages of the transoral and transbuccal methods, we theorized that the transbuccal method would be accessible in the intraoperative period and the transoral technique would reduce the operative time, but both would result in similar postoperative occlusion.

There is limited comparative evidence evaluating transoral and transbuccal approaches specifically for single monocortical superior border miniplate fixation of mandibular angle fractures, particularly with respect to operative time, intraoperative accessibility, and postoperative occlusal stability. This study aims to compare the use of transoral and transbuccal approaches in the open reduction and internal fixation of fractures of the mandible angle to assess the time involved in surgery, accessibility, and postoperative occlusal stability.

METHODS

The prospective comparative study was conducted on patients visiting the Oral and Maxillofacial Outpatient Department (OPD) during 1 year from April 2024 to March 2025. The study was conducted after ethical approval from the Sharif Medical Research Center (SMRC) (Ref. no SMDC/SMRC/331-24). This study was done on 80 patients. The sample size was obtained with the help of the WHO sample size determination software in comparing two proportions. According to the past literature, 94.1% was the estimated success rate of the transoral approach [8]. Based on the assumption of 95% confidence and a desired level of precision (margin of error) of 6% (0.06) to reconcile feasibility and statistical power, a two-sided test with 0.05 = 10 was used. This gave a minimum required sample size of 40 patients per group, which gave a total of 80 patients as the study sample. The precision level of 0.06 was found to be reasonable to identify clinically significant changes in postoperative outcomes, whilst having a manageable size of sample size in a single-center study. After informed consent, using a non-probability convenience sampling technique, patients were allocated into two groups of 40 patients each: group A and group B, until each group reached the required sample size. All patients aged >18 years old diagnosed with isolated unilateral angle fracture, diagnosed on CT scan, were included. Patients with comminuted fractures or having other facial fractures associated with angle fractures were excluded from this study. Patients in group A were treated with a transoral approach, and group B underwent a transbuccal approach. All patients underwent a comprehensive preoperative evaluation, including general physical examination and a maxillofacial assessment for swelling, ecchymosis, step deformity, tenderness, occlusion, and neurosensory function. Preoperative radiographic assessment was performed using a Siemens SOMATOM Definition Flash CT scanner. Axial and coronal images were acquired with 0.5 mm slice thickness, 120 kVp, and 200 mA. Three-dimensional reconstruction was performed using the Siemens Syngo software to confirm fracture location and displacement before surgery. After general anesthesia and aseptic measures, local anaesthesia infiltration (2% lignocaine with 1:100,000) was done at the site of exposure. All fractures were fixed with OM (Orthopaedic and Medical Germany) ®5-hole titanium miniplates with 0.9 mm thickness, and 7mm screws. In group A, the incision was given in the buccal vestibule distal to the second premolar till ascending ramus with Monopolar cautery, and full full-thickness mucoperiosteal flap was raised till the lower border of the mandible. The fracture was exposed and reduced, the occlusion was achieved with intermaxillary fixation, and the fracture was fixed with a 5-hole plate and 4 screws. The incision was closed with vicryl 4.0. In group B, a transoral incision was made along with a small extraoral stab puncture to make room for a transbuccal cannula. The position of the facial vessels and the fracture line were taken into consideration when choosing the incision site. Similar to that of the transoral method, a long drill bit was used for drilling and screw placement following blunt dissection and trocar insertion. After fixation of the fracture with a 5-hole plate and 4 screws, the trocar was taken out, and vicryl 4.0 and Prolene 5.0 sutures were used to close the mucosa and skin incision. A single team of surgeons who operated used a Visual Analogue Scale (VAS), which was also used to measure the subjective rating in clinical and surgical research, to determine intraoperative accessibility at the fracture site on a 10-cm Visual Analogue Scale. VAS is composed of a horizontal line that has anchors on both ends with descriptors indicating extremes of accessibility: 1 good access, 2 fair access, and 3 poor access. The operating surgeon indicated the point of the scale that corresponded to the perceived access when placing the plates. The straight line between the lowest point in the scale and the mark gave the accessibility score of each patient. This is a way of standard and reproducible

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measurement of subjective intraoperative experiences [10, 11]. For every patient, the same electronic clock was used to record the amount of time needed for the surgery from the point of incision to the skin's closure [10]. On the 1st post-operative day, the occlusion was assessed by a gap in the upper and lower molars. Occlusion was classified as satisfactory (0mm gap), mildly deranged (1–2mm gap), or deranged (>2mm gap) during maximum intercuspation [12]. Data were analyzed using SPSS version 24.0. Descriptive statistics were computed for all variables, and the Mann-Whitney U test was applied to compare outcomes between groups. A p-value <0.05 was considered statistically significant.

RESULTS

Eighty patients were included (40 per group). Group A (transoral) had a median age of 32 [22–45] years with 28 male (70%) and 12 female (30%). Group B (transbuccal) had a median age of 34 [21–47] years, with 26 males (65%) and 14 females (35%). Most fractures were on the left side (Group A: 23; Group B: 21) and were caused primarily by road traffic accidents (Group A: 25; Group B: 27). Preoperative CT confirmed isolated unilateral angle fractures with minimal displacement in 45% and moderate displacement in 55% of patients in both groups (Table 1).

Table 1: Demographic and Baseline Characteristics of Patients

Characteristics	Group B (Transbuccal) (n=40)	Group A (Transoral) (n=40)
Age		
Median [IQR] (Years)	32 [22–45]	34 [21–47]
Sex, n (%)		
Male	28 (70%)	26 (65%)
Female	12 (30%)	14 (35%)
Side of Fracture, n (%)		
Left	23 (57.5%)	21 (52.5%)
Right	17 (42.5%)	19 (47.5%)
Cause of Fracture, n (%)		
Road Traffic Accident	25 (62.5%)	27 (67.5%)
Assault / Fall / Other	15 (37.5%)	13 (32.5%)
Preoperative Displacement, n (%)		
Minimal	18 (45%)	18 (45%)
Moderate	22 (55%)	22 (55%)

Median VAS scores for accessibility were 2 [0] in Group A and 1 [1] in Group B, showing better access with transbuccal fixation. Median surgical time was significantly shorter for the transoral group (41 [15] min) compared to the transbuccal group (69 [4] min). On postoperative day 1, occlusion was satisfactory (0 mm gap) in 38 patients in Group A and 37 patients in Group B; mild derangement (1–2 mm gap) was seen in 2 patients (Group A) and 3 patients (Group B). No patient had a severely deranged occlusion (>2 mm gap). Mann–Whitney U test confirmed significant differences in surgical time (U = 4.000, p<0.001) and accessibility (U = 314.000, p<0.001), whereas postoperative occlusion did not differ significantly (U = 783.000, p=0.765) (Table 2).

Table 2: Intraoperative and Postoperative Parameters

Parameters	Group A (Transoral) Median [IQR]	Group B (Transbuccal) Median [IQR]	Mann–Whitney U	p-value
Surgical Time (min)	41 [15]	69 [4]	4.000	<0.001
Intraoperative Accessibility (VAS)	2 [0]	1 [1]	314.000	<0.001
Postoperative Occlusion (mm gap)	0 [0]	0 [0]	783.000	0.765

DISCUSSION

This study examined the differences in postoperative occlusion, accessibility, and surgical time between transoral versus transbuccal methods for fixing mandibular angle fractures. In contrast to the transbuccal method, which offered greater accessibility to the fracture site, our data showed that the transoral approach dramatically decreased surgery time. The two methods' postoperative occlusal results were similar. The transoral approach's shortened surgical time is in line with earlier research showing that transbuccal instrumentation and avoiding an external incision shorten operating stages and overall length [13, 14]. But in cases of complex or adversely displaced fractures, this method is frequently linked to restricted access from the posterior mandible [15]. Present results of the transbuccal approach's greater accessibility are consistent with previous studies showing that transbuccal instrumentation improves angulation and visualization for screw placement, especially in the posterior mandible region [16, 17]. The transoral approach in the current study had a very big influence because it shortened the surgical time when compared to the transbuccal approach (median difference = 28 minutes; 41 [15] vs. 69 [4] minutes; U = 4.000, p<0.001; effect size r=0.82), and thus, a big effect. The transbuccal method was more accessible (median difference = 1 point; 1 [1] vs. 2 [0]; U = 314.000, p<0.001; r=0.57), which is a moderate-to-large effect size. The difference in postoperative occlusion was not significant (0 [0] vs. 0 [0]; U = 783.000, p = 0.765), and this indicates a small impact. The addition of these effect sizes and median differences indicates the additional benefit of not just statistical significance but also clinical significance of the reported differences. Postoperative occlusal results were similar between the two methods in spite of the variations in operational factors [18]. This is consistent with previous research showing that the two methods can produce similar functional and aesthetic outcomes when used properly [17]. This implies that the surgeon's preference, the complexity of the case, and the weight assigned to surgical time compared to

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intraoperative accessibility may all influence the method selection [19, 20]. Current findings generally favored the transoral method in simpler cases requiring shorter operational times and less external scarring, even though the transbuccal procedure might be useful in circumstances requiring superior access for precise reduction and fixation. More multicenter trials with larger sample sizes and longer follow-up are recommended to further evaluate patient-centered outcomes such as pain after surgery, neurosensory defects, and scarring.

This study was limited by its single-center design and relatively small sample size, which may restrict the generalizability of the findings. Additionally, complex and severely displaced mandibular angle fractures were underrepresented, potentially limiting the applicability of the results to such cases. More multicenter trials with larger sample sizes and longer follow-up are recommended to further evaluate patient-centered outcomes such as pain after surgery, neurosensory defects, and scarring.

CONCLUSIONS

In patients having an isolated fracture of the mandibular angle, the transoral and transbuccal approach can produce similar postocclusional effects. The transbuccal method offers better intraoperative exposure, whereas the transoral method saves on a lot of surgical time. Hence, surgical technique must be based on clinical priorities, weighing between the necessity of better access to the fracture site and the surgery efficiency as well as the aspect of patient cosmetics.

Authors' Contribution

Conceptualization: MK
Methodology: MK, UBA, KA, MAK, MJ, AA
Formal analysis: KA
Writing and drafting: MK, UBA, MJ, AA
Review and editing: MK, UBA, KA, MAK, MJ, AA

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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Factors Associated with Poor Compliance of Antiepileptic Drugs in Children with Epilepsy

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ABSTRACT

Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal electrical discharges in the brain. **Objectives:** To determine the factors associated with poor compliance with antiepileptic drugs in children with epilepsy. **Methods:** This cross-sectional study was conducted at the Outpatient Department of Neurology of the National Institute of Child Health, Karachi, Pakistan, from January 2025 to June 2025. A total of 185 children aged 1–12 years with epilepsy, diagnosed ≥6 months earlier, were recruited by non-probability consecutive sampling. Compliance with antiepileptic drugs was assessed using the Morisky Medication Adherence Scale (MMAS-8), classifying scores ≥6 as compliant. Factors behind non-compliance were noted. Data were analyzed using SPSS v26 with chi-square and binary logistic regression applied, taking $p<0.05$ as significant. **Results:** In a total of 185 children, the mean age was 7.4 ± 3.1 years, and 104 (56.2%) were males. Respondents were 117 (63.2%) mothers and 68 (36.8%) fathers, with a mean parental age of 34.8 ± 6.7 years. Residence was urban in 118 (63.8%), and rural in 67 (36.2%). Low socioeconomic status was noted in 92 (49.7%), and 47 (25.4%) parents were illiterate. Overall, 119 (64.3%) children were compliant and 66 (35.7%) non-compliant. Non-compliance was significantly associated with rural residence (AOR 1.9, 95% CI 1.0–3.6), low socioeconomic status (AOR 2.5, 95% CI 1.1–5.7), and illiteracy (AOR 6.9, 95% CI 2.4–20.5). **Conclusions:** Non-compliance with AEDs in children with epilepsy in Karachi was strongly influenced by rural residence, low socioeconomic status, and low parental education.

INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures resulting from abnormal electrical discharges in the brain [1]. Approximately 7.6 per 1000 individuals are affected by epilepsy globally, accounting for nearly 70 million people across all age groups [2]. The highest incidence is reported during infancy, with 102 new cases per 100,000 annually, particularly within the 1–12 years age range [3]. In contrast, children aged 11–17 years demonstrate a lower incidence, ranging between 21 and 24 per 100,000 annually [4]. In the context of epilepsy, compliance refers to the degree to which patients follow prescribed antiepileptic drug (AED) regimens in terms of both dosage and timing. Medication adherence is fundamental for seizure prevention and reduction, with significant implications for overall quality of life [5]. Poor adherence represents one of the most critical challenges in epilepsy management, as it compromises seizure control and undermines therapeutic outcomes. Evidence suggests that with appropriate and consistent use of AEDs, seizure freedom can be achieved in nearly 70% of individuals; non-adherence therefore constitutes a major barrier to attaining this goal [6]. Rates of adherence to AEDs are variable in different studies, ranging between 20 and 80%. In children, however, these rates are even lower, estimated between 25 and 75% [7]. A study by Dima and Shibeshi on adherence of AEDs in children reports 65.0% adherence and 35.0% non-adherence. Commonly reported factors of non-adherence were family size (>5), 59.7%, low

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monthly income, 31.3%, financial problems, 59.7%, duration of illness (≥3 years), 43.3%, seizure attacks in the last three months, 77.6%, and duration of treatment (≤2 years), 56.7% [8]. Another study by Ejeliogu *et al.* reported 44.8% non-adherence in children [9]. A Pakistani study by Malik *et al.* on factors influencing medication adherence in children with epilepsy reported 58.0% non-adherence in children. Factors significantly associated with non-adherence were polypharmacy (79.0%), uncontrolled seizure (57.0%), unaffordability (71.0%), poor counseling (86.0%), unavailability of AEDs (29.0%), and no parental/caretaker education (43.0%) [10]. Continuous efforts are being advocated to raise awareness of epilepsy related disorders, strengthen health system responses, and reduce its global burden [11].

Despite these efforts, research addressing medication adherence in children with epilepsy remains limited, and the factors influencing adherence are not fully understood. In Pakistan, data on pediatric adherence to AEDs are particularly scarce. This study was planned with a research question: What are the factors behind non-compliance to AEDs among children with epilepsy attending a tertiary care hospital in Karachi, Pakistan? There is a pressing need to characterize adherence patterns in this population, identify determinants of non-adherence, and develop evidence-based strategies to improve compliance. This study aimed to determine factors associated with poor compliance with antiepileptic drugs in children with epilepsy among the local population of Karachi, Pakistan.

METHODS

This cross-sectional study was commenced at the Outpatient Department of the Neurology, National Institute of Child Health, Karachi, Pakistan, from January 2025 to June 2025, after obtaining prior approval from the ethical review committee of the institution (IERB-41/2024). A sample size of 185 was calculated using the "Online Open Epi Sample Size Software", considering the poor counseling by physicians as the most common factor of non-adherence occurring in 86.0% of the children with epilepsy, taking the confidence level at 95%, and the margin of error at 5% [10]. All enrolled children were evaluated and diagnosed by consultant pediatric neurologists at the Department of Neurology, NICH, Karachi, Pakistan. Inclusion criteria comprised children aged 1–12 years of either gender with a confirmed diagnosis of epilepsy. Diagnosis of epilepsy was made in accordance with the International League Against Epilepsy (ILAE) criteria, based on clinical history, neurological examination, and supporting investigations such as electroencephalography (EEG) and neuroimaging (CT or MRI) when indicated. Only those children with a confirmed diagnosis of epilepsy for at least six months and who were currently receiving antiepileptic therapy were included. Children with acute symptomatic seizures due to infection, trauma, metabolic abnormalities, or other transient causes were excluded. Each child had a documented neurological evaluation in their hospital record at diagnosis, and the appropriateness of the prescribed treatment plan was verified by the attending neurologist. The sample selection was carried out using the non-probability consecutive sampling technique. Informed and written consent was obtained from all parents once they were informed of the objective of the study. They were also assured about the secrecy of their provided information. Demographics of the eligible subjects, which included gender (male/female), age, age group, residential status (rural/urban), monthly income (PKR), and level of education (illiterate/primary/matric/intermediate/graduation/post-graduation), along with socioeconomic status (low/middle/high), were documented. Parents were interviewed using the Morisky Medication Adherence Scale (MMAS-8) to assess the compliance of children towards AEDs. MMAS contained 8 questions, having a response choice of yes or no for questions 1-7 [12]. Each question (1-7) was given a score of 1 for 'no' and 0 for 'yes', except question 5, where a score of 1 was given for 'Yes' and 0 for 'No'. Question 8 had a five-point Likert response scale and was measured based on 0-4 scores standardized by dividing the result by 4 to calculate a summated score. Total scores on the MMAS-8 ranged from 0 to 8 and were classified as compliance (scores 6-8) and non-compliance (scores <6) [12]. The eight-item MMAS-8 was used under fair academic use for non-commercial, hospital-based research. All rights to the scale remain with the original developer [12]. Each parent was investigated about different factors of non-compliance, which comprised polypharmacy (children on treatment of more than one AED), uncontrolled seizures (children having seizure attacks in the last three months), financial problems (parents either unable or having difficulty affording medications), availability of prescribed AEDs (prescribed AEDs either easily available or not available), physician counseling (parents either properly counseled or poorly counseled or not counseled about appropriate use of AEDs), parental education (parents either illiterate or having some level of education), and adverse effects (children suffer either from minor or significant adverse effects). The data were recorded on a specifically predesigned proforma by the researchers themselves. The statistical analysis was performed using "IBM-SPSS Statistics" version 26.0. The qualitative variables were shown as frequency and percentage. The normality of the quantitative data was checked using the Shapiro-Wilk test. For the numeric variables, means and standard deviations (SD) or medians and interquartile

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ranges (IQR) were computed. The effect modifiers were controlled through stratification, and a post-stratification chi-square test was applied to see the effect of effect modifiers on the outcome (non-compliance), taking a p-value <0.05 as significant. To identify independent predictors of non-compliance with AEDs, binary logistic regression analysis was performed. Variables with a p-value <0.10 in univariate analysis were subsequently entered into a multivariate binary logistic regression model using the enter method. The results were expressed as adjusted odds ratios (AOR) with 95% CI, and a p-value <0.05 was considered statistically significant.

RESULTS

In a total of 185 children, the mean age was 7.4 ± 3.1 years, and 104 (56.2%) were male. The respondents were 117 (63.2%) mothers, 68 (36.8%) fathers, and the mean age of parents was 34.8 ± 6.7 years. In terms of residence, 118 (63.8%) belonged to urban areas, while 67 (36.2%) lived in rural areas. Based on socioeconomic status, 92 (49.7%) families were classified as low income, 63 (34.1%) as middle income, and 30 (16.2%) as high income. Regarding parental education, 47 (25.4%) were illiterate, 39 (21.1%) had primary to secondary education, 58 (31.4%) had matriculation to intermediate education, and 41 (22.1%) were graduates or above (Table 1).

Table 1: Characteristics of Children (n=185)

Characteristics		Frequency (%)
Gender (Child)	Male	104 (56.2%)
	Female	81 (43.8%)
Parents	Mother	117 (63.2%)
	Father	68 (36.8%)
Age in Years (Child)	1-5	63 (34.1%)
	>5 to 12	122 (65.9%)
Age in Years (Parents)	20-29	42 (22.7%)
	30-40	108 (58.4%)
	>40	35 (18.9%)
Residence	Urban	118 (63.8%)
	Rural	67 (36.2%)
Socio-Economic Status	Low	92 (49.7%)
	Middle	63 (34.1%)
	High	30 (16.2%)
Parental Education	Illiterate	47 (25.4%)
	Primary to Secondary	39 (21.1%)
	Matriculation to Intermediate	58 (31.4%)
	Graduate or above	41 (22.1%)

On assessment with the MMAS-8 tool, 119 (64.3%) children were compliant, and 66 (35.7%) were non-compliant with AEDs. The reported factors of non-compliance are shown in figure 1, where poor physician counselling was documented in 57 (30.8%) cases, financial difficulties in 51 (27.6%), and unavailability of prescribed AEDs in 38 (20.5%) (Figure 1).

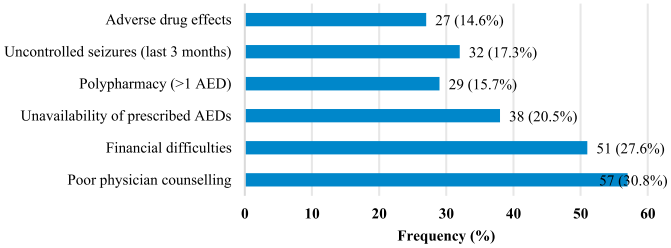

Figure 1: Factors Behind Non-Compliance with Antiepileptic Drugs

Non-compliance was observed in 35 (33.7%) males, and 31 (38.3%) females (p=0.515). Among parents, 44 (37.6%) of 117 mothers, and 22 (32.4%) of 68 fathers had non-compliant children (p=0.472). Non-compliance was reported in 19 (30.2%) children aged 1–5 years and 47 (38.5%) of 122 children aged >5–12 years (p=0.260). Among parents aged 20–29, 16 (38.1%) were associated with non-compliance, compared with 37 (34.3%) aged 30–40 years, and 13 (37.1%) aged >40 years (p=0.747). Non-compliance was significantly higher in children from rural areas, reported in 31 (46.3%), compared with 35 (29.7%) from urban areas (p=0.023). With respect to socioeconomic status, non-compliance was identified in 43 (46.7%) families with low income, 16 (25.4%) with middle income, and 7 (23.3%) with high income (p=0.007). For parental education, non-compliance was found in 29 (61.7%) children of illiterate parents, 17 (43.6%) with primary to secondary education, 14 (24.1%) with matriculation to intermediate education, and 6 (14.6%) of graduate or above parents (p<0.001) (Table 2).

Table 2: Association of Children and Parental Characteristics with Respect to Compliance Status of Antiepileptic Drugs (n=185)

Characteristics		Compliant (n=119)	Non-Compliant (n-66)	p-value
Gender (Child)	Male	69 (57.9%)	35 (53.0%)	0.515
	Female	50 (42.1%)	31 (47.0%)	
Parents	Mother	73 (61.3%)	44 (66.7%)	0.472
	Father	46 (38.7%)	22 (33.3%)	
Age in Years (Child)	1-5	44 (37.0%)	19 (28.8%)	0.260
	>5 to 12	75 (63.0%)	47 (71.2%)	
Age in Years (Parents)	20-29	26 (21.8%)	16 (24.2%)	0.747
	30-40	71 (59.7%)	37 (56.1%)	
	>40	22 (18.5%)	13 (19.7%)	
Residence	Urban	83 (69.7%)	35 (53.0%)	0.023
	Rural	36 (30.3%)	31 (47.0%)	
Socio-Economic Status	Low	49 (41.2%)	43 (65.2%)	0.007
	Middle	47 (39.5%)	16 (24.2%)	
	High	23 (19.3%)	7 (10.6%)	
Parental Education	Illiterate	18 (15.1%)	29 (43.9%)	<0.001
	Primary to Secondary	22 (18.5%)	17 (25.8%)	
	Matriculation to Intermediate	44 (37.0%)	14 (21.2%)	
	Graduate or above	35 (29.4%)	6 (9.1%)	

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Children residing in rural areas had 1.9-fold higher odds of non-compliance (95% CI 1.0–3.6, p=0.041) compared with urban residents. Low socioeconomic status was significantly associated with non-compliance (AOR 2.5, 95% CI 1.1–5.7, p=0.034), while middle socioeconomic status showed no significant effect (AOR 1.1, 95% CI 0.4–2.8, p=0.923) compared with high socioeconomic status. Parental education was a strong predictor of non-compliance as children of illiterate parents had 6.9 times higher odds of non-compliance (95% CI 2.4–20.5, p<0.001), and those with parents educated up to primary to secondary level had 3.3 times higher odds (95% CI 1.1–10.2, p=0.041) compared with those of graduate or above parents. Matriculation to intermediate education did not show a statistically significant association (AOR 1.4, 95% CI 0.5–4.3, p=0.537)(Table 3).

Table 3: Multivariate Binary Logistic Regression Analysis for Predictors of Non-Compliance of Antiepileptic Drugs

Variables		95% Confidence Interval	P-value
Residence	Rural	1.9 (1.0-3.6)	0.041
	Urban	Reference	
Socio-Economic Status	Low	2.5 (1.1-5.7)	0.034
	Middle	1.1 (0.4-2.8)	0.923
	High	Reference	
Parental Education	Illiterate	6.9 (2.4-20.5)	<0.001
	Primary to Secondary	3.3 (1.1-10.2)	0.041
	Matriculation to Intermediate	1.4 (0.5-4.3)	0.537
	Graduate or above	Reference	

DISCUSSION

The current study identified non-compliance with AEDs in 35.7 with epilepsy. Wang *et al.* reported a 37.2% rate of poor compliance in China [13], while a study from Ethiopia identified non-adherence in 35% of children with epilepsy [8]. In India, Singh *et al.* pooled nine studies with 1772 participants and found that almost half were non-adherent to AEDs, with a prevalence of 50.1% [14]. In Uganda, Nazziwa et al. reported markedly higher adherence by self-report at nearly 80%, though serum drug levels showed only 22.1% had therapeutic concentrations [7]. Variations across studies can be partly explained by differences in measurement tools, population characteristics, and healthcare delivery systems. The factors of non-compliance identified in this study included poor physician counselling (30.8%), financial difficulties (27.6%), and non-availability of prescribed drugs (20.5%). Clinical contributors were polypharmacy in 15.7%, uncontrolled seizures within three months in 17.3%, and adverse effects in 14.6%. Rana *et al.* in a local study from Lahore, observed that high cost and forgetfulness were the most frequent factors of non-compliance to AEDs, with financial barriers reported by 57.5% of patients [15]. Shahbaz *et al.* in another study from Karachi, demonstrated high cost as the leading factor in 62.1%, and drug non-availability in 5.9% [16]. Bekele in Ethiopia confirmed that side effects and polypharmacy were independent predictors of poor adherence [17]. The alignment between the present study and others across Asia and Africa highlights that adherence is influenced by a combination of financial constraints, medication complexity, inadequate counselling, and drug side effects. Clinically, these findings support the need for improved drug availability in public hospitals, simplification of regimens where feasible, and consistent reinforcement of counselling at each clinic visit. The association of residence with adherence status was evident in this study, where 46.3% children from rural areas were non-compliant, compared with 29.7% children living in urban areas, whereas logistic regression confirmed rural residence as an independent predictor with nearly two-fold higher odds of non-compliance. Data from western China demonstrated that place of residence was significantly associated with treatment adherence [18]. The barriers described in that population included difficulty in scheduling appointments and receiving timely feedback from the care team. In the present context, rural settings may limit access to specialist centers, continuity of drug supply, and counselling opportunities. The linkage of rural living with poor adherence has clinical implications for Pakistan, where pediatric neurology services are concentrated in a few tertiary centers [19]. Expanding outreach clinics and ensuring community-level counselling may reduce the rural–urban disparity. Socioeconomic status was also a major determinant of non-compliance to AEDs in this study, as low socioeconomic status independently predicted non-compliance (AOR 2.5, 95% CI 1.1–5.7). Wang *et al.* from China where a monthly household income of less than 5000 RMB was associated with nearly 3-fold increased odds of poor compliance [13]. Rana *et al.* also identified high medication cost as the leading factor for non-compliance in adults with epilepsy in Lahore, where 57.5% cited financial burden as the main barrier [15]. Shahbaz *et al.* from Karachi reported that 62.1% of patients attributed poor adherence to high drug cost [16]. The repeated observation of financial constraint across settings highlights its clinical significance. The results suggest that provision of subsidized or free antiepileptic drugs in public sector facilities could markedly improve adherence in lower-income families [20, 21]. Parental education was the most powerful predictor of non-compliance, as 61.7% of these parents were illiterate, and 43.6% had an education to primary or secondary level, compared with 14.6% graduated or above. These findings mirror those of Zhang *et al.* who reported parental educational level as a key determinant with an odds ratio of

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2.8 [22]. Wang *et al.* also found that lower parental education strongly correlated with poor adherence [13]. The consistency of these results across diverse contexts underscores the central role of caregiver understanding. Lack of comprehension of disease chronicity, drug dosing schedules, and side effects may increase the likelihood of missed doses and premature discontinuation [23]. Education-based interventions for parents are therefore a cornerstone for improving adherence in pediatric epilepsy [24, 25].

There are few limitations to the present study. The potential for social desirability bias in self-reported adherence is present. The single-center design, which may limit generalizability to the whole of Pakistan. The lack of objective adherence measures (e.g., pill counts, serum levels) was also another limitation. Prospective cohort designs with follow-up over time would better clarify temporal associations. Compliance was measured using the MMAS-8 scale, which though validated, relies on self-report and may be influenced by recall or social desirability bias.

CONCLUSIONS

Non-compliance with AEDs in children with epilepsy in Karachi was strongly influenced by rural residence, low socioeconomic status, and low parental education. These findings highlight that social and educational determinants are as important as clinical ones in shaping adherence. Addressing these factors through system-level interventions, including subsidized drug provision, decentralized epilepsy services, and structured caregiver education, may improve compliance, enhance seizure control, and reduce the long-term burden of pediatric epilepsy.

Authors' Contribution

Conceptualization: SK
Methodology: LK, SK, WH
Formal analysis: LK
Writing and Drafting: LK, WH
Review and Editing: LK, SK,WH

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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Correlation Between Brain MRI Findings and Serum Ammonia Levels in Hepatic Encephalopathy

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ABSTRACT

Diagnosis or seeing prognosis of hepatic encephalopathy (HE) from a diagnostic laboratory testing or imaging modality point of view lacks a gold standard. **Objectives:** To correlate the brain MRI findings and serum ammonia level in HE patients for better diagnosis and prognosis. **Methods:** Retrospective cross-sectional analytical research was conducted at Shahida Islam Medical College and Hospital for six months, from August 2024 to January 2025. After ethical approval, using non-probability consecutive sampling, all patients with documented increased levels of ammonia and HE with MRI Brain were included. SPSS version 23.0 was used for data analysis. For correlating the ammonia levels with MRI brain findings, point-biserial Pearson correlation was applied, keeping $p<0.05$ as statistically significant. **Results:** The study of 207 hepatic encephalopathy patients found a mean serum ammonia level of 111.55 ± 41.8 µmol/L, with higher levels in severe cases (134.8 ± 37.45 µmol/L). MRI abnormalities included white matter changes (54.11%), basal ganglia changes (46.86%), and cortical atrophy (31.4%). A strong positive correlation ($r=0.62$, $p<0.001$) was observed between serum ammonia levels and MRI severity scores. **Conclusions:** Serum ammonia levels showed a significant positive correlation with the severity of brain MRI findings in hepatic encephalopathy, indicating that higher ammonia levels are associated with more pronounced neuroimaging abnormalities.

INTRODUCTION

Hepatic encephalopathy (HE) is a reversible neuropsychiatric disorder that occurs in patients with liver dysfunction or portosystemic shunting, manifesting as a spectrum of cognitive and motor disturbances [1]. Currently, there is no gold standard for diagnosing HE based solely on laboratory testing or imaging modalities [2]. Diagnosis primarily relies on a thorough clinical history and neurological examination to detect subtle or overt neuropsychiatric impairment [3]. The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) has developed a classification system to standardize the diagnosis and staging of HE [4]. Additionally, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) have issued joint guidelines emphasizing a multimodal diagnostic approach

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incorporating both clinical findings and supportive investigations, such as laboratory tests and neuroimaging [5]. One of the commonly evaluated biochemical markers in HE is serum ammonia, derived mainly from the gastrointestinal tract and detoxified by the liver [6]. In patients with liver dysfunction, ammonia clearance is impaired, leading to its accumulation in systemic circulation, where it acts as a neurotoxin and contributes to HE pathogenesis [7]. While ammonia levels are frequently elevated in HE presents in up to 90% of cases [1], its diagnostic utility remains controversial. This is due in part to its non-specificity, as elevated levels can be seen in various other conditions such as infections, renal failure, and certain metabolic disorders [8, 9]. Furthermore, pre-analytical variables like sample handling, the time between collection and analysis, and the use of tourniquets can significantly influence ammonia test results, complicating interpretation [10]. Despite these limitations, the measurement of ammonia levels may still provide diagnostic and prognostic insight when interpreted in the context of clinical features and imaging findings [11]. Recent recommendations suggest that elevated ammonia levels, in conjunction with compatible clinical features and imaging abnormalities, can aid in more confidently diagnosing HE. In this regard, MRI has emerged as a valuable non-invasive tool to evaluate structural and metabolic brain changes in HE. Although other imaging modalities such as CT and PET have been used, MRI remains the most sensitive for detecting characteristic brain abnormalities in HE [12]. MRI can assess neural tissue integrity, metabolism, and water content, offering insights into both acute and chronic changes associated with HE [13]. In chronic HE, MRI typically reveals bilateral symmetrical hyperintensities in the globus pallidus and evidence of cerebral atrophy. In acute HE, symmetric cortical signal changes may also be observed, although less commonly [14]. Despite its diagnostic potential, MRI is not routinely used in clinical practice due to variability in interpretation and lack of consensus on standardized MRI criteria for HE [15, 16]. Nevertheless, as research advances, integrating MRI findings with clinical and laboratory data may significantly enhance diagnostic accuracy and understanding of the pathophysiological mechanisms of HE.

Hepatic encephalopathy (HE) remains a diagnostic challenge due to the absence of a definitive laboratory or imaging gold standard, with diagnosis largely dependent on clinical assessment. Although serum ammonia is commonly evaluated and MRI can demonstrate characteristic brain changes in HE, both tools suffer from limited specificity, variability in interpretation, and inconsistent clinical application. There is a lack of integrated evidence correlating biochemical abnormalities with neuroimaging findings in HE patients. Addressing this gap, the present study aims to evaluate the relationship between serum ammonia levels and brain MRI findings in patients with hepatic encephalopathy to improve diagnostic confidence and clinical understanding.

METHODS

The retrospective cross-sectional analytical research was conducted at Shahida Islam Medical College and Hospital for six months, from August 2024 to January 2025. Ethical approval was received from the Ethical Review Committee of Shahida Islam Medical Complex, IRB letter no. SIMC/ET.C./0039/24. Non-probability consecutive sampling was done, and the Open EPI online software was used for sample size calculation. Keeping the prevalence rate of HE at 16 % as reported in local research 95 % confidence level, and a margin of error of 5 %, the sample size came out to be 207 [17]. All patients with documented increased levels of ammonia and HE with MRI Brain were included in the research. Informed consent was sought from all subjects before inclusion in the study. All patients included in the study had a clinical diagnosis of hepatic encephalopathy (HE) based on the International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) classification, supported by documented elevated serum ammonia levels. Diagnosis of HE required the presence of neuropsychiatric symptoms, ranging from altered sleep patterns and confusion to asterixis and coma, as assessed through clinical examination. Only those patients who underwent MRI brain scans as part of their routine diagnostic workup were considered eligible. MRI findings were evaluated for characteristic features of HE, such as bilateral symmetrical hyperintensities in the globus pallidus or cortical signal abnormalities, using standard T1- and T2-weighted imaging sequences. Cases were included irrespective of the HE grades, but were required to have both biochemical and radiological evidence consistent with the diagnosis. Informed consent was obtained from all participants before inclusion in the study. Patients were excluded if they had pre-existing neurological or psychiatric disorders unrelated to hepatic encephalopathy that could confound the assessment of neuropsychiatric symptoms. Individuals with acute intracranial events such as stroke, brain tumors, or head trauma evident on imaging were also excluded. Patients with renal failure requiring dialysis, active systemic infections, or sepsis at the time of MRI were not included, as these conditions may independently influence serum ammonia levels and brain imaging findings. Furthermore, individuals on medications known to alter mental status (e.g., sedatives, antipsychotics) or those with metabolic encephalopathies unrelated to liver disease were excluded. MRI scans of poor

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quality or with significant motion artifacts that hindered accurate interpretation were also excluded. The study categorized MRI findings into an imaging-based HE grade (MRI-HE grade), adapted for this study to enable correlation with clinical severity and ammonia level: MRI-HE Grade 0 — No abnormality on routine sequences, MRI-HE Grade 1 — T1-weighted bilateral globus pallidus hyperintensity only (typical chronic liver-related change), MRI-HE Grade 2 — Symmetric cortical and/or subcortical FLAIR hyperintensity without diffusion restriction (suggesting vasogenic/toxic injury), MRI-HE Grade 3 — Cortical and/or deep gray-matter diffusion restriction on DWI/ADC (consistent with cytotoxic edema/acute severe injury) and/or diffuse cerebral edema, MRI-HE Grade 4 — Complications: frank hemorrhage or multiple microhemorrhages on SWI, large-volume edema with mass effect. Using electronic medical records, the collection of laboratory and clinical data was done for each patient. Patient' age, gender, and grade of HE was all taken into account. Due to decreased level of consciousness in HE, all patients were admitted to the intensive care unit (ICU) of the hospital. All patients had undergone an MRI within 3 to 10 days of symptom onset. All images of MRI were analyzed by a trained neuro-radiologist. All patients had presented with reduced consciousness levels secondary to acute liver failure with high ammonia levels. MRI of the brain for each patient was performed on a T-3 MRI scanner (Siemens Healthineers; Magnetom Skyra) with a 20-channel phased-array head coil. The protocol for imaging had axial fluid attenuated inversion recovery (FLAIR), sagittal and axial T1-weighted images, coronal and axial T2-weighted images, and axial echo planar. The severity of HE was categorized according to the West Haven criteria and classified as follows: grade I- mild confusion, impaired attention, grade II-disorientation, lethargy, grade III-marked confusion, stupor, and grade IV- coma. The normal range of ammonia was kept at 11-32 umol/1. Ammonia levels beyond the normal range were classified as hyperammonemia. Using SPSS version 23.0 for data analysis, the categorical variables were reported as frequency (%) while the continuous variables were reported as mean ± standard deviation. For correlating the ammonia levels with MRI brain findings, Pearson correlation was applied, keeping $p<0.05$ as statistically significant.

RESULTS

The study included a total of 207 patients diagnosed with hepatic encephalopathy (HE). The mean age of participants was 54.6 ± 11.1 years, and the mean BMI was 24.2 ± 4.3 kg/m^2. Among them, 128 (61.84 %) were male, and 79 (38.16 %) were female. The mean serum ammonia level among all patients was 111.55 ± 41.8 µmol/L. Patients with mild HE (Grade I–II) had a mean ammonia level of 98.3 ± 29.4 µmol/L Patients with severe HE (Grade III–IV) had a higher mean of 134.8 ± 37.45 µmol/L than those with mild HE (Grade I-II), i.e., 97.5 ± 30.2 µmol/L (Table 1).

Table 1: Demographical and Clinical Characteristics of HE patients(n=207)

Variables		Mean ± SD / Frequency (%)
Mean Age (Years)		54.6 ± 11.1
Gender	Male	128 (61.84%)
	Female	79 (38.16%)
Mean BMI (kg/m^2)		24.2 ± 4.3
Mean Serum Ammonia (µmol/L)		111.55 ± 41.8
Mild HE (Grade I-II) Ammonia		97.5 ± 30.2
Severe HE (Grade III-IV) Ammonia		134.8 ± 37.45

The grading of HE patients according to the West Haven Criteria is depicted in figure 1. According to the West Haven grading, the distribution of HE severity was as follows: Grade I included 46 patients (22.22 %), Grade II included 78 (37.68 %) patients, Grade III included 55 (26.57 %) patients, while Grade IV included 28 (13.53 %) patients (Figure 1).

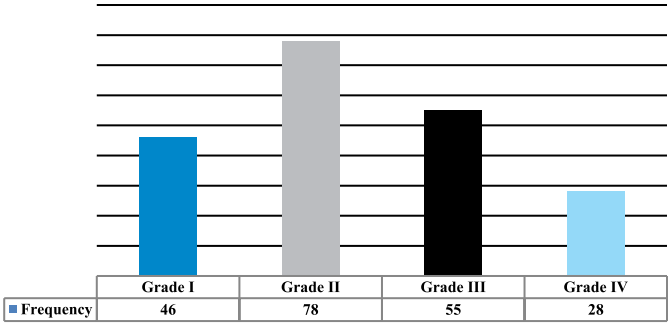

Figure 1: Classification of HE Patients According to Severity (Using West Haven Criteria)(n=207)

The MRI brain findings in HE patients included in the study are presented. MRI findings revealed characteristic changes in: Cerebral white matter hyperintensities in 112 patients (54.11%), bilateral basal ganglia signal changes in 97 patients (46.86%), cortical atrophy in 65 patients (31.4%), and no abnormal MRI findings in 43 patients (20.77%). The linear correlation graph shows the relationship between serum ammonia levels and MRI severity scores. The trend line showed a positive linear relationship, indicating that as ammonia levels increase, the severity of brain MRI findings also tends to increase (Figure 2).

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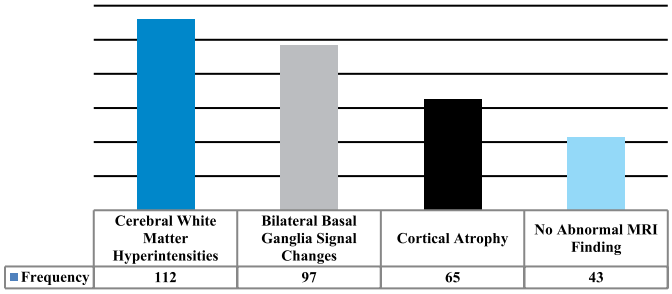

Figure 2: MRI Brain Findings in HE Patients (n=207)

A positive correlation (r=0.62, p<0.001) was observed between serum ammonia levels and MRI-detected brain changes. White matter changes showed the highest correlation (r=0.62), followed by basal ganglia changes (r=0.58) and cortical atrophy (r=0.47), indicating a moderate to strong positive relationship (Figure 3).

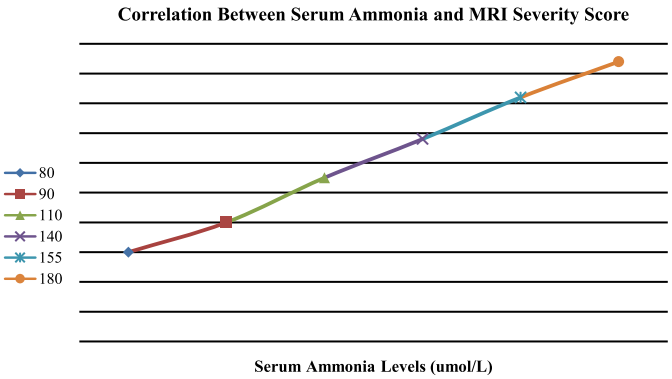

Figure 3: Correlation Between Serum Ammonia Levels and MRI Severity Score (n=207)

The study displays the Axial brain MRI images illustrate characteristic findings across key sequences: (A) T1-weighted image showing bilateral globus pallidus hyperintensity associated with chronic hepatic dysfunction; (B) FLAIR image demonstrating cortical and subcortical hyperintensities suggestive of toxic-metabolic edema; (C) DWI highlighting multiple cortical foci of restricted diffusion consistent with cytotoxic injury; and (D) SWI showing scattered susceptibility foci indicative of microhemorrhages or mineral deposition (Figure 4).

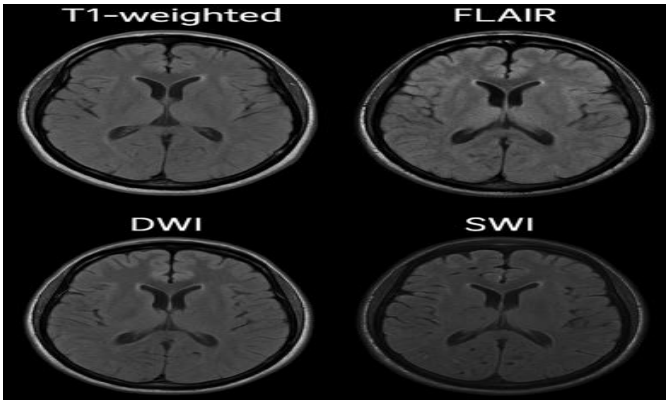

Figure 4: MRI Sequences in Hepatic Encephalopathy

DISCUSSION

In this study of 207 patients with hepatic encephalopathy (HE), the mean age was 54.6 ± 11.1 years, and the mean BMI was 24.2 ± 4.3 kg/m^2. Most patients were male (61.84%). The mean serum ammonia level was 111.55 ± 41.8 µmol/L, with patients having mild HE (Grade I–II) showing lower levels (97.5 ± 30.2 µmol/L) compared to those with severe HE (Grade III–IV) (134.8 ± 37.45 µmol/L). According to the West Haven Criteria, 22.22% had Grade I, 37.68% Grade II, 26.57% Grade III, and 13.53% Grade IV HE. Brain MRI findings revealed white matter hyperintensities in 54.11%, basal ganglia changes in 46.86%, and cortical atrophy in 31.4% of patients, while 20.77% had no abnormal MRI findings. A positive correlation was found between serum ammonia levels and MRI severity scores (r=0.62, p<0.001), with the strongest association noted in white matter changes (r=0.62), followed by basal ganglia involvement (r=0.58) and cortical atrophy (r=0.47). These results suggest a moderate to strong relationship between hyperammonemia and the severity of MRI-detected brain changes in HE. A study reported that 91 out of 150 (60.66 %) HE patients included in their study were found to have mild HE [18]. In our study, mild HE was reported in 124 (59.9 %), which is in line with the above study. This study made use of the West Haven criteria for classifying HE. Studies have regarded the criteria as the gold standard for diagnosing HE [19]. It classifies grades I and II as mild HE, while grades III and IV. In the mildest form of HE, it is characterized by dysfunctional neuro-cognition, where clinically evident findings on brain MRI are often not observed. In the more severe cases, brain MRI findings become positive [20]. The region of the brain most likely affected by HE includes cerebral white matter, bilateral basal ganglia, and cortical atrophy [21]. Similarly, in our study as well, most of the patients, viz. 112 (54.11 %) were reported to have hyperintensity in the cerebral white matter, followed by bilateral basal ganglia signal changes in 97 (46.86 %) of patients. 65 (31.4 %) of patients were found to have cortical atrophy on MRI. In HE, due to impaired excretion of ammonia because of hepatic damage, elevated levels of ammonia tend to cross the blood-brain barrier and metabolize astrocytes via glutamine synthetase. The increase in levels of glutamine leads to astrocytes causing shifting of water into them, leading to cerebral edema and hence resulting in cerebral dysfunction, as evident on MRI [22]. Study observed that while brain MRI findings become more evident from grade II HE onwards, ammonia levels start to increase right from grade I [23]. Separately, both MRI findings and ammonia levels tend to demonstrate different characteristics, but synergism is seen, and better interpretation of findings can be made when both modalities are combined. Likewise, in our research, a rapid increase in serum ammonia levels was observed, leading to a decline in the consciousness of

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patients and the severity of HE. At the same time, brain MRI showed cortical atrophy in severe HE and high ammonia levels [24]. Brain MRI findings in HE tend to involve various structures of the brain, including the basal ganglia, thalami, cortical regions, peri-ventricular white matter, and brainstem. Their correlations with higher levels of ammonia have been reported inconsistently in HE patients [25]. The present study reported a significant positive correlation ($r=0.62$, $p<0.001$).

However, the study had some limitations. Firstly, this was a single-centered study with a limited sample size. The findings cannot be generalized to the whole population. Furthermore, the retrospective nature of the study could have possibly included some bias, as first-hand information from the patients could not be obtained. Moreover, in case files having any missing data, their data were excluded from the research. Further, multi-centered studies with a greater sample size and a longitudinal nature of the study would be enlightening to the findings reported in this research.

CONCLUSIONS

This study demonstrates a significant positive correlation between serum ammonia levels and the severity of brain MRI findings in patients with hepatic encephalopathy (HE). As ammonia levels increased, the extent of MRI-detected abnormalities, particularly white matter hyperintensities, basal ganglia changes, and cortical atrophy also increased, highlighting the impact of hyperammonemia on cerebral function and structure. These findings support the role of serum ammonia as a clinical marker of neurological involvement in HE and suggest that MRI can serve as a valuable adjunct tool in assessing disease severity and guiding management in affected patients.

Authors' Contribution

Conceptualization: MFA
Methodology: MI
Formal analysis: SA, NM
Writing review and editing: MI, SA, NM, KA, SI
Review and Editing: MFA, MI, SA, NM, KA, SI

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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Wound Closure Techniques: Subcuticular Vs Interrupted Transdermal Sutures in Paediatric Patients Undergoing Open Appendectomy for Complicated Appendicitis: A Randomized Controlled Trial

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ABSTRACT

Paediatric patients who undergo open appendectomy for complicated appendicitis face risks of surgical site infections (SSIs) and poor wound healing. **Objectives:** To compare continuous subcuticular versus interrupted transdermal sutures to determine their effects on SSI rates, scar cosmesis, and overall wound healing. **Methods:** A randomized controlled trial (TCTR20250527004) was conducted from September 2024 to March 2025, enrolling patients aged ≤12 with complicated appendicitis. Patients of both genders aged up to 12 years presenting to the paediatric surgery emergency with acute appendicitis grade 2 and above. Patients were randomized equally into two groups: Group A (continuous subcuticular closure) and Group B (interrupted transdermal closure). Primary outcomes were SSI, wound dehiscence, and Manchester Scar Scores up to 30 days post-op. Statistical analysis was done using SPSS version 23.0, with t-tests and logistic regression. **Results:** A total of 112 patients were included in the study, with 56 in each group. The mean number of patients with surgical site infection (SSI) in group A was 1.30 ± 0.46, and in group B mean SSI was 1.37 ± 0.49, with a p value of 0.43. However, the grade of appendicitis was a significant predictor of infection, with higher grades correlating with increased odds of infection (OR=1.83, p<0.001). The Manchester scar score showed that Group A had a mean of around 15.5+3.24 versus Group B mean of about 17.8 ± 2.92, p-value <0.005. **Conclusions:** The current study concludes that while both continuous subcuticular and interrupted transdermal suturing led to similar SSI rates.

INTRODUCTION

Appendicitis is defined as an acute inflammation of the vermiform appendix [1]. Evidence shows that acute appendicitis is the most common abdominal surgical emergency [2], with around 50,000 and 300,000 acute appendectomies performed annually in the UK and in the US, respectively [3]. Research reveals that appendectomy, the surgical removal of the vermiform appendix, is the primary treatment for acute appendicitis. However, antibiotic therapy can be effective for certain patients with uncomplicated acute appendicitis [4-6]. Although the use of laparoscopy is increasing but traditional open approach remains common practice worldwide [6]. Although appendectomy is a common surgical procedure, it is often viewed with caution due to

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the considerable risk of surgical site infections (SSIs), especially those with a degree of contamination (Garner class II–IV). These infections can occur at the incision site, in deeper tissues, or in organs at the operative site within 30 days after surgery [7, 8]. Post-appendectomy surgical site infections (SSIs) are a major postoperative concern, increasing financial costs for both the healthcare system and patients. They also negatively impact the patient's health-related quality of life [8, 9]. The optimal wound closure technique for paediatric patients undergoing open appendectomy for complicated appendicitis remains a subject of clinical debate. The risk factors associated with wound-related complications are multifactorial and include the method of wound closure [3].

Although previous studies have reported both advantages and limitations of subcuticular and interrupted transdermal suturing techniques, a definitive consensus regarding their comparative efficacy is still lacking. A meta-analysis by Sharma et al. suggests superior cosmetic outcomes and lower wound dehiscence with subcuticular sutures, whereas interrupted transdermal sutures remain preferred for their simplicity and perceived protection against wound infection. [1] However, evidence from well-designed comparative trials remains limited. Therefore, this randomized controlled trial aims to compare the clinical outcomes of subcuticular versus interrupted transdermal sutures in the target patient population.

METHODS

This randomized control trial was carried out from September 2024 to March 2025 after getting approval from the College of Physicians and Surgeons Pakistan (CPSP) ref no: CPSP/REU/PSG-2022-066-561, ethical approval from Institutional Review Board King Edward Medical University, ref no: 580/RC/KEMU, and trial registration with the Thai Clinical Trial Registry, registration number TCTR20250527004. Patients undergoing open appendectomy for complicated appendicitis were assessed for eligibility from the Department of Paediatric Surgery in King Edward Medical University (KEMU)/Mayo Hospital, Lahore. Patients of both genders aged up to 12 years presenting to the paediatric surgery emergency with acute appendicitis grade 2 and above. Individuals with a prior history of abdominal surgery, malnutrition, or comorbidities such as liver disease and tuberculosis, as well as those who were immunocompromised, were excluded from the study. A total sample size of 116 participants (58 per group) was determined, based on a statistical power of 80% and a 5% level of significance. Sample Size was calculated to be 56 in each group at 95% Confidence Interval and 80% power of the study using the formula as directed by Wang *et al.* [9]. $N = (z_1 + z_2)^2 [P_1(1-P_1)P_2(1-P_2)] / (P_1 - P_2)^2$. The anticipated proportion of patient satisfaction regarding wound healing was 91.42 % with subcuticular stitching and 71.42% with interrupted suturing [3]. Participant enrolment was performed through probability-based simple random sampling. 4 patients were lost to follow-up and were excluded. Written informed consent was obtained from all patients' parents/guardians. Baseline data were recorded using a predesigned research proforma. All procedures were conducted under general anaesthesia, following appropriate preoperative fluid and electrolyte correction. Antibiotics administered included intravenous ceftriaxone at a dose of 25 mg/kg and metronidazole at 7.5 mg/kg [5]. Participants were randomized in a 1:1 ratio to either Group A (continuous suture closure) or Group B (simple interrupted suture closure). The randomization sequence was generated using computer-based allocation software. Allocation concealment was ensured with sequentially numbered, opaque, sealed envelopes, each containing the assigned closure method for a single participant. Appendectomy was performed via Lanz incision, and intraoperative findings (Grade of appendicitis) were recorded (Table 1).

Table 1: Grades of Appendicitis

Grades	Characterization
Uncomplicated Acute Appendicitis	
Grade 0	Macroscopically Normal Appendix / Histological Endoappendicitis
Grade I	Inflamed Appendix (hyperemia, edema ± fibrin)
Complicated Acute Appendicitis	
Grade II (Necrosis)	Segmental
	Involving the Base
Grade III (Perforated Inflammatory Tumor)	with Phlegmon
	with < 5 cm Abscess
	with > 5 cm Abscess
Grade IV	Perforated Appendix with Diffuse Peritonitis

Polypropylene sutures of size 4-0 or 3-0 were utilized for wound closure in all enrolled patients. In Group A, wounds were closed using continuous sutures. A single thread of suture is introduced at one end of the incision, approximately 1 cm from the wound margin. Six knots are secured at the starting point, after which the suture is advanced continuously along the incision and exited at the opposite wound edge, where an additional six knots are tied to complete the closure. In Group B, the interrupted suturing method has been employed, in which simple individual sutures were placed, and each was secured with six knots. All wound closures have been done by postgraduate paediatric surgery residents under the supervision of a consultant with more than five years of experience. Postoperative intravenous antibiotics were administered for 24 hours in cases of complicated appendicitis (Grade II and above). In the postoperative

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period, wounds were inspected in the surgical wards at discharge, followed by reassessment on the 7th postoperative day and on day 30 during follow-up. The assessment was done by the principal investigator. There is a risk of bias because, by looking at the wound for assessment, the group allocation would be obvious to the assessor. Wounds were evaluated for surgical site infection (SSI) and wound dehiscence. SSI was defined as postoperative wound erythema, purulent discharge, warmth, swelling, or tenderness requiring dressing changes or antibiotics within 30 days. Verberk et al. reported that surveillance of surgical site infections by clinicians demonstrated high reliability of a mean 95% (range 90–100%), substantial inter-rater Kappa estimates ranging from 0.61 to 0.94, indicating good reliability and moderate validity of clinician-based SSI ascertainment [10]. Scar outcomes were assessed using the Manchester Scar Scor [11]. Manchester scar score has 5 sub-domains, including colour, distortion, texture, finish, and contour, with the highest score 18 and the lowest 5. A lower score means a better scar, and 18 is the worst. Interrater and interrater intraclass correlation coefficients (ICCs) for scar assessments ranged roughly 0.71–0.87 [12]. Visual Analogue Scale (VAS) demonstrated good reliability for pain assessment (ICC = 0.87) and construct validity (correlation with clinical pain intensity, r = 0.65, p<0.001). Cases with wound infections were managed with appropriate wound care and systemic antibiotics. Data analysis has been done with SPSS version 23.0. Quantitative data have been expressed as mean ± standard deviation (SD), whereas qualitative variables were presented as frequencies and percentages. Normality of the data was checked using Shapiro Wilk test. Comparisons between the two groups were conducted using the independent sample t-test for parametric data and by using Mann Whitney U test for non-parametric data, with a p-value of ≤0.05 as statistically significant (Figure 1).

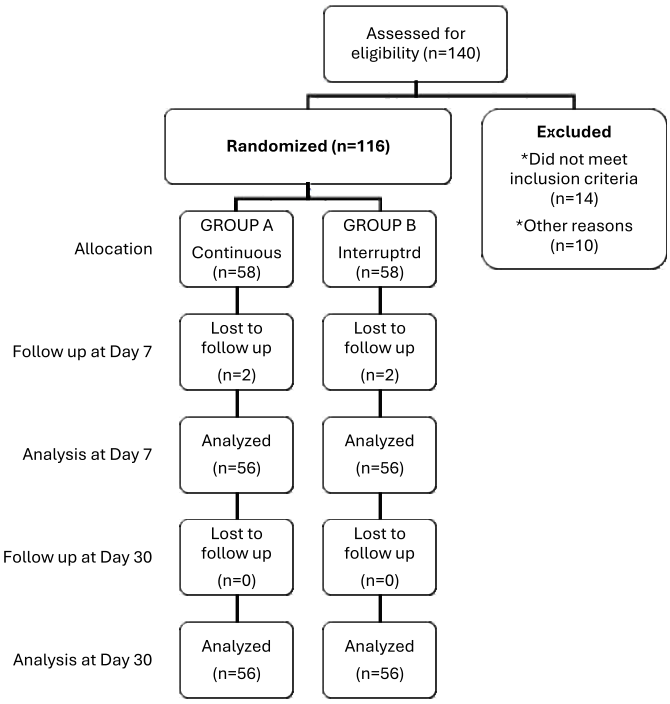

Figure 1: CONSORT Diagram Adjusted for the Study

RESULTS

A total of 112 patients were enrolled in the study, with 56 patients in each group. In group A, continuous closure, the mean age was 9.61 ± 2.47 years. In group B, the interrupted closure mean age was 9.30 ± 2.85 years. In group A, the mean weight was 24.32 ± 6.8 kg. In group B mean weight was 26.84 ± 6.25 kg. In group A, there were 45 male and 11 female, and in group B, there were 43 male and 13 female. Normality of age and weight was assessed using the Shapiro–Wilk test, and both were analyzed with the independent t-test. In group A, the most common grades were Grade 2a and Grade 3a, with 24 and 6 cases, respectively. In contrast, group B exhibited a higher frequency of Grade 2b, Grade 3a, and Grade 3c with 13, 4, and 9 cases, respectively. Grade 4 was rare, observed in only one patient in the interrupted group (Table 2).

Table 2: Baseline Characteristics

Variable	Continuous (Group 1)	Interrupted (Group 2)	Total	p-value	Test
Age (Years)	9.61 ± 2.47	9.30 ± 2.85	9.46 ± 2.66	0.548	t-test
Weight (kg)	24.32 ± 6.80	26.84 ± 6.25	25.58 ± 6.63	0.044*	t-test
Grade	3.0 [2.0-4.0]	3.0 [2.0-4.2]	3.0 [2.0-4.0]	0.397	M-W

Continuous: Mean ± SD; Ordinal: Median [IQR]; Categorical: n (%).
* p-value <0.05. p-values calculated using t-test for continuous variables, Mann-Whitney U for ordinal variables.

The mean number of patients with surgical site infection (SSI) 1-week post-op in group A was 1.30, SD 0.46, and in group B mean SSI was 1.37, SD 0.49, with a p value of 0.43. The logistic regression analysis revealed that the grade of appendicitis is a significant predictor of wound infection

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status, with higher grades corresponding to increased odds of infection (odds ratio = 1.83, 95% CI: 1.33–2.52, p<0.001). In contrast, the method of wound closure (continuous versus interrupted) does not significantly influence infection rates (odds ratio = 1.17, 95% CI: 0.50–2.75, p = 0.711)(Figure 2).

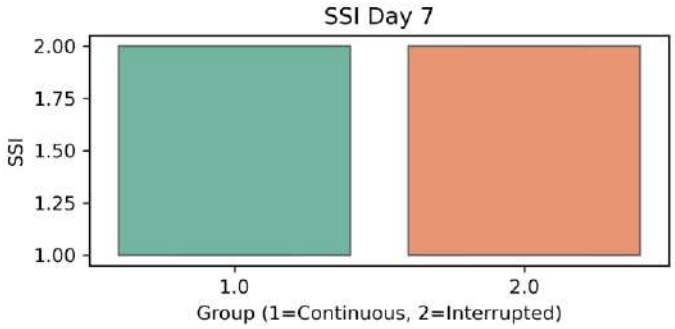

Figure 2: Surgical Site Infection at Day 7 Between Group 1 and Group 2

The ordinal logistic regression analysis demonstrated a significant association between appendicitis grade and the depth of wound infection. For each unit increase in appendicitis grade, the odds of having a deeper category of wound infection (moving from superficial to deep, or from deep to intraperitoneal) increased by 94% (odds ratio = 1.94, 95% CI: 1.43-2.65, p<0.001). The visual analogue scale (VAS) score, at day 7 in group A was 3.32, SD 1.22, and in group B was 4.93, SD 1.17, p value <0.005. Using Cohen's d, the effect size was 1.34, which exceeds the conventional threshold for a "large" effect (|d| ≥ 0.80). The negative sign simply indicates that the continuous-suture group reported lower pain than the interrupted-suture group (Figure 3).

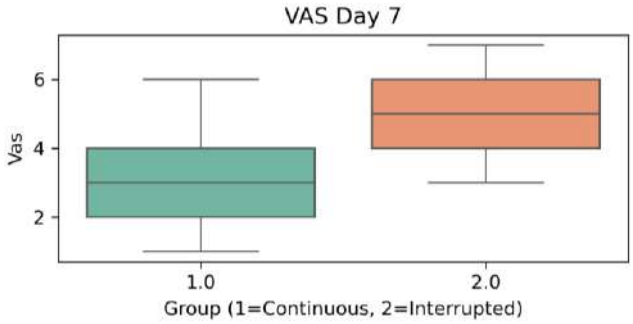

Figure 3: Visual Analog Score (VAS) at day 7 Between Group 1 and Group 2

The Manchester scar score at Day 7 showed that Group A had a mean of around 15.5, SD 3.24, versus Group B's mean of about 17.8, SD 2.92, p-value <0.005 using the independent sample t-test. Manchester scar score on Day 30 also showed a significant difference, group A with a mean score of 7.21 ± 1.87 vs. group B with a mean score of 9.34 ± 2.08. Cohen's d is equal to -1.07 shows a large effect size (Figure 4).

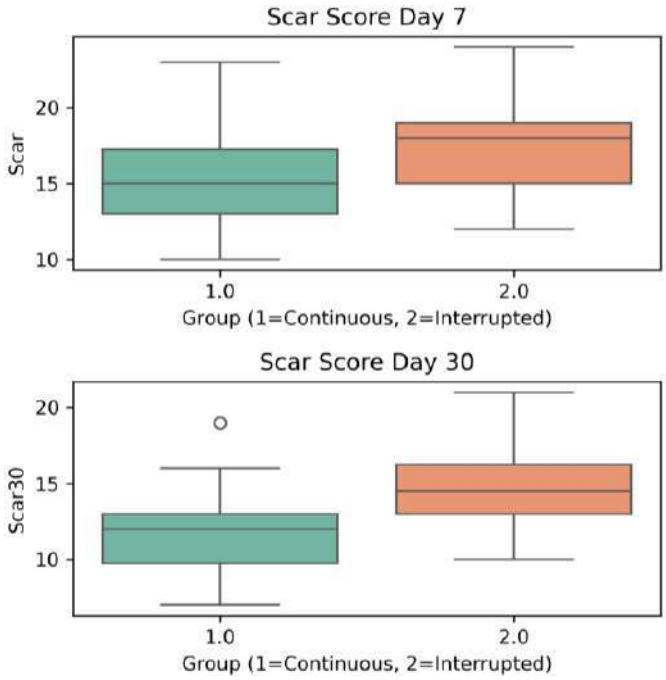

Figure 4: Box plot showing Manchester Scar Score at day 7 (a) and day 30 (b) between Group 1 and Group 2

Across all five Manchester Scar Scale sub-scores, continuous closure produced consistently more favourable scar characteristics than interrupted closure. Colour showed the greatest separation. Group A scars blended almost a half-point closer to the surrounding skin (1.91 ± 0.61 vs 2.45 ± 0.60), a highly significant difference (p<0.001). Texture and contour were likewise better with continuous subcuticular stitches (texture 1.71 ± 0.59 vs 2.18 ± 0.69, p ≈ 0.0002; contour 1.57 ± 0.57 vs 1.84 ± 0.50, p ≈ 0.009), indicating flatter, less palpable scars. Distortion, which captures wound contracture or puckering, remained lower as well (1.86 ± 0.59 vs 2.14 ± 0.35, p ≈ 0.002), suggesting less tissue deformation. Shine, the only domain not reaching significance, was marginally lower in Group A (1.16 ± 0.37 vs 1.21 ± 0.41, p=0.47), implying comparable reflective quality between techniques (Table 3).

Table 3: Inferential Statistics – Continuous vs Interrupted Wound Closure

Variables	Continuous (Group 1) Mean ± SD	Interrupted (Group 2) Mean ± SD	p-value
SSI Day 7	1.30 ± 0.46	1.38 ± 0.49	0.429
VAS Day 7	3.32 ± 1.22	4.93 ± 1.17	<0.001*
Scar Score Day 7	15.50 ± 3.24	17.84 ± 2.92	<0.001*
Scar Score Day 30	11.62 ± 2.79	14.64 ± 2.88	<0.001*

* Significant p-value <0.05

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DISCUSSION

A meta-analysis of skin closure techniques post-appendectomy reported that infection risk does not substantially vary between continuous and interrupted sutures, provided that aseptic technique and appropriate perioperative antibiotic coverage are ensured [11]. Similarly, a Cochrane review concluded that the overall incidence of SSI in non-obstetric surgeries did not significantly differ between subcuticular and transdermal approaches, even in potentially contaminated fields [11]. However, this study contributes meaningfully by demonstrating that subcuticular suturing provides significantly better outcomes. This was reflected in both the lower VAS scores and better Manchester Scar Scores in the subcuticular group on postoperative days 7 and 30. These findings are particularly important in paediatric populations, where visible scarring can have long-term psychological implications for both children and their caregivers. Subcuticular sutures are associated with more uniform tension distribution, better wound edge apposition, and reduced skin puncture marks, all contributing to improved scar appearance. This is consistent with scar physiology literature, which suggests that lower mechanical stress and uniform tension across wound edges promote optimal collagen alignment and healing [12, 13]. From a surgical standpoint, although interrupted transdermal sutures are widely regarded as being more secure in contaminated fields due to their ability to localize infection to individual stitch sites [2], this theoretical advantage did not translate into clinical significance in our trial. This supports an evolving view that when infection control measures such as appropriate wound irrigation, debridement, and systemic antibiotics are followed, the closure technique itself may play a secondary role in determining infection outcomes. Another key finding from this study is the strong correlation between the grade of appendicitis and both the incidence and depth of wound infection. Logistic regression analysis showed that higher grades of appendicitis were associated with a nearly twofold increase in the odds of developing deeper infections. This highlights the biological plausibility that more severe intra-abdominal inflammation and contamination contribute to impaired wound healing, independent of skin closure strategy [14]. Similar studies have been done in adult laparotomies as well, with comparable outcomes [15]. Importantly, the improved aesthetic outcome observed with subcuticular closure offers valuable implications for practice, especially in paediatric settings where psychological and emotional factors related to body image are increasingly recognized. Better cosmetic outcomes can positively affect patient satisfaction and reduce parental anxiety [12]. Moreover, the potential for reduced dressing needs and easier wound management may translate into cost savings and fewer outpatient visits, an area worthy of future health-economic analysis [16-19]. The lack of a statistically significant difference in infection rates, combined with the clearly superior scar outcomes in the subcuticular group, has important clinical implications. In paediatric settings, where cosmetic outcomes and minimal skin trauma are priorities, subcuticular suturing may be the preferred technique, especially when coupled with standardized intraoperative protocols and postoperative care [11]. Moreover, the use of subcuticular closure may reduce dressing requirements, promote ease of wound care, and improve parental satisfaction [16, 20].

Despite the strengths of this trial, including randomization, clearly defined outcome measures, and standardized operative protocols, some limitations should be acknowledged. The follow-up duration of 30 days may not be sufficient to see hypertrophic scar formation, which may take months to develop. Since this study was done at a single tertiary hospital with dedicated paediatric surgical teams, its generalizability to other settings, especially those with fewer resources, could be limited. Future studies should include longer follow-up periods to adequately assess late scar outcomes such as hypertrophic scarring.

CONCLUSIONS

In this randomized controlled trial comparing subcuticular continuous sutures with interrupted transdermal sutures for skin closure in paediatric patients undergoing open appendectomy for complicated appendicitis, both techniques were found to have comparable rates of surgical site infections (SSI). However, continuous intradermal suturing yielded scars that were better blended in colour, flatter in contour, smoother in texture, and less distorted, while maintaining similar surface shine. Given their favourable scar profiles and clinical safety, subcuticular sutures should be considered the preferred method of skin closure in paediatric open appendectomies.

Authors' Contribution

Conceptualization: BF, MKB, MA
Methodology: MRW, BF, SSHZ, BS
Formal analysis: ZA Writing and
Drafting: MRW, ZZ, ZA
Review and Editing: MRW, BF, SSHZ, ZZ, BS, ZA, MKB, MA

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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Acute Kidney Injury and Its Short-Term Outcomes among Children with Malaria Admitted to the National Institute of Child Health

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ABSTRACT

In Pakistan, the overall reported contribution of malaria to acute kidney injury (AKI) is not well studied. **Objectives:** To determine the frequency and short-term outcomes of AKI in children presenting with malaria. **Methods:** This analytical, cross-sectional study was conducted at the National Institute of Child Health, Karachi, Pakistan, during 13th January 2025 to 13th July 2025. Children aged 1-16 years with confirmed malaria were analyzed. Detailed demographic, clinical, and laboratory data were collected. AKI was staged using KDIGO criteria. Outcomes included need for dialysis, hospital stay, and mortality. Data were analyzed using IBM-SPSS Statistics, version 26.0. Statistical significance was set at $p<0.05$. **Results:** Among 237 children, 135(57.0%) were male, while the mean age was 7.9 ± 3.6 years. AKI was identified in 28 (11.8%; 95% CI: 7.9-16.5%) children. Fever was universally present in all children. Oliguria was significantly more frequent in children with AKI (64.3% vs. 7.2%, $p<0.001$). Oliguria (64.3% vs. 7.2%, $p<0.001$), dehydration (57.1% vs. 22.0%, $p<0.001$), and hypotension (25.0% vs. 4.3%, $p<0.001$) were significantly more common among children with AKI. Dialysis or renal replacement therapy was required in 21.4% children with AKI ($p<0.001$). Mortality occurred 10.7% children with AKI vs. 0% without AKI ($p<0.001$). **Conclusions:** AKI affects a notable proportion of children hospitalized with malaria. AKI in malaria is linked to more severe clinical presentation and significantly worse short-term outcomes.

INTRODUCTION

Malaria is considered to be a major public health issue, especially in endemic regions, affecting millions of children annually. Globally, around 500 million individuals suffer from malaria [1]. Local data reports pooled malaria prevalence around 23.3% [2]. Mortality due to malaria can be multifactorial. Severe forms of malaria can lead to multiple organ dysfunction, with acute kidney injury (AKI) being one of the severe and under-recognized complications in pediatric populations [3]. AKI in pediatric patients is not commonly reported, presumably as a result of a low suspicion index. In Pakistan, the reported contribution of AKI to malaria ranges between 2-39%, but in the pediatric population, there is a significant lack of data [4]. Malaria-associated AKI can be influenced by the severity of the disease, host immunity, and co-existing comorbidities [4]. The pathophysiology involves hemodynamic instability, intravascular hemolysis, and immune-mediated renal damage and dehydration [5]. The early diagnosis of AKI in malaria and identifying key risk factors can help develop targeted interventions [6]. The impact of AKI on the duration of hospitalization, need for dialysis, complete or partial recovery, and electrolyte imbalance, in particular with hyperkalemia, is not well understood in the pediatric population [7]. The rising

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incidence of malaria in children and the potential for fatal outcomes due to AKI necessitate research in this subject [8]. Studies from high-burden regions describe AKI in 24–59% of children with severe malaria, with clear associations with longer hospital stays, dialysis requirement, neurodisability at discharge, and elevated mortality that rises stepwise with AKI severity [9]. Despite the growing recognition of malaria-associated AKI in adults, significant gaps remain in understanding its burden, clinical profile, and outcomes in children, particularly in South Asian settings where malaria epidemiology differs from African regions. Pediatric AKI may be underdiagnosed due to limited routine monitoring of renal function, variability in clinical presentation, and lack of standardized surveillance in resource-constrained environments. Existing reports from Pakistan largely describe adult populations, leaving substantial uncertainty regarding the true frequency, severity, and short-term consequences of AKI among children with malaria.

Generating local pediatric data is essential to guide early recognition, inform management protocols, improve prognosis, and support resource allocation in high-volume tertiary centers. This study was therefore undertaken to address this evidence gap by evaluating the frequency and short-term outcomes of AKI in children presenting with malaria. This study aimed to determine the frequency and short-term outcomes of AKI in children presenting with malaria.

METHODS

This analytical, cross-sectional study was conducted across all medical units and the Department of Nephrology at the National Institute of Child Health (NICH), Karachi, Pakistan, from 13th January 2025 to 13th July 2025, following approval from the Institutional Ethical Review Board (IERB-53/2024). Written informed consent was obtained from parents or legal guardians after providing a thorough explanation of the study objectives and procedures. A sample size of 237 was calculated, taking the anticipated frequency of AKI in malaria as 33.2% [10], with a 95% confidence level and 6% margin of error. Using non-probability consecutive sampling, children aged 1 to 16 years, admitted with a confirmed diagnosis of malaria, were included. Malaria diagnosis was established using Giemsa-stained thick and thin blood films or the malaria parasite immunochromatographic test. Pre-existing chronic kidney disease (CKD), congenital renal anomalies, or sepsis unrelated to malaria, or current use of nephrotoxic medications were excluded. For each enrolled child, demographic data (age, gender, residential status) and detailed clinical information including presenting symptoms, duration of fever, dehydration status, vital signs, oliguria, type of therapy provided, and the stage of AKI. AKI was defined and staged according to the Kidney-Disease: Improving Global Outcomes (KDIGO) guidelines [11]. Stage 1 AKI was defined as an increase in serum creatinine to 1.5–1.9 times baseline or an absolute rise of ≥0.3 mg/dL within 48 hours, or a reduction in urine output to <0.5 mL/kg/h for 6–12 hours. Stage 2 AKI was defined as an increase in serum creatinine to 2.0–2.9 times baseline or urine output <0.5 mL/kg/h for more than 12 hours. Stage 3 AKI was defined as an increase in serum creatinine to ≥3.0 times baseline, or to ≥4.0 mg/dL, initiation of renal replacement therapy, or, in children younger than 18 years, a decrease in estimated glomerular filtration rate (eGFR) to <35 mL/min/1.73 m^2; urine output <0.3 mL/kg/h for more than 24 hours or anuria for ≥12 hours. All patients received standard management for malaria and AKI according to institutional protocols. Short-term renal outcomes like need for dialysis or renal replacement therapy (RRT), along with the length of stay, and in-hospital mortality, were recorded. All data were collected using a standardized data collection proforma. Statistical analysis was performed using IBM-SPSS Statistics version 26.0. Quantitative data were presented as means with standard deviation (SD) or median with interquartile ranges (IQR), as assessed for normality using the Shapiro-Wilk test. Quantitative data were compared using an independent sample t-test, or Mann-Whitney U test, while chi-square test or Fisher's exact were employed for the comparison of categorical data. Survival analysis was performed using Kaplan-Meier survival analysis and the log-rank test. Variables with p<0.10 in univariate analysis were entered into a multivariable binary logistic regression model to identify independent predictors of AKI. Adjusted odds ratios (aOR) with 95% confidence intervals (CI) were reported. Model fitness was assessed using the Hosmer–Lemeshow test, and multicollinearity was evaluated through variance inflation factors. A p-value <0.05 was considered statistically significant for all inferential statistics.

RESULTS

In a total of 237 children, 135 (57.0%) were males, with a mean age of 7.9 ± 3.6 years. Among these, 165 (69.6%) resided in urban areas. AKI was identified in 28 (11.8%; 95% CI: 7.9-16.5%) children with malaria. Of these 28 children, 13 (46.4%) were classified as Stage-1, 8 (28.6%) as Stage-2, and 7 (25.0%) as Stage-3. Fever was universally present in all children. Oliguria was significantly more frequent in children with AKI (64.3% vs. 7.2%, p<0.001). Children with AKI were significantly more likely to be clinically dehydrated (57.1% vs. 22.0%, p<0.001) and had a higher incidence of hypotension at admission (25.0% vs. 4.3%, p<0.001). Significantly lower mean hemoglobin (p<0.001) and lower platelet count (p=0.001) were noted among children with AKI (Table 1).

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Table 1: Comparison of Study Variables (n=237)

Characteristics	AKI (n=28)	Non-AKI (n=209)	p-value
Male	16 (57.1%)	119 (56.9%)	0.984
Female	12 (42.9%)	90 (43.1%)	
Age (Years)	8.2 ± 3.3	7.9 ± 3.7	0.684
Residence (Urban)	21 (75.0%)	144 (68.9%)	0.510
Residence (Rural)	7 (25.0%)	65 (31.1%)	
Fever	28 (100%)	209 (100%)	1
Dehydration	16 (57.1%)	46 (22.0%)	<0.001
Hypotension	7 (25.0%)	9 (4.3%)	<0.001
Hemoglobin (g/dL)	8.9 ± 1.6	10.2 ± 1.8	<0.001
Platelets (109/L)	110 (75-135)	146 (120-185)	<0.001
Leukocyte Count (109/L)	13.2 ± 5.1	12.0 ± 4.8	0.219
Serum Creatinine (mg/dL)	2.2 (1.8-3.0)	0.7 (0.5-0.9)	<0.001
Blood Urea Nitrogen (mg/dL)	32 (22-48)	14 (10-21)	<0.001
Alanine Aminotransferase (U/L)	49 (31-87)	41 (26-63)	0.140
Aspartate Aminotransferase (U/L)	68 (44-102)	52 (36-81)	0.115

In terms of outcomes, children with AKI had a significantly longer median hospital stay compared to those without AKI (8 (6–10) days vs. 5 (4–7) days, p<0.001). The requirement for dialysis or RRT was limited to the AKI group (21.4% vs. 0%, p<0.001). In-hospital mortality was confined to the AKI children (10.7% vs. 0%, p<0.001) (Table 2).

Table 2: Comparison of Short-Term Outcomes (n=237)

Outcomes	AKI (n=28)	Non-AKI (n=209)	p-value
Required Dialysis / Renal Replacement Therapy	6 (21.4%)	–	<0.001
In-Hospital Mortality	3 (10.7%)	–	<0.001
Hospital Stay (Days)	8 (6-10)	5 (4-7)	<0.001

Kaplan–Meier survival curves showed significantly lower survival probabilities among children with AKI compared with those without AKI (log-rank p=0.002). The survival probability at Day 10 was 0.90 in the AKI group and 1.00 in the non-AKI group. Median survival time could not be estimated for either group because survival remained above 50% throughout the hospitalization period. All deaths occurred in the AKI group, whereas all non-AKI children were censored at discharge (Figure 1).

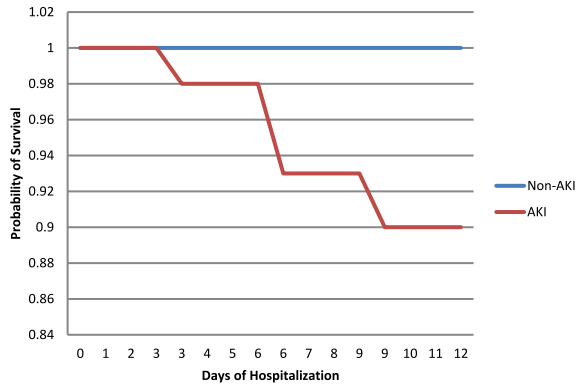

Figure 1: Kaplan-Meier Survival Curve

Dehydration (aOR 4.21, p=0.002) and hypotension at admission (aOR 5.94, p=0.004) remained strong independent predictors of AKI. Lower hemoglobin levels independently increased AKI likelihood (aOR 1.31 per 1 g/dL decrease, p=0.028). Higher blood urea nitrogen was associated with AKI (aOR 1.04 per mg/dL, p=0.013). Platelet count showed a borderline association (p=0.062). The details about multivariate binary logistic regression are shown (Table 3).

Table 3: Multivariate Binary Logistic Regression Analysis for the Predictors of Acute Kidney Injury in Children with Malaria

Predictor*	Adjusted Odds Ratio (95% Confidence Interval	p-value
Dehydration	4.21 (1.72-10.33)	0.002
Hypotension at Admission	5.94 (1.78-19.79)	0.004
Hemoglobin (per 1 g/dl decrease)	1.31 (1.03-1.68)	0.028
Platelet Count Per (10^9/L decrease)	1.01 (1.00-1.02)	0.062
Blood Urea Nitrogen (mg/dl increase)	1.04 (1.01-1.07)	0.013

*Serum creatinine was removed due to multicollinearity with blood urea nitrogen

DISCUSSION

This study showed that AKI was detected in 11.8% of hospitalized children with malaria. Kwambele and colleagues [12], in a study from Uganda, documented AKI prevalence of 47.7% in children with malaria, while Namazzi *et al.* reported an AKI frequency of 45.3% in a large multicenter cohort [7]. Oshomah-Bello *et al.* also documented AKI in 59% hospitalized children for severe malaria in Nigeria [13]. These higher frequencies are likely multifactorial and may reflect differences in malaria epidemiology, healthcare access, study inclusion criteria, and the spectrum of disease severity across populations. Several contextual factors might explain the lower AKI prevalence found in the current study. Pakistan is characterized by a mix of Plasmodium species, with Plasmodium vivax predominating, in contrast to sub-Saharan Africa, where Plasmodium falciparum is more frequently encountered and associated with more severe systemic and renal complications. Local malaria case management protocols, relatively earlier healthcare access, and broader inclusion of both moderate and severe cases in this study may have also contributed to lower AKI detection rates. Bugti *et al.* observed renal failure in 54.2% of malaria admissions, underscoring the wide geographic variation in AKI prevalence [14]. Some differences in AKI frequency may also arise from the criteria and timing used for AKI assessment, as studies incorporating serial creatinine measurements or biomarker-based diagnostics such as Cystatin C or NGAL have tended to identify more cases, especially in early or evolving stages, compared to single-point creatinine estimation. Hawkes *et al.* found higher rates of AKI in non-malarial febrile illness compared

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to malaria, but found severe AKI to be comparably prevalent in both groups [15]. This further suggests that population context, comorbidities, and care practices influence reported AKI rates. Children with malaria-associated AKI experienced longer hospitalizations, higher need for RRT, and markedly higher in-hospital mortality. The clear stepwise decline in survival among AKI patients, as demonstrated by the Kaplan-Meier analysis, mirrors findings from studies such as Conroy *et al.* who noticed increased mortality with greater AKI severity [16]. A recently published meta-analysis of over 133,000 pediatric AKI cases worldwide similarly noted an overall in-hospital mortality rate of 18.3%, rising from 8.2% in Stage 1 to nearly 28% in Stage 3 AKI [17]. The present study's observed mortality for children with AKI (10.7%) aligns most closely with mortality rates for moderate (Stage-2) AKI reported in the global literature, although the absolute mortality may be somewhat lower, potentially reflecting differences in patient mix and access to early supportive interventions [17]. The need for dialysis or RRT was observed in 21.4% of AKI patients, consistent with data from Teuwafeu et al. who reported that nearly three-quarters of children with AKI required dialysis, though only a minority received it due to resource constraints [18]. In contrast, the current study site, as a large tertiary center, was able to provide RRT to all indicated patients, which may explain the absence of mortality in non-AKI children and the relatively lower mortality rate among AKI cases compared to resource-limited settings where dialysis is less accessible. The consistently high mortality observed among children requiring dialysis across studies emphasizes the urgent need for improved access to RRT and early detection of AKI to prevent progression to advanced stages [19, 20]. Namazzi *et al.* found that 15.6% of pediatric severe malaria cases with AKI had persistent kidney dysfunction at one-month follow-up [7]. Chisavu *et al.* highlighted that persistent AKI was associated with increased risk of CKD and higher mortality [21]. Barriers to timely AKI diagnosis and management remain substantial, with access to laboratory testing, dialysis, and pediatric nephrology expertise often concentrated in urban referral centers [22, 23]. These disparities are further exacerbated by socioeconomic determinants, as children with less educated caregivers were at increased risk of AKI, emphasizing the need for broader community education and health system strengthening [12]. Future strategies to address these barriers may include capacity building for district and rural hospitals, decentralized training on AKI detection, and establishment of referral networks to facilitate rapid access to specialist care. Expanded use of point-of-care creatinine testing and novel biomarkers may further improve early detection and risk stratification, especially where laboratory infrastructure is limited [24, 25].

A shortcoming of this study is that generalizability may be limited due to single center to other settings with different malaria epidemiology and healthcare access. In addition, AKI assessment relied largely on single-point serum creatinine measurements, potentially underestimating early or evolving AKI compared with studies using serial measurements or novel biomarkers. Larger multicenter studies are required to confirm predictors, evaluate stage-dependent risk gradients, and assess long-term renal outcomes in pediatric malaria.

CONCLUSIONS

This study demonstrated that AKI complicates a significant proportion of pediatric malaria admissions among hospitalized children with malaria. AKI in children with malaria is associated with more severe clinical and laboratory profiles at presentation and predicts adverse short-term outcomes. Routine risk assessment, enhanced monitoring, and timely interventions for AKI should be prioritized in pediatric malaria care, especially in endemic regions, to mitigate morbidity and mortality related to this preventable complication.

Authors' Contribution

Conceptualization: BN, LA
Methodology: AQS, BN, HF
Formal analysis: LA
Writing and Drafting: WH
Review and Editing: AQS, BN, HF, LA, WH

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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Ultrasonographic Features in Recognition of Malignant Thyroid Nodule with Fine Needle Aspiration Cytology as the Gold Standard

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ABSTRACT

A thyroid nodule is a discrete lesion within the thyroid gland that is radiologically distinct from the surrounding tissue. The diagnosis of these nodules is a common clinical procedure globally. **Objectives:** To determine the sensitivity, specificity, and predictive values of ultrasound for identifying malignant thyroid nodules, using fine-needle aspiration cytology (FNAC) as the gold standard. **Methods:** In this cross-sectional study, 209 consecutive patients with suspected thyroid nodules were enrolled after providing written consent. Each participant underwent a cervical ultrasound performed by an experienced radiologist, which was followed by an FNAC. The Bethesda System was used for the cytological diagnosis. The diagnostic performance of ultrasound was calculated against the FNAC results, and data were analyzed using SPSS version 26.0. **Results:** The mean age of the 209 patients was 43.58 ± 9.87 years. Using FNAC as the gold standard, ultrasound demonstrated a diagnostic accuracy of 88.04%. The sensitivity was 86.3%, the specificity was 89.7%, the positive predictive value (PPV) was 88.89%, and the negative predictive value (NPV) was 87.27%. **Conclusions:** The study concludes that ultrasound characteristics are a highly sensitive and accurate method for identifying malignant thyroid nodules, with an overall diagnostic accuracy of 88.04%.

INTRODUCTION

Thyroid nodules, defined as focal lesions within the thyroid gland that are sonographically distinct from surrounding parenchyma, are diagnosed frequently throughout the world [1]. The lifetime risk of developing a palpable nodule is 5-10%; however, due to the ubiquitous high-resolution imaging, this number has had significant growth [2]. The large majority (>90%) of these nodules, however, are benign, but the main clinical challenge remains to distinguish between benign and malignant (7-15% of cases) [3]. Initial assessment of a thyroid nodule combines history and physical examination with diagnostic studies. Clinical history and the physical examination are important for risk stratification, with male sex, history of childhood neck irradiation, a family history of thyroid carcinoma, along with the presence of firm or fixed mass or lymphadenopathy, which increases such suspicion [4]. The single most valuable laboratory test to perform initially is a sensitive assay for TSH. In current diagnostic algorithms, ultrasonography represents the mainstay of the initial investigation because it is safe, cost-effective, and available in virtually all institutions [5]. It is important information regarding

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nodular characteristics and directs further management [6, 7]. Nevertheless, ultrasonography has operator dependency and its accuracy is not conclusive for cancer diagnosis [5]. A study reported the US's sensitivity (89%) and specificity (93%) in the diagnosis of malignant nodules, with a positive predictive value of 65.5% for US compared to FNAC [8]. The gold standard to diagnose these is still FNAC, which may be the most specific and sensitive method for detecting doubtful lesions that in many cases must be approached surgically [9, 10]. It is important because these benign diagnoses are going to spare many surgeries without indication [11]. However, FNAC is invasive and more time-consuming, and more costly than an ultrasound examination for the aspiration due to laboratory technicians' support cost; therefore, it was important to clearly what the role of ultrasonography is in screening and triage [12]. The most important initial laboratory test is a sensitive thyroid-stimulating hormone (TSH)assay. For a single nodule with normal TSH, no further tests are routinely needed unless autoimmune disease is suspected. Surgeon-performed ultrasound has been shown to significantly impact surgical planning, with one study finding it changed management for 17.6% of patients, for example, by identifying previously missed malignant lymph nodes [13–15]. Advanced imaging, like CT or MRI are not a first-line investigation due to cost. A study by Bakkar et al. suggests that nodules ≥3 cm diagnosed as benign on FNAC may still harbor malignancy, with a reported cancer risk of 22.8% in their cohort [16].

This study fills in a gap in the literature, given that many investigations were small samples and showed no firm conclusions. Through a comprehensive assessment, we hope to offer insight into which detected ILL features may help in the coordination of diagnosis and treatment of thyroid nodules.This study aimed to assess the diagnostic value of ultrasonography as a tool for detecting cancerous thyroid nodules in relation to FNAC, also in terms of common metabolic factors, recognizing that metabolic syndrome components such as hypertension and dyslipidemia may influence tissue vascularity and echogenicity.

METHODS

This descriptive cross-sectional study was conducted in the Department of Radiology, Bolan Medical College/ Hospital, Quetta, Balochistan, via a non-probability consecutive sampling technique. In this study, a total of 209 patients fulfilling the inclusion criteria were enrolled and referred from the surgical Department to the Radiology for ultrasound assessment, followed by cytology at Bolan Medical Complex Hospital, Quetta. Permission was taken from the hospital with CPSP no: CPSP/REU/RAD-2020-001-3096. The duration of this study was from November 2022 to April 2023. For the study, the sample size is calculated by using a sensitivity specificity calculator with a confidence level (1-a) was considered as 95%, with a desired precision (d) of 0.07, expected sensitivity (89% specificity (93%) with an approximate population estimation of 36.9 % taken from the parent study [3, 8]. For all the values entered, the calculated sample size was 209. The inclusion criteria included any individual aged between 25 and 60-years having evidence of a suspected thyroid nodule of either gender. All patients with multinodular goiter, any patient having a history of either hypothyroidism or hyperthyroidism, and any patient with known bleeding diathesis were excluded from the study. All the included patients underwent a detailed history and clinical examination by the surgery team before being sent to the Department of Radiology. Proformas were filled out for all those patients who had given written consent to be included in the study. The first serum TSH assessment was performed along with scintigraphy when a functional nodule was confirmed. Thereafter, all individuals with thyroid nodule undergone ultrasound assessment followed by cytology. Cervical ultrasound scanning was performed by a qualified Consultant Radiologist, who possessed at least more than 15 years' experience in ultrasound scanning of the thyroid. The criteria for the identification of ultrasound features indicative of thyroid malignancies were developed based on the findings of Lew et al parameters The Bethesda System for reporting thyroid cytopathology was used for diagnosis of the FNAC procedure [7]. FNAC was done without local Anesthesia in a few of our patient we used 23 and in a few others 24 needle in a few others. Smears were fixed using 95% alcohol solution, or staining was done using hematoxylin and eosin stain. The study used the Bethesda System for reporting thyroid cytopathology, in which there are six main diagnostic groups, in which Thy-5 and Thy-6 were considered as malignant. Above-mentioned information, such as height, age, gender, weight, BMI, nodule size, ultrasound, and cytology reports, was recorded and noted down in a pre-designed proforma. In addition to core demographic and nodule characteristics, baseline systolic/diastolic blood pressure and serum cholesterol levels were recorded. These variables were included in a secondary, exploratory analysis to assess their potential influence on the sonographic appearance and diagnostic classification of thyroid nodules. The Exclusion criteria were followed strictly to manage effect modifiers and bias in study outcomes. Data were entered and analyzed using SPSS version 26.0. Mean value and standard deviation or Median IQR for non-normal data were calculated for quantitative variables like height, age, BMI, and weight. Normality of data was assessed by using the Shapiro-Wilk test.

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RESULTS

209 patients were selected for this study. Patients' mean age was 43.58 ± 9.87 years. The mean systolic BP was 125.37 ± 8.69 mmHg. The mean diastolic BP was 77.86 ± 7.71 mmHg. The mean weight recorded was 75.49 ± 8.33 kg. The mean height recorded was 1.65 ± 0.03 meters. The mean BMI was 27.56 ± 3.34 kg/m^2, and the mean serum cholesterol level was 161.20 ± 17.27 mg (Table 1).

Table 1: Baseline Characteristics of the Study Population (n=209)

Variables	Mean ± SD
Age (Years)	43.58 ± 9.870
Systolic BP (mmHg)	125.37 ± 8.691
Diastolic BP (mmHg)	77.86 ± 7.710
Weight (kg)	75.4 ± 8.333
Height (meter)	1.6563 ± .03788
BMI	27.5676 ± 3.34202
Gender (Female)	0.551 ± 0.497
Serum Cholesterol (mg)	161.20 ± 17.274

According to age distribution, there were 55 (26.3%) patients between the age group of 25 to 35 years, 61% patients were in the age group of 36 to 45 years, and 93 (44.5%) patients were in the age group of 46 to 60 years (Figure 1).

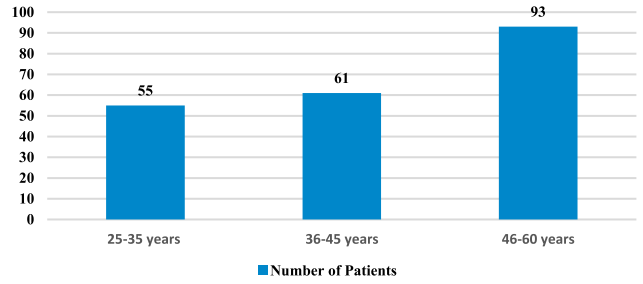

Figure 1: Age Distribution of the Patient Population

In our research, the frequency of female patients was 120 (57.4%), and the frequency of male patients was 89 (42.6%) (Figure 2).

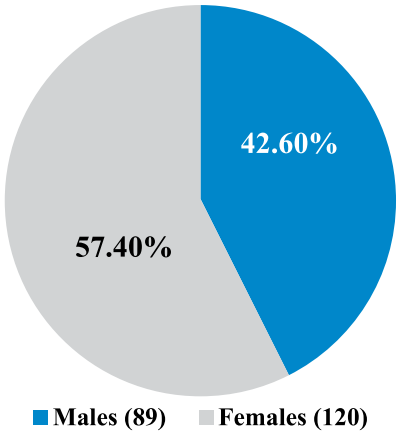

Figure 2: Distribution of Patients Based on Gender

Regarding the size of the nodule, 119 (56.9%) patients had a size of nodule <2mm while 90 (43.1%) patients had a size of nodule ≥ 2 mm (Figure 3).

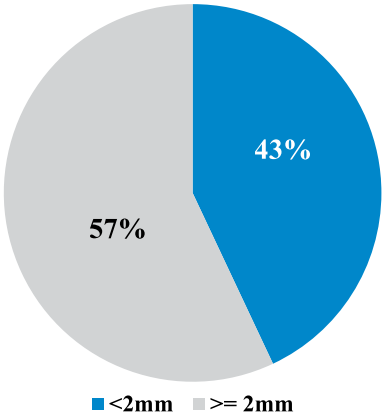

Figure 3: Distribution of Thyroid Nodules by Size

According to the BMI distribution, 54 (25.8%) patients had a BMI between 20 and 24.9 kg/m^2, 107 (51.2%) had a BMI between 25 and 29.9 kg/m^2, and 48 (23%) had a BMI ≥ 30 kg/m^2 (Figure 4).

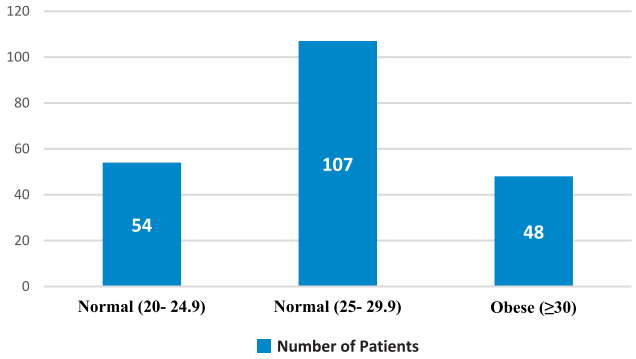

Figure 4: BMI Distribution of Patients

Among the FNAC results, 88 (86.3%) patients were True Positives (TP), 11 (10.3%) patients were False Positives (FP), and among the negative FNAC results, 14 (13.7%) were False Negatives (FN), and 96 (89.7%) were True Negatives (TN). This shows sensitivity: 86.3%, Specificity: 89.7%, PPV: 88.89%, NPV: 87.27%, and diagnostic accuracy: 88.04% (Figure 5).

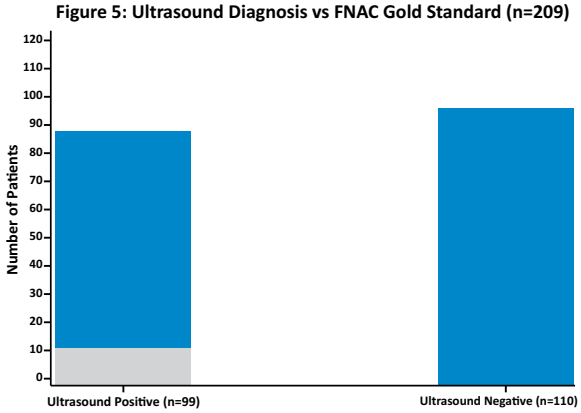

Figure 5: Ultrasound Diagnosis vs FNAC Gold Standard (n=209)

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By using FNAC, the diagnostic performance of ultrasound stratified by age group, like 25 to 35 years, 36-45 years, and 46 to 60 years, and gender, like male and female (Table 2).

Table 2: Diagnostic Performance of Ultrasound Stratified by Age Group and Gender, Using FNAC as the Gold Standard

Characteristics			FNAC		Total	p-value
			Positive	Negative		
Age						
25 to 35 years	Ultrasound Characteristics	Positive	25 (80.6%)	0 (0.0%)	25 (45.5%)	<0.001
		Negative	6 (19.4%)	24 (100.0%)	30 (54.5%)	
	Total		31 (100.0%)	24 (100.0%)	55 (100.0%)	
36 to 45 years	Ultrasound Characteristics	Positive	30 (88.2%)	1 (3.7%)	31 (50.8%)	<0.001
		Negative	4 (11.8%)	26 (96.3%)	30 (49.2%)	
	Total		34 (100.0%)	27 (100.0%)	61 (100.0%)	
46 to 60 years	Ultrasound Characteristics	Positive	33 (89.2%)	10 (17.9%)	43 (46.2%)	<0.001
		Negative	4 (10.8%)	46 (82.1%)	50 (53.8%)	
	Total		37 (100.0%)	56 (100.0%)	93 (100.0%)	
Gender						
Male	Ultrasound Characteristics	Positive	42 (91.3%)	7 (16.3%)	49 (55.1%)	<0.001
		Negative	4 (8.7%)	36 (83.7%)	40 (44.9%)	
	Total		46 (100.0%)	43 (100.0%)	89 (100.0%)	
Female	Ultrasound Characteristics	Positive	46 (82.1%)	4 (6.2%)	50 (41.7%)	<0.001
		Negative	10 (17.9%)	60 (93.8%)	70 (58.3%)	
	Total		56 (100.0%)	64 (100.0%)	120 (100.0%)	

The diagnostic accuracy of ultrasonography in identifying and characterizing the cancerous thyroid nodule, taking FNAC (fine needle aspiration cytology) as gold standard, was 88.04% with a sensitivity 86.3%, a specificity 89.7%, a PPV 88.89%, and an NPV 87.27% (Table 3).

Table 3: Diagnostic Performance of Ultrasound Stratified by Nodule Size (<2 mm vs. ≥2 mm), Using FNAC as the Gold Standard

Nodule Size			FNAC		Total	p-value
			Positive	Negative		
< 2 mm	Ultrasound Characteristics	Positive	54 (90.0%)	7 (11.9%)	61 (51.3%)	<0.001
		Negative	6 (10.0%)	52 (88.1%)	58 (48.7%)	
	Total		60 (100.0%)	59 (100.0%)	119 (100.0%)	
> = 2 mm	Ultrasound Characteristics	Positive	34 (81.0%)	4 (8.3%)	38 (42.2%)	<0.001
		Negative	8 (19.0%)	44 (91.7%)	52 (57.8%)	
	Total		42 (100.0%)	48 (100.0%)	90 (100.0%)	

The comparison of ultrasound findings with FNAC results, stratified by systolic (≤130 mmHg vs. >130 mmHg) and diastolic (≤80 mmHg vs. >80 mmHg) blood pressure groups. Ultrasound demonstrated consistently high diagnostic accuracy across all BP categories, with sensitivity ranging from 78.7% to 92.7% and specificity from 88.9% to 90.3%. The statistically significant p-values (0.0001) indicate that ultrasound performance is reliable irrespective of the patient's blood pressure (Table 4).

Table 4: Diagnostic Performance of Ultrasound Stratified by Blood Pressure Categories, Using FNAC as the Gold Standard

Characteristics			FNAC		Total	p-value
			Positive	Negative		
Systolic Distribution						
110 to 130 mmHg	Ultrasound Characteristics	Positive	62 (86.1%)	7 (10.0%)	69 (48.6%)	<0.001
		Negative	10 (13.9%)	63 (90.0%)	73 (51.4%)	
	Total		72 (100.0%)	70 (100.0%)	142 (100.0%)	
> 130 mmHg	Ultrasound Characteristics	Positive	26 (86.7%)	4 (10.8%)	30 (44.8%)	<0.001
		Negative	4 (13.3%)	33 (89.2%)	37 (55.2%)	
	Total		72 (100.0%)	70 (100.0%)	142 (100.0%)	
Diastolic Groups						
65 to 80 mmHg	Ultrasound Characteristics	Positive	0.0001 (92.7%)	6 (9.7%)	57 (48.7%)	<0.001
		Negative	4 (7.3%)	56 (90.3%)	60 (51.3%)	
	Total		55 (100.0%)	62 (100.0%)	117 (100.0%)	

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> 80 mmHg	Ultrasound Characteristics	Positive	0.0001 (78.7%)	5 (11.1%)	42 (45.7%)	<0.001
		Negative	10 (21.3%)	40 (88.9%)	50 (54.3%)	
	Total		47 (100.0%)	45 (100.0%)	92 (100.0%)	

Results evaluate ultrasound performance against FNAC when stratified by BMI categories (normal, overweight, obese) and serum cholesterol levels (≤150 mg vs. >150 mg). Ultrasound maintained high sensitivity (82.9%–93.8%) and specificity (85.2%–95.8%) across all subgroups. The consistently significant p-values (0.0001) confirm that diagnostic accuracy remains robust across varying BMI and cholesterol levels (Table 5).

Table 5: Diagnostic Performance of Ultrasound Stratified by BMI Categories and Serum Cholesterol Levels, Using FNAC as the Gold Standard

Characteristics			FNAC		Total	p-value
			Positive	Negative		
BMI Distribution						
20 to 24.9 kg/m^2	Ultrasound Characteristics	Positive	23 (85.2%)	4 (14.8%)	27 (50.0%)	<0.001
		Negative	4 (14.8%)	23 (85.2%)	27 (50.0%)	
	Total		27 (100.0%)	27 (100.0%)	54 (100.0%)	
25 to 29.9 kg/m^2	Ultrasound Characteristics	Positive	45 (88.2%)	6 (10.7%)	51 (47.7%)	<0.001
		Negative	6 (11.8%)	50 (89.3%)	56 (52.3%)	
	Total		51 (100.0%)	56 (100.0%)	107 (100.0%)	
>= 30 kg/m^2	Ultrasound Characteristics	Positive	20 (83.3%)	1 (4.2%)	21 (43.8%)	<0.001
		Negative	4 (16.7%)	23 (95.8%)	27 (56.2%)	
	Total		24 (100.0%)	24 (100.0%)	48 (100.0%)	
Serum Cholesterol						
130 to 150 mg	Ultrasound Characteristics	Positive	30 (93.8%)	4 (11.8%)	34 (51.5%)	<0.001
		Negative	2 (6.2%)	30 (88.2%)	32 (48.5%)	
	Total		32 (100.0%)	34 (100.0%)	66 (100.0%)	
> 150 mg	Ultrasound Characteristics	Positive	58 (82.9%)	7 (9.6%)	65 (45.5%)	<0.001
		Negative	12 (17.1%)	66 (90.4%)	78 (54.5%)	
	Total		70 (100.0%)	73 (100.0%)	143 (100.0%)	

DISCUSSION

The usage of ultrasonography is increasing in identifying thyroid nodules, which are a common finding in most of the general population (US). About 50% of people over 40 have thyroid nodularity, which can range in prevalence from 19% to 67% and worsens with age [17]. The need to rule out thyroid cancer, which is found in 5–15% of cases based on sex, age, and history of other risk factors for exposure, is the clinical importance of thyroid nodules [18]. Small papillary thyroid tumors, the most indolent type of thyroid cancer, are primarily responsible for the almost fivefold increase in thyroid cancer incidence during the last 50 years [19]. Hypoechogenicity, Microcalcifications, enhanced intranodular vascularity, absence of a halo, nodular form, and uneven edges are some ultrasonography indicators that have historically been connected with an increased risk of cancer. To diagnose cancer, none of these traits, taken alone, appears to be sufficiently trustworthy. Elastography, an Ultrasound technique, has lately been proposed as a method to identify thyroid nodules that are malignant [20]. This method had a 92% sensitivity and 90% specificity according to a meta-analysis. But only a few studies were included, and only three used histology of the surgical specimens for definite diagnosis. The method for identifying malignant nodules that is thought to be the most accurate is a fine-needle aspiration (FNA) biopsy [21]. It would be very laborious to do biopsies on every patient with a thyroid nodule, and FNA findings do bear some limitations. The suspicious signs are vague and ambiguous and usually encompass individuals with thyroid cancer in their families, those with significant radiation exposure, or those who have several worrisome ultrasound characteristics. The likelihood of the ultrasound characteristics linked to cancer and which combination would be more clinically effective are unknown, though. For patients with inadequate FNA specimens for diagnosis (10%) or if the specimens are inconclusive (15–30%), the latter of which carries a 20–30% malignancy risk, ultrasound characteristics may also be helpful in clinical decision making [22]. Sensitivity ranges from 26% to 87%, and specificities range from 40% to 93%, according to a recent meta-analysis examining the accuracy of ultrasound to predict malignancy in thyroid nodules. The highest diagnostic odds ratio (OR) for cancer was observed in this investigation for shapes that were taller than wide [23]. The studies included in that meta-analysis, however, used cytology rather than histology to determine the final diagnosis for benign nodules.

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Additionally, it did not assess how well elastography predicts cancer. Furthermore, the likelihood ratio of ultrasound features linked to malignancy was not described. Besides sensitivity and specificity, the probability ratio would provide further information and data that could be utilized in thyroid nodules in the clinical decision-making process [24]. Despite the advantages of ultrasonic imaging that have been highlighted, there is inconclusive information about its ability to predict thyroid cancer. Therefore, it is necessary to compare the ultrasound scanning's diagnostic accuracy to the outcomes of a gold standard test. The best, most trustworthy, and low-cost method for determining the identity of thyroid nodules is fine needle aspiration cytology (FNAC) [25]. Thyroid nodules are a frequent clinical presentation to surgical clinics; as a result, a patient's treatment will be greatly impacted by an accurate identification of any probable malignancy. In light of this, it's critical to make the best use of ultrasound imaging tools, particularly when determining which instances call for urgent surgical procedures [26]. The diagnostic accuracy of ultrasonography in identifying and characterizing the cancerous thyroid nodule, taking gold standard FNAC (fine needle aspiration cytology) as reference in our study, was 88.04% with a sensitivity 86.3%, specificity of 89.7%, PPV being 88.89%, and NPV being 87.27%. Our results are very much in line with studies [3, 8], which showed that the expected sensitivity in the identification of malignant thyroid was 89% and the specificity was 93%. Furthermore, our finding of superior sensitivity for smaller nodules (<2mm) at 90.0% is clinically significant. This supports the utility of high-resolution ultrasound in detecting small malignancies, a capability that is crucial for adhering to modern management systems like ACR TI-RADS [15], which emphasize feature-based risk stratification over size alone. This finding also contextualizes the concern by Bakkar *et al.* [16] regarding malignancy in larger nodules by demonstrating that ultrasound remains a sensitive tool for smaller, potentially early-stage cancers.

This study is limited by reliance on FNAC as the reference standard, which may miss some malignancies compared to histology, and by a lack of evaluation of ultrasound elastography and likelihood ratios for malignancy. Additionally, the optimal combination of ultrasound features for clinical decision-making remains unclear. Future research should assess the combined use of high-resolution ultrasound, elastography, and standardized risk stratification systems to improve diagnostic accuracy for thyroid malignancy.

CONCLUSIONS

This study confirms that cervical ultrasonography is a highly accurate and reliable tool for detecting malignant thyroid nodules. Using FNAC as the gold standard, ultrasound demonstrated high sensitivity and specificity, making it an excellent first-line investigation for effectively triaging patients for further diagnostic procedures.

Authors' Contribution

Conceptualization: AS
Methodology: AS, NKK, ASM, SS
Formal analysis: SS
Writing and Drafting: AS
Review and Editing: AS, NKK, ASM, SS

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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Evaluating the Diagnostic Accuracy of Heart Diseases with Chest Pain

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ABSTRACT

Cardiac diseases refer to sudden, severe cardiac events with life-threatening consequences, often linked to underlying cardiovascular issues, requiring immediate medical intervention. **Objectives:** To determine the predictive accuracy of the HEART score versus electrocardiogram (ECG) changes for predicting Cardiac events in patients with chest pain. **Methods:** The study was carried out at the Mekran Medical College, Turbat, from September 2020 to March 2021. The cross-sectional study included 385 patients. The samples of blood were collected and measured. Patients' HEART scores were calculated. The data were stratified by gender, age, duration of symptoms, smoking, and diabetes. The positive and negative predictive value, sensitivity, specificity, and diagnostic accuracy of the HEART score for each stratum were calculated. **Results:** There were 269 (69.9%) male and 116 (30.1%) female. The average age was 62.34 ± 8.48, and the age ranged from 35 to 75 years old. The mean duration of the symptom was 4.71 ± 2.24 hours. In predicting adverse events on the HEART score, results showed that 327 (84.9%) were positive, while 373 (96.9%) were positive for ECG changes. The sensitivity, specificity, positive and negative predictive value for predicting adverse events on the HEART score versus ECG changes were 86.7%, 66.7%, 98.7%, and 13.7% respectively. **Conclusions:** The HEART score effectively predicts major adverse events in chest pain patients, suggesting its continued validation as a clinical tool for risk stratification in emergency departments.

INTRODUCTION

In emergency departments throughout the world, chest pain is the major complaint [1, 2]. But only 10-20% were diagnosed with acute coronary syndrome [2]. This is a serious condition that requires to be assessed and management. Chest pain may arise from many kinds of causes, from harmless to fatal. Therefore, to provide appropriate care and avoid overusing resources. Patients suffering chest pain must be categorized according to their risk of major adverse cardiac events (MACE) [3, 4]. MACE was recorded in 19% of individuals with chest discomfort [5]. Acute coronary syndrome is a variety of disorders that often arise from a sudden drop in coronary artery blood flow and can be challenging to identify. Emergency physicians need to develop a prognostic method for those who may have acute coronary syndrome, given the diagnostic difficulties. To assist in identifying patients who are more likely to experience unfavorable outcomes, several prediction models have been developed. The initial model to be created, validated, and tested in clinical settings on patients who may have acute coronary syndrome and are admitted to the Emergency Department is the HEART Score. [6]. Both men and women may develop myocardial infections (MI), although males tend to develop them earlier in life. After menopause, the incidence rises in

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women. Men and women experience their first MI at ages 65.1 and 72 years, respectively [7, 8]. The earlier mortality rates have been higher at 30 days in women with STEMI, even after controlling for primary percutaneous coronary intervention, medication, and other underlying co-morbidities [9]. The most widely used risk stratification techniques are the Global Registry of Acute Coronary Events (GRACE) scores, thrombolysis in myocardial infarction (TIMI), age, risk factors, electrocardiogram (ECG), and history that have been created throughout the years [10, 11]. The major objectives of treatment are to minimize future remodeling, which may adversely affect ventricular function and prognosis, and to prevent myocardial damage by rapidly restoring myocardial blood flow [12].

Although tools such as ECG and established risk scores are widely used, uncertainty remains regarding their comparative effectiveness in early risk prediction. Limited local evidence exists comparing the HEART score with ECG changes alone for timely identification of high-risk patients. Therefore, this study aims to compare the utility of the HEART score versus ECG changes in screening chest pain patients to enable early prevention of MACE and optimized management strategies.

METHODS

The cross-sectional study was conducted at Mekran Medical College, Turbat. The study duration was 7 months, from September 2020 to March 2021. The ethical review committee (ERC 05/2020) of Mekran Medical College of Turbat has given written Permission. 385 patients who fulfilled the selection criteria were enrolled. Informed consent was obtained. The confidence level was 95%, taking the expected percentage of MACE, i.e., 19% with a sensitivity of HEART score, i.e., 95.9% with 5% margin of error, and a specificity of HEART score, i.e., 44.6% with 5% margin of error [13]. Non-probability consécutive sampling was used. Their demographic information (name, age, gender, duration of symptoms, diabetes (BSR>186 mg/dl and smoking) was also noted. The blood sample was obtained by using a 5cc disposable syringe for assessment of troponin and CK-MB levels at the time of presentation. The study used cardiac biomarker evaluation and electrocardiographic monitoring to assess adverse cardiac events. ECGs (Bionet, MODEL: Cardiocare-2000(EKG-2000) were used to examine ischemia or arrhythmic alterations, while immunoassay methods evaluated cardiac biomarkers like CK-MB and Troponin, indicating myocardial damage. Troponin and CK-MB were measured using immunoassay techniques and enzymatic kinetic methods. Cardiac Troponin was measured photometrically by an immunochemical ELISA method on plates of microtitre plates by using reagents from Roche Diagnostics. CK-MB was measured by using an immunochemical microparticle technique by the Abbott CK-MB assay. This method uses a monoclonal anti-CK-MB antibody bound to latex microparticles. Normal levels were below 0.04 ng/mL and 25 U/L, while elevated values indicate damage. To ensure accuracy and provide a sensitive assessment of cardiac damage, proper sample handling, reagent storage, and quality control were provided. Suspected MI was defined as the presence of chest pain or compression >30 minutes at rest and dyspnea, sweating on clinical examination, and pain in the left arm or shoulders. MACE: On the HEART score, it was labeled as positive if the score was ≥ 4. On clinical findings, it was labeled as ECG changed >1mm ST segment elevation in II, III, and aVF (STEMI), or no ST-elevation (NSTEMI), CKMB >25, and troponin>100 present during 3 months. True positive (TP): If the HEART score ≥4 and MACE is present clinically. True negative (TN): If the HEART score <4 and MACE is not present clinically. False positive (FP): If the HEART score is ≥4, but MACE is not present clinically. False negative (FN): If the HEART score <4, but MACE is present clinically. Sensitivity: TP / (TP + FN) x 100. Specificity: TN / (TN + FP) x 100. PPV: TP / (TP + FP) x 100. NPV: TN / (TN + FN) x 100. Reports were assessed, and patients' HEART score was calculated, and patients were labelled as positive or negative (as per operational definition). The patient followed up for 3 months for MACE, including STEMI and NSTEMI attacks, was labelled (as per operational definition). All this information was recorded on a proforma. Patients aged 35-75 years of either gender presenting with suspicion of MI (as per operational definition) were included. Patients with recurrent myocardial infarction, congestive heart failure, valvular heart disease, previous bypass surgery, percutaneous intervention (on medical record), and Patients with abnormal liver profile, renal failure, respiratory disease, and anaemia were excluded. SPSS version 25.0 was used and statistically analyze the gathered data. The mean and standard deviation were applied to display quantitative information (age and illness duration). Frequencies and percentages were used to display qualitative characteristics such as MACE, diabetes, smoking, and gender. The HEART score's diagnostic accuracy, sensitivity (Sp), specificity (Se), positive predictive value (PPV), and negative predictive value (NPV) were calculated using 2x2 tables. Data were stratified for age, gender, duration of symptoms, diabetes, and smokingFollowing stratification, 2x2 tables were created to determine each stratum's Se, Sp, PPV, NPV, and diagnostic accuracy (DA) of the HEART score.

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RESULTS

In our study, male and female were 269 (69.9%) and 116 (30.1%), respectively. The mean age was 62.34 ± 8.48 years, with a minimum of 35 and a maximum of 75 years. The results of the frequency distribution of age groups showed 171(44.4%)patients were in the <50 years age group and 214 (55.6%)were in the>50 years age group. The mean duration of symptoms was 4.71 ± 2.24 hours. The duration of symptom results showed that 334 (86.8%) had <6 hours duration of symptom and 51(13.2%)had >6 hours duration of symptom. The frequency distribution results of diabetes showed that 324 (84.2%) had diabetes. The frequency distribution results of smoking showed that 157(40.8%)had the habit of smoking(Table 1).

Table 1: Frequency of Demographic

Variables	Frequency (%)
Gender	
Male	269(69.9%)
Female	116(30.1%)
Age Groups	
<50 Years	171(44.4%)
>50 Years	214(55.6%)
Duration of Symptoms	
<6 Hours	334(86.8%)
>6 Hours	51(13.2%)
Diabetes	
Yes	324(84.2%)
No	61(15.8%)
Smoking	
Yes	157(40.8%)
No	228(59.2%)
Adverse Events on ECG Changes	
Positive	373(96.9%)
Negative	12(3.1%)
Adverse Events on the HEART Score	
Positive	327(84.9%)
Negative	58(15.1%)

In our study, for predicting adverse events, on HEART score results showed that 327 (84.9%) were positive, while 373 (96.9%)were positive on ECG changes(Table 2).

Table 2: Cross-tabulation of Adverse Events on HEART Score vs. ECG Changes

Adverse Events on the HEART Score	Adverse Events on ECG Changes		Total	Percentage
	Positive	Negative		
Positive	323	4	327	Sn=86.6%, Sp=66.7% PPV=98.77%, NPV= 13.79%, DA=85.97%
Negative	50	8	58	
Total	373	12	385	

The Se, Sp, PPV, and NPV predicting adverse events on HEART score vs. ECG changes were 86.7%, 66.7%, 98.7% and 13.7% respectively(Table 3).

Table 3: Stratification of Adverse Events on HEART Score vs. ECG Changes with Respect to Gender

Variables	Adverse Events on the HEART Score	Adverse Events on ECG Changes		Total	Percentage
		Positive	Negative		
Gender					
Male	Positive	233	3	236	Sn=89.2%, Sp=62.5%, PPV=98.7%, NPV=15.15%, DA=88.4%
	Negative	28	5	33	
Female	Positive	90	1	91	Sn=80.3%, Sp=75.0%, PPV=98.9%, NPV=12.0%, DA=80.17%
	Negative	22	3	25	
Age Groups					
<50 Years	Positive	126	2	128	Sn=76.83%, Sp=71.43%, PPV=98.4%, NPV=11.62%, DA=76.60%
	Negative	38	5	43	
	Total	164	7	171	–
>50 Years	Positive	197	2	199	Sn=94.2%, Sp=60.0%, PPV=98.9%, NPV=20.0%, DA=93.45%
	Negative	12	3	15	
Duration of Symptoms					
<6 Hours	Positive	283	4	287	Sn=87.08%, Sp=55.5%, PPV=98.60%, NPV=10.63%, DA=86.22%
	Negative	42	5	47	
>6 Hours	Positive	40	0	40	Sn=83.3%, Sp=100.0%, PPV=100.0%, NPV=27.3%, DA=84.31%
	Negative	8	3	11	
Diabetes Mellitus					
Yes	Positive	272	4	276	Sn=86.6%, Sp=60.0%, PPV=98.5%, NPV=12.5%, DA=85.8 %
	Negative	42	6	48	
No	Positive	51	0	51	Sn=86.4%, Sp=100.0%, PPV=100.0%, NPV=20.0%, DA=86.8%
	Negative	8	2	10	

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Smoking					
Yes	Positive	144	1	145	Sn=93.5%, Sp=66.7%, PPV=99.3%, NPV=16.6%, DA=92.9%
	Negative	10	2	12	
No	Positive	179	3	182	Sn=81.7%, Sp=66.6%, PPV=98.3%, NPV=13.04%, DA=81.14%
	Negative	40	6	46	

DISCUSSION

Our research shows that the HEART score provides exceptional diagnostic precision. Age, ECG alterations, and troponin components shared by the HEART score are the most predictive of the TIMI, according to a prior study [14]. Therefore, doctors should use the HEART score as the preferred tool, assessing the ultimate probability of MACE in their patients who present with chest pain, after applying their clinical judgment to estimate the pretest risk of MACE. A patient with a score below the threshold (≤3) and pretest likelihood of 25% for MACE, for instance, would have a posttest probability of 3.0%. The posttest likelihood for the same patient would be 7.8% if their TIMI score was below the low-risk cutoff (≤1). The GRACE score's predictive accuracy could not be evaluated since the included studies that examined it used different evaluation thresholds [15, 16]. These proven results have significant ramifications for pertinent clinical policies and guidelines. As previously stated, the AHA/ACC guidelines presently advise physicians to use a clinical tool when determining a patient's risk for chest discomfort [14]. Our findings imply that the HEART score ought to be the go-to instrument for these objectives, especially when looking to detect a low-risk that can be discharged right away. When estimating chest pain, the emergency physician's priority is to effectively diagnose "clinically significant" cardiac ischemia. However, as discussed extensively in the cardiovascular literature, there is no objective criterion standard to establish this diagnosis. Consequently, MACE is most frequently used as the benchmark for a practical method of identifying clinically severe ischemia based on the incidence of negative consequences or the requirement for significant intervention. In this study of diagnostic test accuracy, the target outcome was clinically severe cardiac ischemia, using the score as the index test and MACE as the reference standard. Although MACE is frequently used result of a notable risk of incorporation when the diagnostic test aids. The issue of identifying the diagnostic value of troponins for identifying "clinically significant" ischemia that necessitates revascularization is one example. This condition lacks a standard of care, and the presence of elevated troponins is likely to influence any prospective outcome assessor. Furthermore, the use of composite outcomes suggests that each segment has similar significance. It is crucial to keep in mind that men have a much higher risk of MACE across all HEART risk categories when using the HEART score to support clinical decision-making. Men with acute chest pain appear to be less safe to be discharged early with a low-risk HEART score than women [17]. According to one study, the HEART score (≥4) had a specificity of 44.6% (95% CI = 38.8% - 50.5%) and sensitivity of 95.9% (95% CI = 93.3% - 97.5%) [13]. According to another study, the HEART score demonstrated 53% specificity and 100% sensitivity for MACE [18]. In contrast, the HEART score for MACE in the Indian population exhibited an 86.7% sensitivity and a 50.2% specificity [19]. In China, the HEART score for MACE had a 52.9% sensitivity and an 83.2% specificity [20].

This study is limited using MACE as a composite reference standard, which may introduce incorporation bias and assumes equal weight for all outcome components. Additionally, variability in HEART score performance across different populations and sexes may affect generalizability. Future research should validate the HEART score across diverse populations and settings, considering sex-specific risk differences and standardized outcome definitions.

CONCLUSIONS

For patients experiencing chest pain, the HEART score is a reliable indicator of significant unfavorable cardiac events. It is recommended that the HEART score be further verified as a clinical risk assessment tool for Emergency Department patients with chest pain.

Authors' Contribution

Conceptualization: AA
Methodology: AA, TH, SU, BM
Formal analysis: MS, MM
Writing and Drafting: AA
Review and Editing: AA, TH, MS, SU, BM, MM

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 Common Bile Duct Dilatation at the Porta Hepatis in Patients with Obstructive Jaundice on Ultrasonography and Magnetic Resonance Pancreatography

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ABSTRACT

Obstructive jaundice is a frequent clinical issue that, in most cases, is related to choledocholithiasis, strictures, or malignant lesions. **Objective:** To compare the level of diagnostic accuracy of USG to that of MRCP in identifying CBD dilatation. **Methods:** There were 165 patients with clinical suspicion of obstructive jaundice, who were enrolled in six months between 1st July 2024 and 31st December 2024. MRCP was used as the reference standard to assess the diagnostic performance of USG. Calculations were made on sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), diagnostic accuracy, and likelihood ratios. The Receiver Operating Characteristic (ROC) analysis was conducted, and age, gender, BMI, and symptom duration were determined post-stratification to assess diagnostic accuracy. **Results:** The average age of the participants was 52 years, and 57.6% were men. MRCP was positive in 60.6% of patients with CBD, and USG was positive in 54.5% of patients. USG proved to have a sensitivity of 85.0, specificity of 92.3, and PPV of 94.4 and NPV of 80.0, and a general diagnostic accuracy of 87.9 compared with MRCP. **Conclusions:** USG offers high specificity and accuracy of diagnosis of CBD dilatation and should be used as a primary imaging tool. MRCP is to be used in cases of inconclusive or negative USG when there is high clinical suspicion.

INTRODUCTION

Obstructive jaundice is a typical clinical manifestation that develops because of mechanical obstruction of bile flow anywhere in the biliary tree. It is linked to life-threatening conditions such as cholangitis, pancreatitis, and progressive liver dysfunction, and timely and accurate diagnosis is vital [1]. Hepatobiliary diseases are significant healthcare system burdens in the world, and early imaging is essential to inform therapeutic decisions [2, 3]. Transabdominal ultrasonography (US) is still the initial imaging modality of choice in patients with suspected biliary obstruction. It is cheap, very common, non-invasive, and free of ionizing radiation. The common bile duct (CBD) is easy to see anterior to the portal vein at the porta hepatis, and sonographic measurement of CBD dilatation is usually done at this landmark [4]. The upper normal limit of the common bile duct diameter is thought to be 6 to 7 mm in adults, although it may increase with age or after cholecystectomy [5, 6]. Although it is useful, ultrasound has significant drawbacks, with distal bile ducts and the pancreatic head being frequently obscured by bowel gas or

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body habitus, which decreases the accuracy of diagnostics [7]. Magnetic resonance cholangiopancreatography (MRCP) is the most sensitive, non-invasive imaging modality for assessing the biliary tree [8]. It gives multiplanar visualization, which has a high contrast resolution, and the level and cause of obstruction are effectively detected. MRCP has reported sensitivity of between 85% and 98% with specificity of over 90%; hence, it is a good substitute for invasive diagnostic tests like the ERCP [9, 10]. The results of comparative studies indicate that MRCP is better than ultrasound in the localization and etiology of obstruction, especially in choledocholithiasis and malignant strictures [11, 12].

Although extensive studies have been conducted to compare ultrasound and MRCP in the diagnosis of obstructive jaundice, very minimal research has been carried out on the CBD diameter measurement at the porta hepatis, which is a significant anatomical landmark in detecting obstruction at a very early stage. By establishing this correlation, not only will the reliability of ultrasound in the initial screening be validated, but the time when MRCP should be a priority will be established to maximize diagnostic algorithm and resource use. The purpose of the present study was to compare the common bile duct dilatation measured at the porta hepatis on ultrasonography (US) to magnetic resonance cholangiopancreatography (MRI) in patients with obstructive jaundice.

METHODS

This cross-sectional validation study was conducted at PAEC General Hospital, Islamabad, for six months from 1st July 2024 to 31st December 2024. The ethical approval was obtained from the Institutional Ethical Committee (IEC) of PAEC General Hospital, Approval no: PGHI-IRB (DMe)-RCD-06-092. A sample size of 165 patients was calculated using a sensitivity and specificity calculator, based on an expected sensitivity of 85%, specificity of 79%, prevalence of 78.0%, desired precision of 10%, and a confidence level of 95% [2, 9]. Patients were recruited using a non-probability consecutive sampling technique. All patients presenting with clinical signs and symptoms of obstructive jaundice, such as right hypochondrial pain, upper abdominal pain, fever, and malaise, along with raised total serum bilirubin levels greater than 1.2 mg/dl, were considered eligible. Adults of both genders aged between 30 and 70 years were included. Patients with a history of cholecystectomy or other abdominal surgical interventions, pregnant women, and those with contraindications to MRI, such as claustrophobia, metallic implants, dental and cochlear devices, cardiac pacemakers, or aneurysmal clips, were excluded from the study. Patients meeting the inclusion criteria who presented to the Department of Outpatient Services or the Department of Emergency were enrolled in the study. The participants were informed about the study protocol, and informed consent was obtained along with a brief clinical history, including the procedures of ultrasonography and MRCP. In the case of ultrasonography, patients were positioned in the supine or left lateral position to enable an improved view of the hepatobiliary system. Following the coupling of gel, a transducer was placed on the right upper abdomen, and the liver, gallbladder, and bile ducts were real-time visualized. The presence of stones or masses, the common bile duct (CBD) diameter, wall characteristics, and differentiation between vascular and biliary structures were observed, and Doppler was applied. In adults, a CBD of more than 6 mm was regarded as dilated. Magnetic resonance cholangiopancreatography (MRCP) was done with the patient lying supinely in the MRI scanner, where abdominal coils were used. T2-weighted sequences were acquired to emphasize fluid-filled structures to give clear images of the biliary tree and pancreatic ducts. Coronal and axial images provided close anatomical detail, whereas other sequences blocked the fat signal and enhanced the ductal visualization. Obstructive jaundice was characterized as a high level of serum bilirubin (more than 2.5 mg/dL) in which there is predominance of direct bilirubin, which is usually characterized by yellowish skin and sclera, dark urine, and pale stool. The test under evaluation was ultrasonography, and the reference standard of diagnosis was MRCP. To assess diagnostic performance, sensitivity was the capacity of ultrasound to identify genuine cases of CBD dilatation, and specificity was used to identify the potential to eliminate non-cases. Positive predictive value (PPV) was used to denote the percentage of true positives of ultrasound positives, and negative predictive value (NPV) was used to denote the percentage of true negatives of ultrasound negatives. True positives, false positives, true negatives, and false negatives were all determined in terms of comparison with MRCP. Data entry and analysis were done using SPSS version 23.0. Quantitative data, or the body mass index, common bile duct size, age, and lab results, were expressed using mean and standard deviation. Qualitative variables like chief complaints, gender, duration of symptoms, and outcomes were presented, such as frequencies and percentages. A 2 x 2 contingency table was developed on MRCP as the reference; the sensitivity, specificity, positive predictive value, negative predictive value, and the overall diagnostic value of the ultrasonography were established. Diagnostic performance of ultrasonography was evaluated against MRCP by the Receiver Operating Characteristic (ROC) curve, and the area under the curve (AUC) was used as a

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summary measure of the overall test performance. A CBD diameter cut-off of 6 mm was used to define dilatation on ultrasonography to generate the ROC curve and the AUC. The stratification was adjusted for the effect modifiers age, gender, BMI, and duration of symptoms. A p-value ≤0.05 was taken to be significant.

RESULTS

The BMI of the study participants was 27.5 ± 4.2 kg/m2 with a mean age of 52.0 ± 10.0. Out of 165 respondents, 57.6 percent were males and 42.4% were females. Jaundice (90.9%) was the most frequent presenting complaint, followed by abdominal pain (72.7%), dark-colored urine (54.5%), pruritus (27.3%), and pale bowel movements (18.2%). In terms of symptom duration, 18.2% had had the symptoms for less than one week, 48.5% less than four weeks, and 33.3% had a longer duration. The MRCP gold standard in this study indicated that 60.6% of participants had common bile duct dilatation, with 39.4% having no dilatation. In ultrasound, 54.5% of the patients showed dilatation, and 45.5% did not have any evidence of dilatation(Table 1).

Table 1: Demographics and Clinical Features and Imaging Findings of the Study Participants(n=165)

Variables	n (%)
Age	
Mean ± SD (Years)	52.0 ± 10.0
Gender	
Male	95 (57.6%)
Female	70 (42.4%)
BMI	
Mean ± SD (kg/m^2)	27.5 ± 4.2
Chief complaint	
Jaundice	150 (90.9%)
Abdominal Pain	120 (72.7%)
Pruritus	45 (27.3%)
Dark Urine	90 (54.5%)
Pale Stools	30 (18.2%)
Duration	
< 1 Week	30 (18.2%)
1–4 Weeks	80 (48.5%)
> 4 Weeks	55 (33.3%)
MRCP (Gold Standard)	
CBD Dilatation	100 (60.6%)
No CBD Dilatation	65 (39.4%)
Ultrasound	
CBD Dilatation	90 (54.5%)
No CBD Dilatation	75 (45.5%)

The laboratory analysis revealed that there were high levels of bilirubin and matching liver dysfunction tests, such as transaminases, alkaline phosphatase, and gamma-glutamyl transferase, which are in agreement with obstruction of the biliary system. Hematological evaluation showed that some patients had mild anemia, and the white blood cell count, as well as the platelet count, mostly fell within the expected clinical levels(Table 2).

Table 2: Laboratory Findings of the Study Participants(n=165)

Laboratory Findings	Mean ± SD
Total Bilirubin (mg/dL)	6.8 ± 3.4
Direct Bilirubin (mg/dL)	4.9 ± 2.6
ALT (U/L)	78 ± 60
AST (U/L)	65 ± 50
ALP (U/L)	320 ± 150
GGT (U/L)	210 ± 120
Hemoglobin (g/dL)	11.8 ± 1.6
WBC (×10^3 /mm^3)	9.5 ± 3.2
Platelets (×10^3 /mm^3)	220 ± 60

Comparison of the results of ultrasonography and MRCP as the gold standard demonstrates that the majority of the cases of common bile duct dilatation on the MRCP were also identified in the ultrasound. Cohen's kappa was calculated from the 2×2 table to assess agreement between ultrasound and MRCP, yielding a value of 0.77, indicating substantial concordance between the two modalities. Of the total, 85 were true positives, 60 were true negatives, 15 cases were missed as false negatives, and 5 were over-reported as false positives(Table 3).

Table 3: Comparison of MRCP Findings with UGS(n=165)

MRCP	USG		Total
	Positive	Negative	
Positive (CBD Dilated)	85 (TP)	15 (FN)	100
Negative (No CBD Dilatation)	5 (FP)	60 (TN)	65
Total	90	75	165

The ultrasonography showed high specificity and positive predictive value, which means that a dilatation detected by sonography has a high probability of being confirmed in MRCP. The negative predictive value and sensitivity were somewhat lower, indicating the possibility of missed cases in some patients. In general, the quality of diagnoses was good, and all the measures were supported by a 95% confidence to obtain precision and enhance interpretability. Moreover, the AUC under the ROC curve was 0.93(95% CI: 0.88-0.97)(Table 4).

Table 4: Diagnostic Performance of USG Using MRCP as the Gold Standard

Measurements	Values	95% Confidence Interval (CI)
Sensitivity	85.0%	76.0–91.0%
Specificity	92.3%	83.0–97.0%
Positive Predictive Value (PPV)	94.4%	86.0–98.0%
Negative Predictive Value (NPV)	80.0%	69.0–88.0%
Overall Accuracy	87.9%	81.0–93.0%

The diagnostic accuracy of USG was not significantly

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different after post-stratification by age groups (p=0.125) or genders (p=0.455). Nevertheless, a substantial difference was also evident regarding BMI, with a decrease in the diagnostic performance of patients with obesity (BMI ≥30 kg/m2) relative to the normal/overweight patients (p=0.044). Likewise, duration of symptoms also played a role in the accuracy of the diagnosis, with lower accuracy among those whose symptoms had a short time frame of one week compared with those whose symptoms had a longer duration (p=0.032) (Table 5).

Table 5: Post-Stratification Diagnostic Performance of USG (n = 165)

Stratum (n)	Sensitivity (%)	Specificity (%)	Accuracy (%)	p-value
Age				
< 50 Years (n=70)	86.0%	90.0%	87.1%	0.125
≥ 50 Years (n=95)	84.5%	93.0%	88.4%	
Gender				
Male (n=95)	85.3%	91.6%	88.4%	0.455
Female (n=70)	84.6%	93.3%	87.1%	
BMI				
< 25 kg/m^2 (n=45)	90.0%	95.0%	92.2%	0.044*
25–29.9 kg/m^2 (n=80)	85.0%	92.0%	88.8%	
≥ 30 kg/m^2 (n=40)	75.0%	85.0%	80.0%	
Duration of Symptoms				
< 1 Week (n=30)	78.0%	86.0%	82.0%	0.032*
1–4 Weeks (n=80)	87.5%	93.0%	90.0%	
> 4 Weeks (n=55)	85.0%	92.0%	88.2%	

The chi-square test was applied* Statistically significant (p≤0.05)

ROC Curve showing the diagnostic performance of USG-measured CBD diameter against MRCP-confirmed dilatation, with an AUC of 0.93, reflecting excellent accuracy (Figure 1).

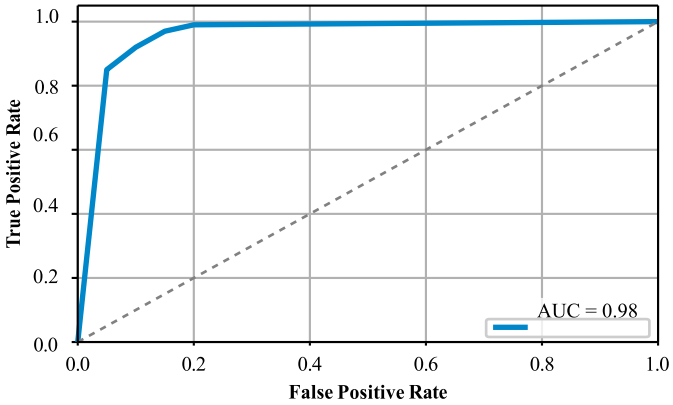

Figure 1: ROC Curve for USG vs MRCP (CBD Dilatation)

DISCUSSION

In the present study cohort of 165 patients, USG showed good diagnostic performance for detecting CBD dilatation when MRCP was used as the reference standard: sensitivity 85.0%, specificity 92.3%, and AUC 0.93. These results place USG in a favorable position compared with several recent reports that evaluated US, MRCP, and other modalities for biliary obstruction. A 2023 single-center study comparing USG and MRCP reported low sensitivity but high specificity for ultrasound in detecting choledocholithiasis, while MRCP showed very high sensitivity and specificity; the authors concluded that MRCP outperformed US, particularly for small or distal stones. Several recent institutional reports and audit-style studies similarly found MRCP to have excellent diagnostic accuracy (often ≥90%) for biliary obstruction and choledocholithiasis, while USG performance was more variable [13, 14]. A 2020 diagnostic efficacy study reported MRCP accuracy near 97% for level and cause of obstruction compared with ultrasound accuracy around 81%, emphasizing MRCP's superior mapping of the biliary tree and cause of obstruction; our USG accuracy (87.9%) lies between those values and likely reflects that our endpoint, CBD dilatation at the porta hepatis, is a sonographic landmark that USG can measure reasonably well in many patients [15]. Other studies have published prospective comparisons showing MRCP sensitivity often above 90% for choledocholithiasis and overall diagnostic accuracy approaching 90%, which supports the role of MRCP as the non-invasive gold standard in many centers [16, 17]. The present study MRCP-based reference standard and the high AUC for USG indicate that ultrasound-measured CBD diameter is a strong discriminator of MRCP-confirmed dilatation, even if ultrasound may miss some cases. Differences in sensitivity between studies appear tied to the prevalence of distal small stones, operator skill, and the specific definition of "positive" [18, 19]. A multicenter analysis has compared MRCP, EUS, and transabdominal ultrasound and showed that MRCP and EUS have superior sensitivity to transabdominal ultrasound for detecting stones and defining the level of obstruction, although specificity is frequently similar across modalities. Where EUS shows higher sensitivity, MRCP remains the preferred non-invasive test for anatomical mapping [13, 20]. Current findings are compatible with this body of evidence; ultrasound demonstrated high specificity and PPV, but NPV was lower (80.0%), indicating that a negative ultrasound could not always exclude MRCP-confirmed dilatation, which mirrors conclusions from recent meta-analyses [21]. This study is limited by its single-center design, operator-dependent ultrasonography, and use of non-probability consecutive sampling, which may introduce selection bias and limit generalizability. Additionally, small distal stones may be missed on ultrasound, and the lack of statistical comparison of continuous CBD measurements between US and MRCP restricts assessment of measurement agreement. Future multicenter studies using standardized imaging protocols should compare continuous CBD

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measurements across modalities and incorporate EUS or MRCP to improve diagnostic accuracy.

CONCLUSIONS

Present study showed that ultrasonography offers strong diagnostic accuracy, high specificity, and an excellent positive predictive value for identifying common bile duct dilatation when compared to MRCP, the gold standard. These results demonstrate its value as a dependable, affordable, and easily accessible first-line screening tool, especially in environments with limited resources. Its negative predictive value and poorer sensitivity, however, highlight how crucial it is to confirm negative ultrasonography results with MRCP in patients who have a high level of clinical suspicion.

Authors' Contribution

Conceptualization: SM
Methodology: SM, NS, NK, MIK
Formal analysis: NK, HG
Writing and Drafting: SM, NS, AN, MIK
Review and Editing: SM, NS, NK, MIK, HG, AN

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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Prevalence of Tuberculosis Trends in District Abbottabad, Pakistan: A Cross-Sectional Survey

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ABSTRACT

Tuberculosis (TB) remains a major public health concern in Pakistan, with the country ranked sixth among high-burden developing nations. Significant regional disparities in TB incidence emphasize the importance of localized surveillance and targeted interventions. **Objectives:** To assess the prevalence of TB in District Abbottabad, explore variations by age and gender, and evaluate trends in TB cases reported by healthcare facilities between January 2022 and December 2023. **Methods:** A retrospective cross-sectional study was conducted from April to October 2024, utilizing secondary data from the TB Control Programme, Khyber Pakhtunkhwa. Purposive sampling included all registered pulmonary tuberculosis patients with positive sputum smear results (PTBSS). Data were entered into Microsoft Excel and analyzed using frequency distributions, histograms, and bar charts to highlight case patterns and temporal trends. **Results:** In 2022, 810 new bacteriologically confirmed TB cases were reported in Abbottabad, increasing to 843 in 2023, representing a 4% rise. Male patients were more frequently affected, with male-to-female ratios of 1.07 and 1.17 in 2022 and 2023, respectively. The PPM ACD center reported the largest share of cases. Moreover, relapsed pulmonary TB cases rose from 78 to 96 between the two years, showing a 23% increase. The overall relapse rate (23%) was higher than the 11.2% previously reported from Pakistan. **Conclusion:** District Abbottabad demonstrates a persistent TB burden with a notable 23% rise in relapse cases, indicating gaps in treatment outcomes. Strengthening follow-up, improving adherence, and enhancing case detection in high-risk groups remain crucial for effective TB control.

INTRODUCTION

Tuberculosis (TB), caused by the acid-fast bacillus Mycobacterium tuberculosis (MTB), is a widespread infectious disease affecting all countries and age groups. Robert Koch first identified Mycobacterium tuberculosis, also known as the tubercle bacillus, as the causative agent of TB in 1882 [1]. While the disease primarily affects the lungs (pulmonary TB), it can also involve other organs if left untreated (extrapulmonary TB). Common symptoms include chronic cough (occasionally with blood), fatigue, weight loss, chest pain, night sweats, and shortness of breath [2]. TB continues to be one of the most significant public health challenges globally. It was among the leading causes of death in 2019 and 2023, ranking as the second deadliest infectious disease after COVID-19, especially in low- and middle-income countries [3]. In 2016, TB was the leading cause of death from a single infectious agent and remains highly endemic in Pakistan [4]. Despite being preventable and treatable, TB claimed 1.6 million lives globally in 2021, including 187,000 deaths among HIV-positive individuals. That same year, an estimated 10.6 million people developed TB worldwide [5]. In recognition of its widespread impact, the World Health Organization

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(WHO) declared TB a global emergency in 1993 [5]. In 2022, the World Health Organization (WHO) reported that the South-East Asian Region accounted for the largest share of global tuberculosis (TB) cases (46%), followed by the African Region (23%) and the Western Pacific Region (18%). Nearly 87% of all new TB cases were concentrated in 30 high-burden countries, with Pakistan, Bangladesh, China, the Democratic Republic of the Congo, India, Indonesia, Nigeria, and the Philippines collectively representing over two-thirds of the worldwide TB burden [6]. Pakistan is among the high-burden countries for TB, with a national prevalence rate of approximately 5% [6]. The country ranks sixth in TB burden among developing nations [7], and a significant gap exists between the estimated incidence and the number of reported cases—approximately 241,688 cases go unreported each year [8]. In the province of Khyber Pakhtunkhwa (KPK) alone, around 5,10,000 new TB cases are reported annually, highlighting its persistent public health impact [7]. A key obstacle in TB control efforts is the emergence of drug resistance, especially multidrug-resistant TB (MDR-TB). Despite advancements in diagnostic tools, sputum smear microscopy remains the most widely used method, though it lacks effectiveness in detecting drug resistance [9]. According to WHO data, there were 10.4 million new TB cases globally, of which 490,000 were multidrug-resistant, and 110,000 were rifampicin-resistant [10]. To address these challenges, Pakistan's National Tuberculosis Control Program (NTP), with support from WHO, implements diagnostic measures including sputum smear microscopy and chest radiography. Patients with at least two sputum samples positive for acid-fast bacilli (AFB) or one positive sample accompanied by radiographic signs of active pulmonary TB are classified as sputum smear-positive (SS+) cases [9, 11]. Furthermore, WHO has advocated the Public–Private Mix (PPM) strategy to enhance TB detection and treatment in high-burden countries. Under this approach, the NTP collaborates with private healthcare providers to bridge the gap between estimated and reported cases [8]. Recent trends from South Asia during 2022–2023 show progress in TB control despite disruptions caused by the COVID-19 pandemic. Pulmonary TB (PTB) epidemiology is shaped by factors such as age, sex, geographic location, immunity, drug resistance, and HIV status. In Pakistan, regional disparities in TB incidence and prevalence persist, necessitating targeted and localized interventions [12]. Concurrently conducting a survey that gauges a population-level indicator of M. tuberculosis transmission, such as risk of M. tuberculosis infection, is necessary to support the interpretation of changes in the prevalence of adult pulmonary disease. However, in the past few decades, these have hardly ever been carried out simultaneously to evaluate load [13]. By identifying and connecting individuals afflicted with tuberculosis, Active case finding (ACF) is one intervention that may help prevent the spread of M. tuberculosis. However, the efficacy of ACF at the population level is still unknown, and these efforts require a lot of resources [14].

A comprehensive search was conducted using PubMed, Google Scholar, and other search engines; however, no studies were found reporting the incidence or prevalence of tuberculosis (TB) in Abbottabad. Therefore, this study was undertaken to fill this gap in the existing literature. By analysing data from 2022 to 2023, this research seeks to understand the local epidemiology of TB, including its distribution by age, gender, and healthcare facility, to inform more effective control and prevention strategies. This study aimed to investigate the trends and patterns of TB prevalence in Abbottabad, a district in Khyber Pakhtunkhwa, Pakistan.

METHODS

This retrospective cross-sectional study was conducted using data from the TB Control Program, Khyber Pakhtunkhwa, recorded between January 1, 2022, and December 31, 2023. Ethical approval for the study was obtained from the Institutional Review Board of Women's Medical College (Ref. No. WMC/Re/IRB//07). The sample included 2,503 patients from 2022 and 2,840 patients from 2023, reported from all tuberculosis centers in District Abbottabad, namely Ayub Teaching Hospital Abbottabad, Civil Hospital Boi, Civil Hospital Nathia Gali, Civil Hospital Sherwan, DTO Clinic, PPM ACD, RHC Havelian, RHC Lora, and the TB Association. The study was carried out over six months from April to October, 2024. Purposive sampling was used to select study participants. The study included all patients with pulmonary tuberculosis who were bacteriologically confirmed through sputum smear positivity and who attended the treatment centers between January 2022 and December 2023. A total of 810 patients from 2022 and 843 patients from 2023 meeting these criteria were included in the analysis. Patients with extrapulmonary tuberculosis or those clinically diagnosed but not bacteriologically confirmed were excluded. Data regarding age, gender, diagnostic method, and facility-wise distribution of TB cases were retrieved from TB07 forms maintained by the TB Control Program, Khyber Pakhtunkhwa. The collected data were entered and analyzed using Microsoft Excel, and the results were presented in the form of tables and graphs. Categorical variables were summarized as frequencies and percentages.

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RESULTS

Data for newly diagnosed bacteriologically confirmed TB cases registered were recorded from seven tuberculosis centers in District Abbottabad for the years 2022 and 2023. During this period, 810 and 843 cases were reported for the years 2022 and 2023, respectively. An overall increase of 4% in new TB cases was observed between the two years. Moreover, the data for relapsed cases of pulmonary tuberculosis recorded from the same centers and dates showed 78 and 96 cases for the years 2022 and 2023, respectively. Thus, an overall increase of 23% was observed in relapsed TB cases between the two years. In 2022, a slightly higher number of cases were reported among males compared to females (447 vs. 441), resulting in a male-to-female ratio of 1.07. This male predominance continued in 2023, with 508 cases in males and 431 in females, reflecting a male-to-female ratio of 1.17. Across all health facilities, males constituted 54.1% of TB cases, while females accounted for 45.9%. Age-wise analysis revealed that the highest number of TB cases in both years occurred in the age group 65 years and older, with 102 cases in 2022 and 114 cases in 2023. The age group over 65 years represented the largest proportion of TB cases (21.9%), followed by the 15–24 years group (19.9%) and the 55–64 years group (15.7%) (Table 1).

Table 1: Association of Pulmonary Tuberculosis with Gender and Different Age Groups

Variables	TB Cases 2022, n (%)	TB Cases 2023, n (%)
Gender		
Male	447 (50.34%)	508 (54.1%)
Female	441 (49.67%)	431 (45.90%)
Age Group		
0-4 Years	5 (0.56%)	8 (0.9%)
5-14	27 (3.04%)	29 (3.1%)
15-24	184 (20.7%)	187 (19.9%)
25-34	114 (12.8%)	140 (14.9%)
35-44	115 (12.9%)	122 (12.9%)
45-54	110 (12.4%)	100 (10.6%)
55-64	124 (13.9%)	147 (15.7%)
>65	209 (23.5%)	206 (21.9%)
Treatment History		
New Cases	810 (91.2%)	843 (89.8%)
Reveals a 4% Increase Per the Formula: 943-910/910 × 100 = 4.07%		
Relapse Cases	78 (8.8%)	96 (10.2%)
Reveals a 23% Increase Per the Formula: 96-78/78 × 100 = 23.08%		

Analysis by the healthcare facility showed that the highest TB prevalence was observed at the PPM ACD center, accounting for 32.7% of cases in 2022 and increasing to 36.8% in 2023. This was followed by Ayub Teaching Hospital, which reported 28.7% of cases in 2022 and 19.8% in 2023 (Table 2).

Table 2: Tuberculosis Health Care Facilities in Abbottabad

Health Care Facility	TB Cases 2022, n (%)	TB Cases 2023, n (%)
Ayub Teaching Hospital	255 (28.7%)	186 (19.8%)
Civil Hospital Boi	15 (1.7%)	10 (1.1%)
Civil Hospital Nathiagali	20 (2.3%)	20 (2.1%)
Civil Hospital Sherwan	07 (0.8%)	06 (0.6%)
DTO Clinic	223 (25.1%)	273 (29.1%)
PPM ACD	290 (32.7%)	34 (36.8%)
RHC Havelian	37 (4.2%)	51 (5.4%)
RHC Lora	31 (3.5%)	40 (4.3%)
TB Association Center	10 (1.1%)	07 (0.8%)
Abbottabad	888	939

DISCUSSION

Pakistan continues to face a high burden of tuberculosis, with significant prevalence, incidence, and mortality rates. The National TB Control Program is focused on increasing the notification of TB cases and improving treatment success rates. However, effective TB control requires accurate and detailed epidemiological data on TB prevalence and distribution. Our study showed an increasing trend of 4% in the prevalence of Tuberculosis over a period of two years. These findings are in contrast to a survey conducted in Karachi that showed a decrease in prevalence in the active microbiologically sputum-positive cases [15]. Another study in South Punjab showed that the incidence rate of Tuberculosis increased in almost all regions, with the Multan division exhibiting the highest incidence, followed by Bahawalpur and D. G Khan [16]. The rate of relapse cases of TB in our study was 23%, which is higher than the previous report (11.2%) from Pakistan published in 2022 [17]. Male were more affected than females in both years of our study period. which. is supported by another study in Bajaur agency, in which male was dominant [18]. Yet another research revealed that the prevalence of active TB was higher among women [19]. However, another research in Abbottabad and Mansehra districts showed that the number of TB cases reported was almost equal in male and female patients (M/F ratio 1.01) [20]. Yet another research showed that pulmonary tuberculosis was significantly more common in female patients than in male [21]. Age-wise, the highest number of TB cases in our study was observed in individuals over 65 years of age for both 2022 and 2023, followed by the 15–24 and 55–64-year age groups. However, our findings are somewhat aligned with the Bajaur study, which reported the highest TB positivity in the 11–20 and 21–30-year age groups [18]. These findings are similar to research that revealed that the median age of participants was 35 (IQR 13.8) and the age distribution was skewed towards older age groups [22]. Yet another study in Peshawar showed that Tuberculosis was more prevalent in people >45 years [23].

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Another research in urban Sindh highlighted that 19-45 years was the most common age group affected [24]. The elevated prevalence among older adults in our study may be due to immune-senescence and the presence of comorbidities, which increase the risk of latent TB reactivation. The 15–24 years age group, which ranked second (19.9%), highlights ongoing transmission in the younger population, possibly due to increased social contact, mobility, and poor health-seeking behaviour. The 55–64 years group (15.7%) also contributed significantly, reflecting the need for targeted TB screening in older adults. When analysing TB prevalence by healthcare facility, the Public-Private Mix Active Case Detection (PPM ACD) center emerged as the leading site for TB detection, accounting for an increasing proportion of diagnosed cases (from 32.7% in 2022 to 36.8% in 2023. This suggests the growing effectiveness or outreach of the PPM ACD program, potentially due to its active case-finding strategies and community engagement. In contrast, the proportion of cases reported by Ayub Teaching Hospital declined in 2023, which may reflect shifting patient preferences, referral patterns, or resource limitations in passive case detection centers. The majority of TB cases in both years were bacteriologically confirmed new cases, comprising over 89% of all cases. This high percentage indicates strong diagnostic capacity and a focus on identifying new infections. However, a noticeable increase in relapse cases—from 78 (8.8%) in 2022 to 96 (10.2%) in 2023 raises concerns about treatment adherence, drug resistance, or gaps in post-treatment follow-up. The rising trend in relapse cases underlines the importance of strengthening treatment monitoring, patient education, and support systems to ensure successful treatment outcomes. Together, these findings underscore the need for age-specific interventions, enhanced active case-finding programs like the PPM ACD, and robust post-treatment support to curb the spread and recurrence of TB. Regarding disease recurrence, the majority of cases in our study were newly diagnosed, with relapse cases accounting for 8.8% in 2022 and 10.2% in 2023. These rates are comparable to those reported in Punjab (9.9%) [16], Bahawalpur (11.4%) [18], and Rawalpindi (11.2%) [20]. However, our relapse rate is higher than that observed in a tertiary care center in Rawalpindi, where it was reported at 5.4% [21]. Overall, our findings highlight the continuing challenges in TB control in Pakistan, emphasizing the need for targeted interventions that consider gender disparities, age-related vulnerabilities, and the importance of monitoring relapse cases to improve disease management.

This study is limited by its reliance on routinely reported surveillance data, which may be affected by underreporting, reporting delays, and variability in diagnostic and recording practices across healthcare facilities. Additionally, the absence of individual-level data on socioeconomic status, comorbidities, and treatment adherence limits causal interpretation of observed trends and relapse patterns. Future studies should incorporate longitudinal, patient-level data and strengthen active case-finding and post-treatment follow-up to better understand drivers of TB prevalence and relapse in Pakistan.

CONCLUSIONS

The study revealed a 4% increase in TB cases in District Abbottabad from 2022 to 2023, with a higher prevalence among males and individuals aged over 65. Most cases were newly diagnosed, while relapse cases increased by 23% during the same period, reflecting potential challenges in treatment adherence and follow-up. The highest burden was reported at the PPM ACD center. These findings highlight the need for strengthened surveillance, targeted interventions for high-risk groups, and improved access to TB care services.

Authors' Contribution

Conceptualization: YI, SM
Methodology: YI, SM, MOM
Formal analysis: MOM, AT, UN, SR
Writing and drafting: MOM, AT, UN, SR
Review and editing: YI, SM, MOM, AT, UN, SR

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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Procalcitonin Level Evaluation for Prediction of Sepsis-Associated Mortality Rate in a Subset of Karachi Population

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ABSTRACT

Procalcitonin (PCT) has been recognized as a crucial biomarker in the diagnosis and prognosis of sepsis, as it reflects the body's response to infection. **Objective:** To identify the association of procalcitonin level for the prediction of sepsis-associated mortality rate in a subset of the Karachi population. **Methods:** It was an analytical cross-sectional study conducted at Ziauddin Medical College with approval of the ERC. The sample size was n=130. The set inclusion criteria were patients in whom sepsis was suspected, who given consent to participate in the study, and were within the range of 18-60 years. The exclusion criteria were patients from other hospitals, patients with malignancies and known ischemic heart diseases, patients with thyroid disorders, patients who had leukopenia, and patients who did not give consent to participate in the study. The data were collected through a pre-developed questionnaire, which included questions regarding demographics, presenting complaint, PCT levels at the time of admission, and outcome as positive (recovered) or negative (died). The minimum PCT levels considered as negative were 0.1 – 0.25ng/mL, if the outcome seemed to be positive. **Results:** Most of the patients with sepsis had 4-6 ng/mL of PCT levels. The increased mortality was found to be significantly associated with high levels of PCT, specifically in patients having PCT 6-8 ng/mL and greater than 8 ng/mL. **Conclusions:** High PCT levels can predict the outcome of sepsis; PCT levels more than 6 were associated with a high mortality rate in a subset of the Karachi population.

INTRODUCTION

Sepsis is a life-threatening medical disorder caused by the body's immune system responding to an infection in an excessive and dysregulated manner, resulting in extensive inflammation that destroys its own tissues and organs [1]. Normally, the immune system fights infections to defend the body. Still, in sepsis, this reaction becomes uncontrolled, resulting in organ failure and, in severe cases, shock or death if not diagnosed and treated very quickly. This inflammatory reaction can induce irregular blood flow, such as the creation of blood clots inside arteries, which deprive organs of oxygen and nutrients, exacerbating the damage [2]. Sepsis can be caused by a variety of factors that include bacterial infections, but fungi, viruses, and parasites can also cause it. Sepsis can quickly progress to severe sepsis, which causes significant organ dysfunction in the kidneys, lungs, liver, or heart, and septic shock, which

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is defined by dangerously low blood pressure that does not respond adequately to fluid resuscitation and necessitates vasopressor support. This development dramatically raises the chance of mortality [3]. Sepsis is a prominent cause of morbidity and mortality and a significant health burden globally. It is thought to be responsible for over 11 million fatalities a year, or 20% of all deaths globally [4]. It has been documented that in underdeveloped nations, sepsis-related mortality is disproportionately prevalent, particularly among infants and young children; the burden is considerably greater [5]. Furthermore, antimicrobial resistance makes treatment more difficult and raises the death rate from sepsis, causing hospital-acquired illnesses. Improving results requires early diagnosis, suitable antibiotic treatment, fluid resuscitation, and supportive care [6]. However, diagnosing sepsis and its consequences in the early stages of its development is difficult, but researchers are working on different markers that can highlight the complications of sepsis and predict mortality in severe cases [7]. Procalcitonin (PCT) has been recognized as a crucial biomarker in the diagnosis, treatment, and prognosis of sepsis, as it reflects the body's response to infection [8]. Unlike traditional indicators such as C-reactive protein or white blood cell counts, PCT rises swiftly and specifically in bacterial sepsis, making it useful for early diagnosis and distinction from non-infectious systemic inflammation. It is a precursor of the hormone calcitonin, which is typically undetectable in healthy people [9, 10]. However, during bacterial infections, its blood levels rise significantly because proinflammatory cytokines and bacterial endotoxins drive increased production in different tissues [11]. Because PCT levels tend to decrease with successful treatment, this feature helps clinicians not only detect sepsis early but also track the efficacy of antimicrobial therapy [12]. In terms of predicting sepsis-related mortality, increased procalcitonin levels are highly correlated with the severity of illness and bad outcomes [13]. According to studies, greater PCT concentrations at the time of ICU admission are related to increased organ failure, as indicated by scores such as the Sequential Organ Failure Assessment (SOFA), as well as higher short-term death rates [14]. A procalcitonin level equal to or greater than roughly 7 ng/mL upon admission has been associated with a considerably higher risk of 28-day death [15]. Considering its effectiveness in the prognosis of sepsis, identifying its association and levels that may predict highly susceptible individuals. The PCT analysis in individuals who may develop organ failure or sepsis-associated complications, such as death, will help inform health professionals about the expected outcome and may facilitate the improvised management to improve the outcome.

Although procalcitonin (PCT) is widely recognized as a useful biomarker for early diagnosis and monitoring of sepsis, its role in accurately predicting sepsis-associated mortality remains variably reported across different populations. Local data correlating PCT levels with mortality outcomes are limited. Therefore, this study aims to evaluate the association between procalcitonin levels and sepsis-related mortality in a subset of the Karachi population to aid early risk stratification and clinical decision-making.

METHODS

It was an analytical cross-sectional study conducted at the Department of Emergency of Ziauddin Medical College with approval of the ERC (Ref code: 2610920TAEM). The sample size n=130 was calculated through the open epi calculator, keeping the proportion of the population at 50% and the prevalence of 37% at 95% confidence intervals and 5% margin of error. The sample was segregated by a non-probability consecutive sampling technique according to the inclusion criteria from July 2022 to December 2024. The set inclusion criteria were patients in whom sepsis was suspected, who given consent to participate in the study, and were within the range of 18-60 years. The exclusion criteria were patients from other hospitals, patients with malignancies and known ischemic heart diseases, patients with thyroid disorders, patients who had leukopenia, and patients who did not give consent to participate in the study. The data was collected through a predeveloped questionnaire which included questions regarding demography, presenting complaint. PCT levels at the time of admission were measured. Outcome was considered positive if the patient recovered or negative if the patient died. The questionnaire was self-developed and validated by a pilot trial on 20 patients; the Cronbach's alpha score was checked, which was 0.8. After validating the questionnaire, the data were collected. At the time of admission, patients with a history of high-grade fever, chills, productive cough, suspected cellulitis, and purulent swelling were considered as potential candidates for the study. For diagnostic reason PCT levels were performed by sending a blood sample in a sterile vacutainer tube to the associated lab. Briefly, PCT levels were measured using an automated quantitative immunoassay technique. The sample was loaded into the automated analyser, and the automated analyser performed PCT analysis as per the lab manual protocol of the sandwich ELISA technique and generated the results as per the detection range of the Kit. The results were received from the lab, and patients with minimum PCT levels of 0.1–0.25ng/mL were excluded from the study. Patients with PCT levels more than 0.25ng/mL were considered septic [16]. The included patients who were diagnosed with sepsis and survived were marked as a

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positive outcome, and those who died during the hospital stay were recorded as a negative outcome. The number of survivors and deaths was associated with the already acquired PCT levels (recorded at the time of admission). Data were analysed by using SPSS version 27.0. PCT levels were categorized into 5 different categories: 0.25-2 ng/mL, 2-4 ng/mL, 4-6, 6-8, and >8. Mean ± SD were calculated for quantitative data, and frequency and percentages were calculated for qualitative data. To generate the association at the marked PCT level, associated mortality was checked as yes or no. Chi- square analyses were performed to generate the association and to identify the significance.

RESULTS

The mean age of study participants was 52.16 ± 6.31; among them, 77 (54.6%) were male and (45.4%) were female. Out of 130 (100%), 71 (54.6%) participants were diabetic, and 63 (48.4%) had a history of hypertension. The study shows the gender wise distribution of associated comorbidities. Most of the patients with sepsis had 4-6 ng/mL of PCT levels (Figure 1).

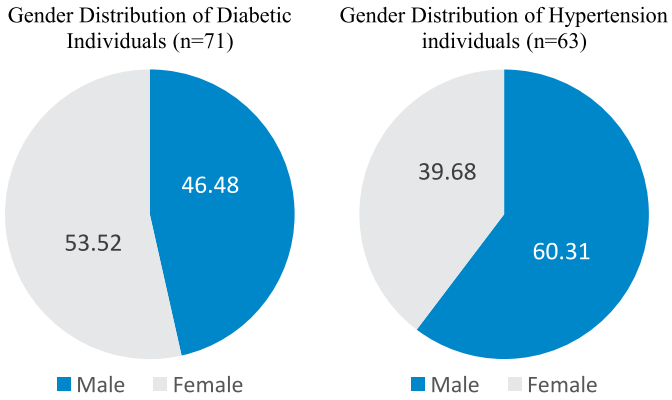

Figure 1: Presence of Comorbidities in the Participants of the Study (Male and Female)

The procalcitonin levels (ng/mL) among admitted participants at the time of hospital admission are illustrated (Figure 2).

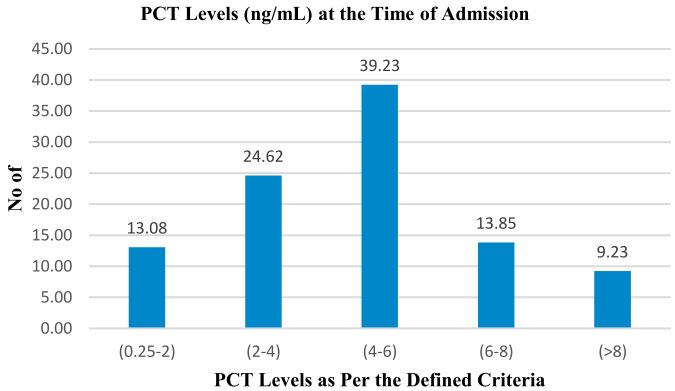

Figure 2: PCT Levels (ng/mL) in the Admitted Participants at the Time of Admission

The increased mortality was found to be significantly associated with high levels of PCT, specifically in patients having PCT 6-8 ng/mL and greater than 8 ng/mL. The mortality among the patients occurred on different days; however, the mean day of mortality was 11.1 ± 2.3 after admission (Table 1).

Table 1: Association of PCT Levels with the Outcome in Diagnosed Patients of Sepsis

PCT Level (ng /mL) (n=130)	Mortality Rate Recorded at Different PCT levels F (%)		p-value
	Yes	No	
(0.25-2) n= 17	0	17 (100%)	–
(2-4) n= 32	3 (9.38%)	29 (90.62%)	0.241
(4-6) n= 51	11 (21.57%)	40 (78.3%)	0.111
(6-8) n= 18	9 (50.00%)	9 (50.00%)	0.012*
(>8) n= 12	8 (66.67%)	4 (0.33%)	0.001*

*Significant p-value (p<0.05)

DISCUSSION

Procalcitonin (PCT) levels have emerged as a crucial biomarker in the setting of sepsis, with a substantial correlation with both sepsis severity and mortality rate, highlighting their relevance in clinical practice [16]. Elevated PCT levels correspond with the severity of systemic inflammation and bacterial infection that characterize sepsis, and multiple studies have shown that greater PCT concentrations are associated with an increased risk of death [17]. The dynamics of PCT, particularly its rise and fall over time, are also key prognostic indicators: a significant drop in PCT within 72 hours of initial evaluation predicts improved survival, whereas persistently high or growing levels indicate treatment failure and increased mortality risk [12]. Beyond prognosis, assessing PCT levels aids in antibiotic therapy by enabling early detection of bacterial sepsis and tracking therapeutic response, reducing wasteful antibiotic use and associated consequences [18]. Given these convincing findings, routine PCT assessment in all patients with suspected sepsis is critical for enabling rapid risk classification, optimizing clinical choices, tailoring antibiotic stewardship, and, ultimately, improving patient outcomes [19]. Therefore, the study was conducted to identify the association of PCT with mortality rate and to document the critical range of PCT in a subset of the Karachi Population. This study examined the correlation between procalcitonin (PCT) levels and sepsis in a sample of 77 men (54.6%) and 59 females (45.4%). The average age was 52.16 ± 6.31 years. In this middle-aged group, measuring PCT gave critical information into the inflammatory state and severity of sepsis, with substantial relationships with clinical outcomes that were independent of patient variables such as age and gender [20]. The balanced gender distribution enabled testing of

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both males and females, demonstrating that PCT elevation as a sepsis marker is constant, independent of gender [21]. The study's findings demonstrate that PCT is a valid indication of sepsis in a typical adult population in their fifth decade of life, which is a frequent age range for septic patients in clinical settings. This shows that frequent PCT assessment might improve early diagnosis and risk classification in sepsis care, allowing for timely and focused therapeutic interventions [22]. In this study, the majority of patients with sepsis had procalcitonin (PCT) levels ranging from 4 to 6 ng/mL at the time of hospital admission, as shown in figure 1, which depicts the distribution of PCT concentrations among admitted participants. This range of PCT increase confirms the biomarker's known significance in reflecting the bacterial load and systemic inflammatory response associated with sepsis [23]. Importantly, our findings demonstrated that greater PCT levels were substantially linked with increased mortality, particularly in individuals with levels between 6 and 8 ng/mL and above 8 ng/mL. This conclusion is consistent with a growing body of recent literature over the last five years, which has repeatedly shown that increased PCT levels are predictive of poor outcomes in septic patients. For example, multiple studies have found that PCT concentrations more than 6 ng/mL serve as a threshold beyond which the risk of death significantly increases, indicating not only the severity of the infection but also the level of organ failure and the body's immunological dysregulation [24]. Clinical scientists conducted a study in early 2020 that found that patients with PCT levels more than 7 ng/mL had significantly higher 28-day death rates, supporting our discovery of increased fatality at PCT values of 6-8 ng/mL and above [25]. Similar findings were observed in a multicentre cohort analysis, where PCT levels more than 8 ng/mL were substantially predictive of ICU mortality, highlighting the biomarker's potential in risk stratification and early clinical decision making [26]. The pathophysiological reason for this connection is PCT production, which occurs largely by parenchymal cells in response to pro-inflammatory cytokines generated during severe bacterial infections [11]. Elevated PCT levels suggest excessive systemic inflammation and the possibility of progressing to septic shock, both of which increase the risk of death. Aside from the threshold effect, temporal dynamics of PCT, such as consistently high or rising levels throughout hospitalization, have been associated with a worse outcome, stressing the necessity of both initial measurement and serial monitoring [1]. Our findings add to the body of data that individuals with PCT levels of 6-8 ng/mL or above are at high risk and should be monitored closely, treated aggressively, and given cautious organ support. Furthermore, compared to patients with PCT levels in the moderate range of 4-6 ng/mL, those with higher values had more frequent acute organ failure, longer ICU admissions, and a greater requirement for vasopressor medication, indicating more severe sepsis courses, as documented in previous research. While some research shows that PCT cut-offs vary among situations and groups, the convergence of numerous independent studies on the mortality hazards associated with PCT levels more than 6 ng/mL supports the biomarker's therapeutic usefulness [27]. In conclusion, our analysis confirms that most septic patients had moderately elevated PCT levels (4-6 ng/mL) at admission, but considerably higher PCT concentrations, particularly between 6 and 8 ng/mL and beyond, are predictive of poor survival. This pattern represents an established and current awareness that PCT is not just a diagnostic tool, but also a potent predictive biomarker.

This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. Additionally, PCT levels were measured only at admission, and serial measurements were not evaluated to assess dynamic prognostic changes. Future multicenter studies with larger samples and serial PCT monitoring are recommended to validate optimal cutoff values and improve prognostic accuracy in sepsis.

CONCLUSIONS

High PCT levels can predict the outcome of sepsis; PCT levels more than 6 were associated with a high mortality rate in a subset of the Karachi population.

Authors' Contribution

Conceptualization: IAA
Methodology: IAA, FT, TAM
Formal analysis: IAA, FT, NJ, MR, SZA, TAM
Writing and drafting: FA, NJ, MR, SZA, TAM
Review and editing: IAA, FT, TAM, NJ, MR, SZA, FA

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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Seasonal Trends, Clinical Profiles, and Outcomes of Diabetic Ketoacidosis in Children and Adolescents with Type 1 Diabetes

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ABSTRACT

Type 1 diabetes mellitus (T1DM) is the most common endocrine disorder in children, and diabetic ketoacidosis (DKA) remains its most serious acute complication. While seasonal variation in DKA incidence has been reported globally, such data are lacking from Pakistan, where the pattern is unknown. **Objectives:** To describe the seasonal trends, clinical profiles, and outcomes of DKA in children and adolescents. **Methods:** This descriptive, cross-sectional, retrospective study was conducted at the Department of Pediatrics, The Aga Khan University Hospital, Karachi. Data were collected from 1st November 2024 to 1st April 2025. Medical records were reviewed retrospectively from January 2019 to December 2022. Children of both genders aged 1–18 years, diagnosed with DKA either as newly diagnosed or known cases of T1Dm, were included. Demographic data, season at the time of presentation, laboratory parameters, clinical course, outcomes, and complications were recorded. The data were analyzed using R software. **Results:** A total of 78 cases were included, with a mean age of 9.6 ± 4.8 years. The mean hospital stay was 3 days. Most patients presented with severe DKA (55.1%). The highest frequency of cases occurred in winter (38.5%), followed by spring (24.4%), summer (23.1%), and autumn (14.1%). Autumn had the highest proportion of severe DKA (82%). Hyponatremia was the most common laboratory abnormality (47.43%). **Conclusions:** Seasonal variation showed slightly higher occurrence of DKA in winter, with most newly diagnosed children presenting with severe DKA. The majority of children (96.2%) had recovered.

INTRODUCTION

The most common endocrine disease in children is T1DM. T1DM is diagnosed in 65000-78000 children each year on average, and close to 80% of them are initially presented with DKA [1, 2]. DKA is a severe acute complication of relative insulin deficiency and is marked by the typical triad of biochemical variables: hyperglycaemia, ketonaemia and/or ketonuria, and acidaemia. The clinical manifestations are dehydration, tachypnoea, gastrointestinal symptoms, and a low level of consciousness induced by a fluctuating duration of polyuria, polydipsia, and weight loss [3]. Close fluid resuscitation, insulin promptly, electrolyte imbalances restoration, and control of contributory factors are the primary DKA management methods. The causes of the electrolyte disturbances can be attributed to osmotic fluid shifts caused by hyperglycemia [4]. According to the International Diabetes Federation (2019), in Pakistan, the rate of IDDM is 0.5 cases per 100,000 children per year [5]. DKA is on an absolute rise as it has an increasing incidence of diabetes [6]. The change is more of an issue in developing nations, where death as a result of DKA is very high [7]. The frequency of DKA in newly diagnosed diabetes

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and known cases was reported in local studies done in Pakistan to be 6.7% and 2.2%, respectively. DKA is the most prevalent hyperglycaemic crisis in diabetic children aged below 10 years and a significant cause of death [8]. Risk factors associated with DKA are younger age, diagnostic errors, ethnic minority, low BMI, infection, and delayed treatment initiation. While higher parental education and first-degree relatives with diabetes are protective factors [9]. As per the World Bank Climate Change Knowledge Portal, Pakistan lies in a temperate zone, and four seasons are recognized here. 1. Winter from December to February. 2. Spring from March to May. 3. Summer, from June to September, and 4. the Autumn from October till November [10]. Seasonal variation is an environmental factor that can trigger the onset of type 1 diabetes and DKA in genetically predisposed individuals. The data about the seasonal variation of DKA varies across the globe. Literature showed no significant increase in DKA in winters [10] versus the seasonality being a major triggering factor in winter and/or spring [10, 11], summer [12-14], fall [15], fall and winter [16-18]. A single study reported from Pakistan has shown an increased incidence in winter [18].

Hence, we have very limited data regarding seasonal variation in DKAin children. This study will help in identifying regional seasonal variations of DKA in children. It will enable physicians to educate parents of children living with diabetes about the periods when their children are more susceptible. It will also enable us to identify the laboratory abnormalities frequently encountered in DKA and the overall outcomes. The results can be utilised to establish protocols for considering essential testing for DKA in emergency settings in resource-limited hospital settings. This study aimed to assess the seasonal trends, clinical profile, and outcomes of diabetic ketoacidosis in children and adolescents.

METHODS

This retrospective cross-sectional study was conducted at the Department of Paediatrics and Child Health, The Aga Khan University Hospital, Karachi, Pakistan. The study was conducted after ERC approval, from 1st November 2024 to 1st April 2025. A retrospective record review was done for all children and adolescents aged 1-18 who presented with DKA from January 2019 to December 2022. After fulfilling the criteria, 78 children were included in the study. The study was conducted in accordance with the Declaration of Helsinki and GCP principles, with an ERC Full Review exemption obtained from AKUH (Approval ID: 2024-10447-31663); all data were anonymized and securely managed to ensure confidentiality. Written informed consent was taken. Inclusion criteria were children of either gender diagnosed with T1DM (newly diagnosed as well as known cases) with an age group from 1 to 18 years, presenting with DKA, satisfying ISPAD 2024 criteria. Exclusion criteria included children less than 1 year of age, newly diagnosed T1DM without DKA, and children with diabetes other than T1DM. Exemption from the Institutional Ethical Research Committee was acquired as the study involved retrospective review of existing medical records and laboratory data without any direct participant contact or disclosure of identifiable information. Demographics of all children were noted. The data including age, gender, known diabetic/ newly diagnosed, residence, season at the time of diagnosis of DKA, length and type of symptoms before presentation, capillary and serum blood glucose on arrival, venous pH, electrolytes, urine ketones, Bun, creatinine levels, SGPT, PT, INR, GAD-65 antibodies, GCS on arrival, admission disposition, length of stay, complications, indication of bicarbonate administration and outcome were recorded. DKA was defined according to ISPAD 2024 as hyperglycemia (blood glucose >200 mg/dl) with venous pH <7.3 or serum bicarbonate <18 mmol/L and ketonemia (blood ß-hydroxybutyrate≥3 mmol/L) or moderate to large ketonuria (≥2+). Mild DKA was labelled as venous pH <7.3 or serum bicarbonate <18 mmol/L, moderate DKA as venous pH <7.2 or serum bicarbonate <10 mmol/L, and severe DKA as venous pH <7.1 or serum bicarbonate <5 mmol/L. A structured proforma designed after a thorough literature review was filled out from reviewing labs and confidential files, and data was recorded on Google Forms. The statistical analysis was conducted using R Studio (version 4.4.3, R Core Team, 2025). Initially, quantitative variables were summarized using the mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The normality of the distribution of quantitative variables was assessed using the Shapiro-Wilk test. Associations between categorical variables were determined using the Chi-square (χ^2) test or Fisher's exact test. A p-value of ≤ 0.05 was considered statistically significant. The computational workflow relied on specialized R packages, including tidyverse (encompassing dplyr for manipulation and ggplot2 for visualization), lubridate (for efficient handling of date-time objects), summarytools (for descriptive statistics), and gtsummary and gt (for generating high-quality, publication-ready tables). Multivariate logistic regression was applied afterwards.

RESULTS

The mean age was 9.6 ± 4.8 years, with 55.7% female and 43.6% male. The majority of patients (92.3%) belonged to urban areas. In our cohort, 62.8% patients were newly diagnosed (n=49). Among known diabetic patients (n=29), a previous history of DKA was positive in 15 patients, out of which 2 children had a history of DKA twice, one child had DKA 5 times, while 12 children had DKA once before. The

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mean duration of symptoms was 3.5 days. 13 patients presented with one symptom only, while the majority of children (60.2%) presented with classic symptoms of DKA. 11 parents reported weight loss along with these symptoms (14.1%). Preceding symptoms of viral infection, such as fever, cough, and flu, were positive in 33.3% (Table 1).

Table 1: Baseline Characteristics of Our Study Population

Variables	Mean ± SD (95% CI) or n (%)	Missings (n)
Age		
Years	9.59 ± 4.81 (8.51, 10.68)	–
Age Categories		
Child	33 (42.31%)	–
Adolescent	45 (57.69%)	–
Gender		
Male	34 (43.59%)	–
Female	44 (56.41%)	–
Residence		
Rural	6 (7.69%)	–
Urban	72 (92.31%)	–
Type I Diabetes		
Known Case	29 (37.18%)	–
Newly Diagnosed	49 (62.82%)	–
Diagnosis (years) (for Known Cases Only)	4.13 ± 2.94 (3.01, 5.25)	–
Symptom Duration		
Days	7.21 ± 9.76 (5.01, 9.41)	–
Recent Viral Infection		
Yes	26 (33.33%)	–
No	52 (66.67%)	–
Length of Stay		
Days	2.92 ± 1.63 (2.56, 3.29)	–
DKA Severity		
Mild DKA	9 (11.54%)	–
Moderate DKA	26 (33.33%)	–
Severe DKA	43 (55.13%)	–
DKA Resolution Time		
Hours	22.58 ± 15.38 (19.09, 26.08)	1
Admission Disposition		
PICU	32 (41.03%)	–
SCU	34 (43.59%)	–
Ward Bed	12 (15.38%)	–
Outcome		
Left Against Medical Advice	3 (3.85%)	–
Recovered and Discharged	75 (96.15%)	–

During the hospital course, the mean length of stay was 3 days, while the time taken for the resolution of DKA was 22.6 ± 15.4 hours. Most of the patients presented with severe DKA (55.1%), followed by moderate (33.3%) and mild DKA (11.5%), respectively. Findings show moderate and severe DKA were more common among female than male, with no statistical significance. Newly diagnosed cases presented with severe DKA compared to known cases of T1DM. The observed association was found to be statistically significant (Table 2).

Table 2: Severity of Diabetic Ketoacidosis (DKA) Stratified by Gender and Diabetes Type

Variables	Mild DKA	Moderate DKA	Severe DKA	Total
Female	2 (4.5%)	17 (39%)	25 (57%)	44 (56%)
Male	7 (21%)	9 (26%)	18 (53%)	34 (44%)
Total	9 (12%)	26 (33%)	43 (55%)	78 (100%)
Known Case	7 (24%)	13 (45%)	9 (31%)	29 (37%)
Newly Diagnosed	2 (4.1%)	13 (27%)	34 (69%)	49 (63%)
Total	9 (12%)	26 (33%)	43 (55%)	78 (100%)

Fisher's exact test = 3.73, p=0.081. Fisher's exact test = 14.92, p=0.001.

The overall number of cases increased over the years from 2019 to 2022. Cases were reported more in winter (38.5%), followed by nearly equal occurrence in spring and summer (24.4% and 23.1% respectively), and followed by the least in autumn (14.1%) (Figure 1).

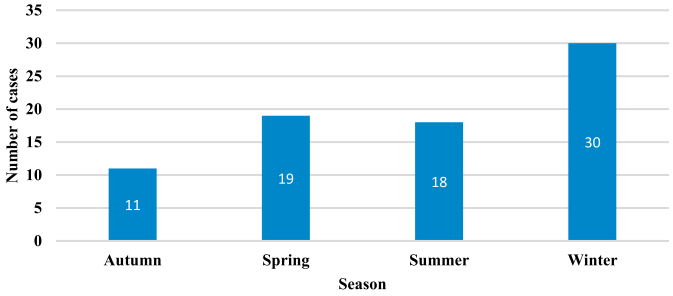

Figure 1: Distribution of DKA Across Seasons

Autumn had the highest proportion of severe DKA (82%), while winter had the highest proportion of mild/moderate cases (57%). Despite these variations, the p-value is 0.2, indicating no statistically significant association between the season and DKA severity (Table 3).

Table 3: Severity of Diabetic Ketoacidosis (DKA) Stratified by Season

Season	Mild/Moderate DKA	Severe DKA	Total
Autumn	2 (18%)	9 (82%)	11 (14%)
Spring	9 (47%)	10 (53%)	19 (24%)
Summer	7 (39%)	11 (61%)	18 (23%)
Winter	17 (57%)	13 (43%)	30 (39%)
Total	35 (45%)	43 (55%)	78 (100%)

Fisher's exact test = 6.44, p=0.20.

Urinary ketone results, as serum ketone testing is not available in our hospital (Table 4).

Table 4: Laboratory Parameters on Arrival of the Study Population

Variables	Mean ± SD (95% CI) or n (%)	Missings (n)
Previous HbA1c (%)	11.46 ± 2.56 (10.42–12.49)	03
Current HbA1c (%)	12.14 ± 2.63 (11.55–12.73)	–

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Capillary Blood Glucose	431.47 ± 103.39 (408.16–454.79)	–
Serum RBS (mg/dl)	480.80 ± 157.09 (438.33–523.27)	23
Venous pH	7.10 ± 0.14 (7.07–7.14)	–
Urinary Ketones 2+	13 (16.67%)	–
Urinary Ketones 3+	14 (17.95%)	–
Urinary Ketones 4+	51 (65.38%)	–
Serum Sodium (mEq/L)	135.29 ± 6.39 (133.85–136.74)	–
Serum Potassium (mEq/L)	4.22 ± 0.85 (4.02–4.41)	–
Serum Bicarbonate (mEq/L)	6.62 ± 3.63 (5.81–7.44)	–
Serum BUN (mg/dl)	13.01 ± 7.49 (11.22–14.81)	9
Serum Creatinine (mg/dl)	0.88 ± 0.44 (0.77–0.98)	9
SGPT (U/L)	20.15 ± 5.98 (18.06–22.23)	44
Prothrombin Time (seconds)	13.93 ± 2.99 (10.79–17.07)	72
CRP (mg/L)	22.62 ± 53.58 (–4.03–49.26)	–
Procalcitonin (ng/ml)	4.63 ± 10.35 (0.04–9.22)	56
Positive Cultures		
Blood CS	4 (5.13%)	–
None	71 (91.03%)	–
Urine CS	3 (3.85%)	–
Organisms in Positive Cultures		
Acinetobacter and Streptococcus Species	1 (1.28%)	–
Bacillus Species	1 (1.28%)	–
Candida Albicans	2 (2.56%)	–
Staph (Not Aureus)	2 (2.56%)	–
GAD-65 Antibodies		
Negative	9 (11.54%)	–
Positive	10 (12.82%)	–
Not checked	59 (75.64%)	–

Values are presented as Mean ± SD (95% Confidence Interval) unless otherwise stated.

In our study, the sodium level on arrival was reported with a mean and S.D. of 135.3 ± 6.4 mEq/L; the commonest electrolyte imbalance was hyponatremia (47.4%), which was severe in 2 children, moderate in 12 children, and mild in 23 children. Potassium level on arrival was 4.2 ± 0.9 mEq/L. Hypokalemia was observed in 14 patients (17.94%), out of which none of the patients had a potassium level <2.5mEq/L. Serum bicarbonate level on arrival was reported low in all patients, consistent with DKA, with a mean and S.D of 6.6 ± 3.6. In the extended clinical profile, SGPT was deranged in one child, who was diagnosed with Acute Viral Hepatitis A. Among septic markers, CRP was done in 18 patients with a mean and S.D of 22.6 ± 53.6, and procalcitonin was sent in 22 patients, with a mean and S.D of 4.6 ± 10.4. Regarding cultures, blood cultures were positive in 4 children (5.1%), urine CS was positive in 3 children (3.8%), while cultures were negative in the majority (91%). Among the positive blood cultures, Bacillus and Staphylococcus, not Aureus, were likely contaminants; all three cultures of urine reported Candida albicans. Serum GAD-65 antibodies were not sent in the majority (75.6%), because this test was introduced late in our centre. This is the single antibody being tested at our centre. After applying logistic regression, the two key factors retained in the Final Multivariable Model were present. Type I Diabetes-Newly Diagnosed (OR=3.14; p=0.041): This is a significant predictor. Being newly diagnosed is associated with 3.14 times the odds of the outcome compared to being a known case. Length of Stay (days) (OR=1.95; p=0.012): This is also a significant predictor. Every one-day increase in the length of stay increases the odds of the outcome by a factor of 1.95 (Table 5).

Table 5: Univariate Logistic Regression and Final Multivariable Model (Backward Elimination)

Predictor	Reference Category	Univariate OR (95% CI)	p-value	Final Model OR (95% CI)
Age	–	0.97 (0.88–1.07)	0.519	–
Age Category: Adolescent	Child	1.04 (0.42–2.58)	0.929	–
Season: Autumn	Summer	2.86 (0.53–22.57)	0.252	–
Season: Spring	Summer	0.71 (0.19–2.61)	0.603	–
Season: Winter	Summer	0.49 (0.14–1.58)	0.236	–
Gender: Female	Male	1.17 (0.47–2.89)	0.733	–
Residence: Urban	Rural	0.22 (0.01–1.48)	0.181	–
Type I Diabetes: Newly Diagnosed	Known Case	5.04 (1.92–14.17)	0.001	3.14 (1.05–9.64)
Diagnosis Years	–	0.83 (0.55–1.12)	0.282	–
Length of Stay (Days)	–	2.38 (1.47–4.28)	0.001	1.95 (1.22–3.50)
Outcome: Recovered and Discharged	Left Against Medical Advice	0.60 (0.03–6.56)	0.685	–
Season: Spring	Summer	0.71 (0.19–2.61)	0.603	–

DISCUSSION

This study presents a detailed overview of the clinical features and biochemical profile of patients with DKA, highlighting the association between seasonal variations and DKA presentation, along with a comprehensive description of laboratory characteristics in the paediatric population. In our study, the mean age of presentation was 9.6 years, with a slightly higher female predominance, aligning with previously published literature [19]. A high proportion of children with DKA had it as their initial presentation (62.8%), with a mean symptom duration of 3.5 days before presentation. This trend, reported globally [20, 21], highlights the challenge of delayed diagnosis, with most seeking care only after significant metabolic decompensation. Most patients were from urban areas (92.3%), reflecting disparities in access to quality healthcare. The highest number of DKA cases occurred in winter (38.5%), consistent with findings from Peshawar, Pakistan [8]. This may relate to the increased incidence of viral infections in colder months that unmask diabetes by contributing to islet autoimmunity and beta-cell destruction [22]. Seasonal variations also influence

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glycemic control, as reported in a Chinese adult study [23], though paediatric data remain limited. In our study, a slightly higher number of DKA cases were observed during the winter season; however, this variation was not found to be statistically significant. Therefore, our findings do not indicate a statistically significant association between seasonality and DKA occurrence. Overall, 60.2% presented with classic symptoms of polyuria, polydipsia, and polyphagia, while a few had only one symptom, highlighting the need for high clinical suspicion. Many had neuroglycopenic symptoms such as altered sensorium, emphasizing timely diagnosis to prevent cerebral edema. About 33.3% had preceding viral symptoms, suggesting mild viral illnesses as common DKA triggers, especially in winter. Although CRP and procalcitonin were elevated in some patients, no growth was reported in 91% of cultures, suggesting systemic inflammation rather than true sepsis. Literature supports that combining procalcitonin and fever can help identify bacterial infection and guide antibiotic use [24]. Biochemical findings matched diagnostic criteria for DKA. Consistent with delayed presentation, severe DKA was most common (55.1%), differing from findings in Peshawar [8]. Electrolyte disturbances were frequent, with hyponatremia in 47.4% and hypokalemia in 17.9%, both linked to osmotic diuresis and insulin therapy. Hypernatremia, though less common (7.7%), was noted and should be considered during fluid replacement to avoid complications. The average hospital stay was 3 days, similar to studies in the US and UK [25, 26], reflecting effective use of standardized ISPAD protocols. Despite being a lower-middle-income country, our outcomes align with those from developed nations, highlighting the success of these management strategies. An upward trend in DKA cases from 2019 to 2022 was observed, possibly reflecting a true rise, better diagnostics, or increased awareness. However, it also raises public health concerns and calls for an investigation into environmental, socioeconomic, and systemic contributors. Potential confounders such as socioeconomic status, comorbidities, and healthcare access were not fully accounted for and may have influenced the observed associations. Larger multicentre studies are needed to confirm our observations and delineate population-specific patterns of seasonal variation and outcomes.

Study limitations include its single-centre design and small data size, restricting its generalizability. The true correlation of seasonal trigger of DKA cannot be accurately determined without larger cohorts. As the study was conducted in a tertiary care hospital, outcomes may differ across other secondary care facilities in Pakistan. Another limitation of our study is missing laboratory data for several variables. Tests like GAD-65 antibodies were not done in 75.6% of patients, while CRP and procalcitonin were available for few, hence, limiting full assessment of laboratory profiles. Larger multicentre studies are needed to confirm our observations and delineate population-specific patterns of seasonal variation and outcomes.

CONCLUSIONS

This study delineates the clinical spectrum and biochemical characteristics of paediatric DKA, showing the predominance of severe presentations and a high proportion of new-onset diabetes at diagnosis. The findings underscore persistent diagnostic delays, reaffirming the need for earlier recognition. Although a seasonal peak in winter was observed, consistent with regional and global trends, it did not reach statistical significance, suggesting multifactorial influences beyond climatic factors. Outcomes achieved through standardized ISPAD-based management highlight the potential for high-quality care even within resource-constrained settings.

Authors' Contribution

Conceptualization: BR
Methodology: BR, BS, HHZ, MA, FM, KNH
Formal analysis: HHZ, SH, MA, FM
Writing and Drafting: BR, KNH
Review and Editing: BR, BS, HHZ, MA, FM, KNH, SH

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 Outcome with Ultrasonic Dissector Versus Electrocautery in Modified Radical Mastectomy

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ABSTRACT

Breast cancer is the most diagnosed cancer globally. Breast-conservative surgeries are done in several ways to treat non-metastatic breast cancer. **Objectives:** To compare the duration of surgery, duration of drains, and incidence of seroma formation between bipolar electrocautery and ultrasonic dissector in patients undergoing modified radical mastectomy (MRM) for breast cancer. **Methods**: This randomized controlled trial was conducted at the Department of Surgery in Bahawal Victoria Hospital, Bahawalpur, from June to December 2024. A total of 138 women aged 35 to 65 years with operable breast cancer planned for MRM were enrolled and randomized into two groups: bipolar electrocautery and ultrasonic dissector. The primary outcome was the incidence of seroma formation, and the secondary outcomes were duration of surgery and drain placement. Data were analyzed using SPSS version 23.0 with an independent sample t-test and chi-square test / Fisher's exact test applied where appropriate. A p-value<0.05 was considered statistically significant. **Results:** Patients had a mean age of 50.5±7.8 years; 52.2% of the patients were obese. Both groups were comparable at baseline. The mean operative time and drain duration were significantly lower in the ultrasonic dissector group (41.5 ± 4.4 min and 4.0 ± 0.8 days) compared to the electrocautery group (52.9 ± 4.2 min and 7.1 ± 1.2 days) (p<0.001). Seroma formation occurred in 10.1% cases and was significantly less frequent in the ultrasonic group (14.3% vs. 85.7%, p=0.009). **Conclusions:** Ultrasonic dissector significantly reduced operative time, drain duration, and seroma formation compared to electrocautery in patients undergoing MRM.

INTRODUCTION

Worldwide, breast cancer is the most prevalent cancer among women [1]. Breast cancer is becoming more common, particularly in developing parts of the world [2]. Halsted radical mastectomy, modified radical mastectomy (MRM), and breast conservative surgery are the three major forms of surgery that are still used to treat non-metastatic breast cancer [3]. One of the key parts of breast cancer surgery is axillary dissection, which can be done in several ways with a scalpel, scissors, electrocautery, or an ultrasonic dissector [4]. Numerous theories have been presented to explain the genesis of seroma development, a frequent consequence that occurs after MRM [5]. Ultimately, the volume of serous discharge predicts the length of hospitalization, postoperative drainage, and medical expenses [6]. Research has indicated that the use of monopolar electrocautery for dissection increases the risk of seroma production because it damages the lymphatics with heat [7]. Nonetheless, it has the benefit of less operating time and intraoperative blood loss [7]. The blades of an ultrasonic dissector vibrate at a frequency of 55,500 Hz. Tissues are sliced and coagulated as a result, and vascular and lymphatic capillaries are then sealed. There is less tissue injury as a result [8]. Though it costs more than monopolar electrocautery. In a study by Deori et al. seventy patients were randomly assigned to one of two groups (group B: electrocautery, group A: MRM using

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ultrasonic dissector). Group A had a shorter operating time (30.86 ± 5.79 vs. 40.63 ± 6.07 minutes), a mean mop count (5.51 ± 1.84) vs. 7.20 ± 1.32), a lower total drain output for the first three days (161.00 ± 40.38 vs. 219.00 ± 60.46 ml), and a shorter drain duration (4.17 ± 0.45 vs. 4.89 ± 0.87 days) than group B [9]. The two groups did not differ statistically. Seventy patients with breast cancer were recruited by Sharma AK et al and divided into two groups of thirty-five each. In MRM, dissection was carried out using either monopolar electrocautery (group B) or an ultrasonic dissector (group A). In group A, the mean length of hospital stays, mean total drain output for the first three days, mean total length of surgery, and mean mop count were 5.00 ± 0.54 days, 161.00 ± 40.38 ml, 77.20 ± 14.79 minutes, and 5.51 ± 1.84 respectively, while in group B, they were 5.83 ± 0.89 days, 219.00 ± 60.46 ml, 90.20 ± 14.47 minutes, and 7.20± 1.32. 8.5% of group B cases had seroma development, compared to none of the group A cases [10]. The findings from local setting will assist the surgeons in choosing the best MRM strategy to reduce the length of time spent in the hospital, the development of seromas, and other morbidities.

While monopolar electrocautery is widely used, it can damage lymphatics and increase seroma risk, whereas ultrasonic dissectors may reduce tissue injury and postoperative morbidity. However, comparative evidence from local settings on surgical outcomes using these two techniques remains limited. The study hypothesized that outcomes would be better for women undergoing modified radical mastectomy using ultrasonic dissector compared to electrocautery. Therefore, this study aims to evaluate and compare the surgical outcomes of axillary dissection in MRM performed with electrocautery versus an ultrasonic dissector to inform optimal surgical practice.

METHODS

This randomized controlled trial (Registry No. NCT07050329) was conducted at the Department of Surgery, Bahawal Victoria Hospital, after approval from the Institutional Ethics Review (ERC: 55/DME/QAMC Bahawalpur) from 4th June 2024 to 3rd December 2024. A total of 138 women, 35-65 years of age, diagnosed with breast cancer and planned to undergo modified radical mastectomy, were consecutively enrolled after written informed consent. Women with breast cancer recurrence, undergone radiotherapy or were planned for immediate reconstruction were excluded from the study. Patients' data on age (in years) was recorded from the interview. Body mass index (BMI) was calculated after measuring patients' height (in meters) and weight (in kilograms) through standard hospital protocol and formula: weight in kg/height in meters squared. BMI ≥30 kg/m2. Patients were randomly assigned to bipolar electrocautery (Monopolar, Electrosurgical pencil, Sabro) and ultrasonic dissector (Harmonic Scalpel Ethicon®) through a lottery method. Allocation concealment was ensured through sequentially numbered, sealed, opaque envelopes prepared by an independent researcher not involved in patient enrollment or data collection. In bipolar electrocautery, the current passes only between the bipolar forceps tips, minimizing lateral thermal spread and reducing the risk of skin flap necrosis or nerve injury. The surgeon grasps the bleeding vessel between the forceps tips, and controlled current is applied to achieve hemostasis. In the ultrasonic harmonic dissector, high-frequency mechanical vibrations (around 55.5 kHz) are used to simultaneously cut and coagulate tissue. The vibrating blade denatures protein within vessel walls, forming a coagulum that seals blood vessels up to 5 mm. These procedures were performed by a single surgery team with ≥5-years of experience in breast-related surgeries as per hospital protocol. Axillary dissection was performed as per the assigned groups. The primary outcome was the incidence of seroma formation, and the secondary outcomes were duration of surgery and drain placement. Surgery duration from skin incision to surgical wound closure was recorded by the in-charge nurse and documented immediately after the procedure. The surgical field was doused with saline postoperatively, and two 18F suction drains were placed, one in the axilla and the other in the skin flaps. Patients were discharged 24-hours postoperatively, all patients with drains in place, when vitally stable, ambulatory with adequate pain control, and after teaching them the drain output measurement technique. Once a weekly follow-up was done for four weeks. The drains were removed during the follow-up period when the patients reported with drainage volume < 30 ml over 24 hours for two successive days. At each visit, seroma formation was clinically assessed by inspection and palpation for localized swelling, fluctuation, or fluid collection at the surgical site, and confirmed on ultrasonography (Toshiba (Japan), Xario 100 / 200) by the presence of an anechoic or hypoechoic fluid collection without internal echoes or septations beneath the wound. Detected seromas were treated by opening stitches and draining fluid till the time the wound became dried then it was closed by delayed primary closure. A minimum sample size of 138 participants was calculated through the WHO sample size calculator, assuming 8.5% seroma formation in the electrocautery group and none in the ultrasonic dissector group at 80% power and 5% significance level [10]. Data were analyzed through SPSS version 23.0. Normality of the numerical data was assessed through the Shapiro-Wilk test. The continuous variables like age, surgery duration, and duration of drain placement are reported as mean and standard deviation, and categorical

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variables like age groups, gender, and seroma formation are reported as frequency and percentages. Duration of surgery (minutes) and drain placement (days) between the groups are compared through an independent sample t-test, and age groups, gender, and seroma formation are compared between the groups using a chi-square test (Fisher's exact test if cell count <5). For all the comparisons, p-value<0.05 was considered significant.

RESULTS

The mean age of the participants was 50.5 ± 7.8 years, 71 (51.4%) were 50-years or below, and 72 (52.2%) were obese. Patients undergoing electrocautery and ultrasonic dissection were comparable in age and obesity (Table 1).

Table 1: Characteristics of Women Undergoing Modified Radical Mastectomy (n=138)

Characteristics	Overall (n=138)	Electrocautery (n=69)	Ultrasonic Dissector (n=69)	p-value*
Age				
Years	50.5 ± 7.8	50.1 ± 7.6	50.9 ± 8.1	0.574
≤50-Years	71 (51.4%)	37 (52.1%)	34 (47.9%)	0.609
>50-Years	67 (48.6%)	32 (47.8%)	35 (52.2%)	
Obesity				
Yes	72 (52.2%)	37 (51.4%)	35 (48.6%)	0.733
No	66 (47.8%)	32 (48.5%)	34 (51.5%)	

*Independent sample t-test for numerical comparison, chi-square test for categorical comparison

The mean duration of surgery was 47.2 ± 7.1 minutes, and drains were placed for an average duration of 5.5 ± 1.8 days. Seroma formation was observed in 14 (10.1%) cases. The mean surgery (41.5 ± 4.4 vs. 52.9 ± 4.2 minutes) and drain duration (4.0 ± 0.8 vs. 7.1 ± 1.2 days) were significantly lower in the ultrasonic dissector group compared to the electrocautery group. Similarly, seroma formation was significantly lower in the ultrasonic dissector group compared to the electrocautery group (14.3% vs. 85.7%, p-value=0.009) (Table 2).

Table 2: Outcomes of Women Undergoing Modified Radical Mastectomy (n=138)

Characteristics	Overall (n=138)	Electrocautery (n=69)	Ultrasonic Dissector (n=69)	p-value*
Surgery Duration (min)	47.2 ± 7.1	52.9 ± 4.2	41.5 ± 4.4	0.001
Drains Duration (days)	5.5 ± 1.8	7.1 ± 1.2	4.0 ± 0.8	<0.001
Seroma Formation				
Yes	14 (10.1%)	12 (85.7%)	2 (14.3%)	0.009
No	124 (89.9%)	57 (46%)	67 (54%)	

*Independent sample t-test for numerical comparison, Fisher's exact test for categorical comparison

After stratification on age and obesity, the mean surgery and drains duration and seroma formation remained significantly lower in the ultrasonic dissector group compared to the electrocautery group (Table 3).

Table 3: Effect of Women's Age and Obesity on Outcomes of Modified Radical Mastectomy (n=138)

Characteristics		Electrocautery (n=69), Mean ± SD, n (%)	Ultrasonic Dissector (n=69), Mean ± SD, n (%)	p-value*
Age				
Surgery Duration (min)	≤50-Years	52.9 ± 4.7	42.0 ± 47	<0.001
	>50-Years	52.6 ± 3.7	41.1 ± 4.0	<0.001
Drain Duration (day)	≤50-Years	7.1 ± 1.1	4.2 ± 0.7	<0.001
	>50-Years	7.0 ± 1.3	3.8 ± 0.7	<0.001
Seroma Formation (yes)	≤50-Years	5 (13.5%)	1 (2.9%)	0.201
	>50-Years	7 (21.9%)	1 (2.9%)	0.023
Obesity				
Surgery Duration (min)	Obese	54.3 ± 4.2	43.3 ± 3.8	<0.001
	Non-obese	51.0 ± 3.6	39.8 ± 4.3	<0.001
Drain Duration (day)	Obese	7.8 ± 0.9	4.5 ± 0.6	<0.001
	Non-obese	6.3 ± 0.8	3.5 ± 0.5	<0.001
Seroma Formation (yes)	Obese	12 (32.4%)	2 (5.7%)	0.006
	Non-obese	–	–	–

*Independent sample t-test for numerical comparison, Fisher's exact test for categorical comparison.

DISCUSSION

In MRM, flap and axillary dissection were traditionally performed with a cold knife. Using a cold knife reduces tissue damage and increases the collagen and tensile strength of the flaps. Bleeding, however, is a significant cold knife complication that hurts the intraoperative surgical field and lengthens the surgical procedure [11]. Decades ago, monopolar electrocautery was developed to treat surgical hemostasis. Although it has significantly decreased operating time and intraoperative hemorrhage, heat dissipation has exacerbated tissue injury in the surrounding area [12]. Research comparing the profile of inflammatory markers found in the drain fluid of MRM patients showed that, in comparison to cold knife and ultrasonic dissector, electrocautery-assisted MRM has the greatest levels of inflammatory mediators [9]. The ultrasonic dissector is based on a new technique that uses vibration instead of heat to coagulate proteins. In our study, the mean surgery time, drain duration, and seroma formation were significantly lower in the ultrasonic dissector group compared to the electrocautery group. In a study by Deori *et al.* the electrocautery group's mean operating time for axillary dissection was substantially longer than that of the ultrasonic dissector group [9]. Earlier investigation by Archana *et al.* also demonstrated this [13]. The benefit of the smokeless field when using an ultrasonic dissector helps to explain this. Seroma formation after MRM has been attributed to a variety of reasons [14]. The dissection technique is one of the many elements that have been extensively researched. In the current study, the ultrasonic dissector group's daily axillary drain output was substantially lower than that of the electrocautery group.

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This was consistent with earlier research [13, 15]. The harmonic-scalpel group experienced a significantly shorter operative time (mean 111 vs. 169.5 minutes, p<0.0001), a significantly lower incidence of seroma formation, less intraoperative blood loss, and a shorter hospital stay in a prospective study of 40 women undergoing MRM. These results closely match ours, confirming that ultrasonic dissection speeds up surgery and lowers the likelihood of seroma [16]. In a 60-patient randomized prospective study, the ultrasonic-shears group removed the drain earlier than the electrocautery group and experienced significantly fewer postoperative sequelae, such as seroma, wound infection, and flap necrosis. The efficacy advantage we reported is supported by reduced seroma and early drain removal, even if the difference in operative time and drain output was not statistically significant [17]. Seroma rates were much lower in the harmonic scalpel group (7.8% vs. 26.6%, p=0.005), with fewer hematomas, marginal necrosis, lymphedema, and wound infections, according to another cohort of 56 MRM patients. Operative time was comparable, but drainage duration and associated morbidity were obviously decreased, which is consistent with our findings of fewer seroma formations and quicker drain removal [18]. When compared to electrocautery, the use of harmonic scalpels during axillary node dissection in 98 patients with breast cancer resulted in a considerably shorter operating time, less blood loss, and an earlier drain removal. Reduced drainage discharge and quicker drain removal imply lower postoperative seroma risk, which is entirely consistent with our MRM-specific findings, even though seroma formation per se was not the main endpoint [19]. It has been hypothesized that electrocautery results in thrombosis of subdermal veins and inadequate closure of lymphatic vessels, which increases fluid coming out in the drain. However, because it causes less tissue damage, the ultrasonic dissector has a better sealing effect on lymphatic capillaries and also causes less immunological reaction, which lowers the drain output [20]. The study's design and patient randomization were among its strong points. Strong causal inference between the surgical technique and postoperative outcomes was made possible by the randomized controlled trial (RCT) design, which also reduced bias. One skilled surgical team carried out all of the procedures, guaranteeing uniformity in operating technique and lowering inter-operator variability. Additionally, baseline characteristics were similar across groups.

There were certain limitations of this study. For instance, the study did not evaluate long-term complications like lymphedema, recurrence, or delayed wound healing; instead, it presented early postoperative outcomes. Because research was only done at one institution, there is little chance that the findings will apply to other contexts, especially ones with different surgical specialties or patient demographics. Multi-center trials with bigger, more varied populations should be carried out in the future to confirm results in various clinical settings. Long-term follow-up studies are required to assess cancer recurrence, lymphedema, and wound healing.

CONCLUSIONS

Ultrasonic dissector significantly outperformed bipolar electrocautery in reducing operative time, drain duration, and seroma formation in patients undergoing MRM. It presents a more effective and clinically advantageous tool for optimizing surgical outcomes in breast cancer management.

Authors' Contribution

Conceptualization: MN
Methodology: MN, TI, SR, GD
Formal analysis: SR
Writing and drafting: MN
Review and editing: MN, TI, SR, GD

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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Clinical Practice of Treating Benzodiazepine Poisoning with Kahwa (Black Tea) in Acute Cases of Overdose

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ABSTRACT

Recently, an increasing trend of using black tea (Kahwa) in many diseases has been noticed due to its numerous health benefits with less to no side effects and easy availability. **Objectives:** To describe the clinical characteristics, management practices, and short-term outcomes of patients with acute benzodiazepine overdose who received Kahwa as part of supportive care. **Methods:** This retrospective descriptive study was conducted at the National Poison Control Center, Jinnah Postgraduate Medical Center, Karachi. Patients aged 13–70 years with confirmed acute benzodiazepine overdose were included using a non-probability consecutive sampling technique. All patients received standard supportive care plus enteral feeding of Kahwa via nasogastric tube (NG). Data were analyzed using IBM-SPSS version 26.0, and significance was set at $p<0.05$. **Results:** A total of 200 patients with acute benzodiazepine overdose were analyzed. There were 50.5% patients who were male, with an overall median age of 24 years (IQR: 20–38). In most cases, 75.5% presented within two hours of ingestion, and 81.5% had taken ten or fewer tablets. Hypertension and diabetes were present in 4.5% and 4.0% of patients, respectively. The most common presenting features were altered consciousness (25.0%) and non-reactive pupils (27.5%). Intubation was required in 2 patients (1.0%), and flumazenil was given to 3 (1.5%). **Conclusions:** This study documents current clinical practice in managing benzodiazepine overdose, including adjunctive Kahwa administration. The results are descriptive and do not indicate the therapeutic effect of Kahwa specifically, as no causal interpretation is possible.

INTRODUCTION

Data from the developed world have highlighted an increased ratio of deaths in the last two decades due to benzodiazepine (BZD) overdose [1, 2]. A study involving 38 states of the US documented a drastic increase of over 500% in mortality secondary to BZD overdose, in just a duration of one year (2019 to 2020) [1]. Benzodiazepine overdose, most commonly involving agents such as diazepam, lorazepam, clonazepam, or alprazolam, typically causes central nervous system depression manifesting as drowsiness, ataxia, confusion, and, in severe cases, respiratory depression or coma [1, 2]. To date, flumazenil has been the mainstay antidote of BZD overdose as it antagonizes BZD activity by binding competitively to the extracellular surface of GABAA receptors [3]. However, Flumazenil should not be used regularly in cases of mixed overdose, prolonged QRS interval, epilepsy, and BZD tolerance, which warrant the trials of better and safer alternatives. Recently, an increasing trend of using black tea (also known as Kahwa) in many diseases has been noticed due to its numerous health benefits with less to no side effects and easy availability [4-6]. According to a recent report, 75-78% of the total worldwide tea

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production and consumption is of black tea [7, 8]. It is predominantly consumed in Western and Asian countries while various constituents such as flavonoids (catechins, TFs and TRs), methylxanthines (caffeine), phenolic acids (CGA, CA, GA and cauramic acid), lipids, proteins, β-carotene, amino acids (theanine), carbohydrates, volatile compounds-fluoride, folate and traces of vitamins C, K, A are available [8-10]. There have been a few reports highlighting the cytoprotective and anti-apoptotic effects of polyphenols, which are found in black tea [11, 12]. It is also known to have been beneficial in the prevention and treatment of hypercholesterolemia and heart disease [10]. Taking all these mechanisms of action and benefits into account, black tea usage in cases of acute BZD overdose is in trial phases. There are no side effects of using Kahwa.

While black tea (Kahwa) has demonstrated cytoprotective and anti-apoptotic effects in preliminary studies, its potential role in the supportive management of acute BZD overdose remains largely unexplored. Limited evidence exists on its safety, efficacy, and impact on short-term clinical outcomes in this context. Therefore, this study aims to describe the clinical characteristics, management practices, and short-term outcomes of patients with acute benzodiazepine overdose who received Kahwa as part of supportive care.

METHODS

This retrospective descriptive study was based on a review of patient medical records, Emergency Department case files, and hospital admission registers maintained at the National Poison Control Center, Jinnah Postgraduate Medical Center (JPMC) Karachi, Pakistan. The study analyzed data collected between August 2023 to April 2024. Approval was obtained from the Institutional Review Board of Jinnah Postgraduate Medical Center (JPMC) (letter no. F.2-81/2023-GENL/98/JPMC). All data were obtained exclusively from existing hospital documentation, including Emergency Department triage sheets, physician admission notes, nursing charts, toxicology assessment forms, medication administration records, and laboratory reports maintained in the medical files of each patient at the National Poison Control Center, JPMC. No new data were collected directly from patients or attendants, consistent with the retrospective nature of the study. The Poison Control Center is a tertiary care facility specializing in the management of acute toxicological emergencies, serving a diverse population from urban and semi-urban areas of Karachi and neighbouring districts. As this was a retrospective review of existing clinical records with no direct patient interaction, the requirement for informed consent was waived by the IRB, in accordance with institutional policy and relevant national ethical guidelines. The sample size of 200 patients represented all eligible cases of acute benzodiazepine overdose admitted during the study period. As this was a retrospective descriptive study, no prospective sample size calculation was performed. However, this sample provided sufficient precision to describe key clinical patterns and allowed post-hoc verification showing >80% statistical power for detecting medium effect sizes (Cohen's $d \approx 0.4$) at $\alpha = 0.05$, using G*Power sample size calculator. Inclusion criteria were patients of either gender, aged 13 to 70 years, and a clinical history consistent with acute benzodiazepine ingestion, confirmed either by self-report, reliable informant history, or supporting laboratory findings where available. Patients were excluded if they had a pre-existing diagnosis of neurodegenerative or age-related brain diseases (such as Alzheimer's or Parkinson's disease), known malignancies, chronic systemic illnesses (such as chronic liver, kidney, or heart disease), genetically determined disorders, or any documented familial diseases that could confound neurological assessment or recovery patterns. Cases involving polypharmacy overdose where other central nervous system depressants or stimulants were involved were also excluded to ensure study homogeneity. A non-probability consecutive sampling technique was employed. All eligible patient records meeting the predefined criteria within the study window were included. Clinical details at presentation were recorded, including the duration since time of overdose (in hours), quantity of pills ingested, and presenting complaints (such as altered consciousness, respiratory depression, or seizures). The presence of any positive danger signs, such as unresponsiveness, respiratory failure, or shock, was specifically noted. The Glasgow Coma Scale (GCS) score at admission was documented, along with an assessment of vital stability upon arrival (including blood pressure, heart rate, and respiratory rate)[13]. As per the clinical protocols at the Poison Control Center, patients diagnosed with acute benzodiazepine overdose received standard supportive care, which included airway protection, monitoring of vital signs, intravenous fluids as necessary, and the administration of activated charcoal where indicated. The diagnosis of acute benzodiazepine overdose was established based on a combination of clinical history, presentation, and, where available, toxicological confirmation. In most cases, ingestion was confirmed through patient self-report or reliable informant history, supported by circumstantial evidence such as empty medication strips or prescription records. Laboratory confirmation of benzodiazepine ingestion was available for 62 (31.0%) patients, performed using urine immunoassay screening at the JPMC toxicology laboratory. The remaining cases were classified as clinically consistent with benzodiazepine overdose based

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on characteristic symptoms (e.g., CNS depression, hyporeflexia, slurred speech) and exclusion of other toxicological causes. In addition to standard management, patients received Kahwa administered enterally via nasogastric tube (NG) as part of the supportive treatment regimen. Kahwa was prepared according to a standardized in-hospital recipe traditionally used at the center as a stimulant beverage. The preparation consisted of green tea leaves (Camellia sinensis, approximately 2–3 g per 150 mL serving) brewed in hot water (90–95 °C) for 5–7 minutes, with optional additions of cardamom pods (1–2) and cinnamon (a small stick) for flavor. No sugar or milk was added. Each serving contained an estimated caffeine content of 25–35 mg per cup, comparable to mild green tea [14]. Patients were given Kahwa orally once they were clinically stable and able to swallow safely, typically one to two cups within the first 6 hours of admission. All patients received standard supportive management according to institutional protocols. Airway protection and gastric decontamination were prioritized upon arrival. Activated charcoal (50 g single dose) was administered via nasogastric (NG) tube in patients presenting within two hours of ingestion, provided they had an intact or protected airway and no contraindications such as altered mental status without intubation [15]. Patients who were fully conscious and able to swallow safely received charcoal orally (PO) instead. The timing and route of administration were documented in clinical charts. Activated charcoal was not given beyond two hours post-ingestion. Supportive care also included intravenous fluids, monitoring of vital signs, and oxygen supplementation when indicated. No gastric lavage or additional pharmacologic interventions were routinely performed other than flumazenil in selected cases. Flumazenil was administered only in selected cases presenting with marked central nervous system depression (GCS ≤ 8) or respiratory compromise, in accordance with institutional toxicology protocols. It was avoided in patients with a history of chronic benzodiazepine use, seizure disorder, or suspected mixed-drug ingestion. Administration was carried out before any adjunctive therapy, including Kahwa, to ensure standard care was not delayed. In all cases, Kahwa was administered only after airway stabilization and completion of essential interventions, including gastric decontamination and, where indicated, flumazenil administration. The total duration of hospital stay (in days) and the final clinical outcome were recorded. The study did not assess the safety or efficacy of Kahwa as a pharmacological intervention. All patients received standard supportive care, and Kahwa was administered as a traditional institutional adjunct. No causal inference or pharmacodynamic interaction analysis was undertaken due to the retrospective, descriptive design. A special proforma was designed to record all relevant study data. Data analysis was performed using IBM-SPSS Statistics, version 26.0. Normality of quantitative variables was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated using Levene's test. For normally distributed variables with equal variances, the independent t-test or one-way ANOVA was applied as appropriate. When assumptions were not met, the Mann–Whitney U or Kruskal–Wallis tests were used. Effect sizes (Cohen's d for t-tests and η^2 for ANOVA) were calculated and interpreted qualitatively as small (<0.2), medium (0.2–0.5), or large (>0.5). A Bonferroni correction was used to adjust for multiple comparisons due to its conservative control of type-I error for small subgroup analyses. P-value<0.05 was taken as significant.

RESULTS

Out of these, 101 (50.5%) were male, and 99 (49.5%) were female, indicating a nearly equal gender distribution. The median age of the study population was 24.0 years ([IQR: 20.0–38.0 years), with the youngest patient aged 13 and the oldest 70 years. About comorbidities, hypertension was present in 9 (4.5%) and diabetes mellitus in 8 (4.0%) patients. There were 151 (75.5%) presented within two hours of benzodiazepine ingestion. The median duration since overdose was 2.0 hours (IQR: 2.0–2.0), ranging from 1 to 72 hours. There were 163 (81.5%) patients who reported ingestion of ten or fewer tablets, with a median pill quantity of 10 (IQR: 10–10), while 37 (18.5%) had consumed more than ten tablets. The number of pills ingested ranged from 3 to 50. The Glasgow Coma Scale (GCS) at presentation was less than 12 in 34 (17.0%) patients (Table 1).

Table 1: Demographic and Clinical Characteristics of Patients (n=200)

Characteristics		Frequency (%)
Gender	Male	101 (50.5%)
	Female	99 (49.5%)
Age Groups (Years)	13-20	58 (29.0%)
	21-30	71 (35.5%)
	31-40	34 (17.0%)
	41-50	12 (6.0%)
	51-60	15 (7.5%)
	61-70	10 (5.0%)
Comorbidities	Hypertension	9 (4.5%)
	Diabetes Mellitus	8 (4.0%)
Drug Addict	–	8 (4.0%)
Duration Since Time of Overdose (Hours)	≤2	151 (75.5%)
	>2	49 (24.5%)
Quantity of Benzodiazepine Pills	≤10	163 (81.5%)
	>10	37 (18.5%)

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Glasgow Coma Scale	<12	34 (17.0%)
	≥12	166 (83.0%)
Vitally Stable at the Time of Reception	Yes	147 (73.5%)
	No	53 (26.5%)

Among danger signs, the most common finding was the presence of mid-dilated, non-reactive pupils, observed in 55 (27.5%) cases. Regarding presenting complaints, altered level of consciousness was the most frequent, reported in 50 (25.0%) patients, followed by disorientation or confusion in 36 (18.0%), vomiting in 34 (17.0%), and stupor in another 34 (17.0%). A detailed breakdown of danger signs and clinical presentations is depicted (Figure 1).

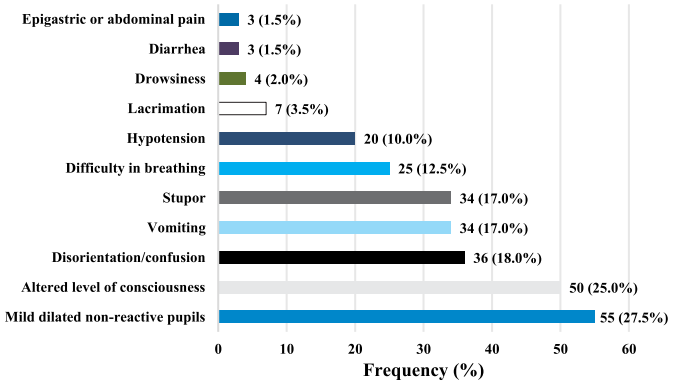

Figure 1: Frequency of Danger Signs and Presenting Complaints/Features (n=200)

Intubation was required in only 2 (1.0%) patients due to respiratory compromise. Flumazenil administration was required in 3 (1.5%) patients. Serial GCS monitoring and precise time-to-awakening data were not routinely documented in patient charts. However, the majority of patients demonstrated rapid clinical improvement, as reflected by a short mean hospital stay (1.36 ± 0.68 days), ranging 1-4 days, and the absence of mortality or severe neurological sequelae (any persistent neurological impairment observed during hospitalization or at discharge, including prolonged unresponsiveness, post-hypoxic encephalopathy, cognitive dysfunction, or new-onset seizures). Most regained full consciousness within 24 hours of admission based on clinical progress notes. There were no deaths reported among the studied subjects. The mean duration of hospital stay was significantly longer in males compared to females (1.5 ± 0.8 vs. 1.2 ± 0.5 days, p=0.001). Increasing age was associated with a progressive rise in hospital stay, with those aged 51–60 years experiencing the longest admissions (2.0 ± 0.8 days, p<0.001). Patients with diabetes mellitus had a significantly longer mean hospital stay than those without diabetes (1.9 ± 0.8 vs. 1.3 ± 0.7 days, p=0.027). A lower GCS score (<12) at presentation was associated with prolonged hospitalization (1.9 ± 0.9 vs. 1.2 ± 0.5 days, p<0.001). Patients who were vitally unstable at presentation had significantly longer duration of hospitalization compared to those who were vitally stable (1.6 ± 0.8 vs. 1.3 ± 0.6 days, p=0.004) (Table 2).

Table 2: Association of Demographic and Clinical Characteristics with Duration of Hospitalization (n=200)

Characteristics		Duration of Hospital Stay (Days)	Effect Size	p-value
Gender	Male	1.5 ± 0.8	d=0.42	0.001
	Female	1.2 ± 0.5		
Age Groups (Years)	13-20	1.2 ± 0.5	n^2=0.14	<0.001
	21-30	1.2 ± 0.4		
	31-40	1.5 ± 0.8		
	41-50	1.8 ± 0.9		
	51-60	2.0 ± 0.8		
	61-70	1.9 ± 0.9		
Hypertension	Yes	1.8 ± 0.9	d=0.61	0.056
	No	1.3 ± 0.5		
Diabetes Mellitus	Yes	1.9 ± 0.8	d=0.75	0.027
	No	1.3 ± 0.7		
Drug Addict	Yes	1.5 ± 0.8	d=0.14	0.539
	No	1.4 ± 0.7		
Duration Since Time of Overdose (Hours)	≤2	1.4 ± 0.7	d=0.14	0.413
	>2	1.3 ± 0.7		
Quantity of Pills	≤10	1.4 ± 0.7	d=0.32	0.196
	>10	1.2 ± 0.5		
Glasgow Coma Scale	<12	1.9 ± 0.9	d=0.97	<0.001
	≥12	1.2 ± 0.5		
Vitally Stable at the Time of Reception	Yes	1.3 ± 0.6	d=0.41	0.004
	No	1.6 ± 0.8		

d = Cohen's d; n^2=Eta-squared

All patients received supportive therapy as the mainstay of management, consistent with standard practice in toxin ingestions. Only 3 patients (1.5%) in this series were administered flumazenil, the benzodiazepine receptor antagonist, and notably, this was done after an initial trial of Kahwa. While most patients recovered with supportive management and adjunctive Kahwa, the retrospective nature of this study precludes any inference of causality between Kahwa use and clinical improvement. No caffeine-related adverse effects were documented among the studied patients. There were no reports of tachycardia, arrhythmia, new-onset seizures, or agitation temporally associated with Kahwa administration.

DISCUSSION

All the patients involved in this research received enteral Kahwa dose via NG as mentioned, along with the rest of the supportive treatment. The sparing use of flumazenil reflects its well-known controversial role in overdose, and hence, with the mentioned approach of including Kahwa in initial supportive therapy, we were able to limit the need for flumazenil [16, 17]. A prior Pakistani study reported zero flumazenil use in 281 benzodiazepine poisoning cases,

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likely for these reasons [18]. Patient outcomes in this study were overwhelmingly positive, as no deaths occurred. This is congruent with the known benign course of isolated benzodiazepine overdose, as fatalities are rare when benzodiazepines are the only substance involved [19]. Benzodiazepine-induced respiratory depression is usually not life-threatening unless compounded by other CNS depressants or underlying pulmonary compromise [20]. Even massive ingestions of benzodiazepines alone are often survived with supportive care, as documented in case series where patients remained sedated but ultimately recovered fully within 24–36 hours. A study in Faisalabad, Pakistan, recorded a 1.4% mortality rate (4 of 281 cases, all male) [18]. Those fatalities may have involved extremely high doses or co-ingestants (the report lacked details on the cause of death), highlighting that outcomes can vary. In this study, the absence of any deaths likely reflects the combination of timely medical intervention, the relative safety margin of benzodiazepines, and possibly the adjunctive use of Kahwa contributing to vigilance. Hospitalization stays were short, as the mean length of stay was only 1.36 ± 0.68 days (range 1–4 days), indicating that most patients required just overnight observation. The most novel aspect of this study is the deliberate use of Kahwa as part of the supportive treatment for benzodiazepine overdose. This is the first clinical study to document caffeinated beverages in managing acute sedative overdose. Kahwa is a traditional preparation in South Asia, typically consisting of green tea leaves brewed with spices like saffron, cardamom, and cinnamon [21]. Administering a caffeine-containing beverage in an overdose setting is a logical, albeit unconventional, attempt to hasten arousal [22]. The proposed mechanism by which Kahwa exerts its effect lies in its caffeine content. Caffeine acts as a central nervous system stimulant by antagonizing adenosine receptors in the brain, counteracting the sedative effects of benzodiazepines, and promoting wakefulness [23]. Unlike flumazenil, which directly displaces benzodiazepines from their receptors, caffeine provides a functional antagonism, improving consciousness while the drug remains in the system [24-26]. Since caffeine's effect is transient, repeated administration may be needed during observation. Kahwa's other components, such as green tea's theophylline and various spices, may also contribute by stimulating respiration, promoting gastric motility, and reducing nausea, thereby supporting overall recovery [27]. The combined effects may help explain the low rate of serious complications, including aspiration, observed in this study. Clinically, using Kahwa is attractive due to its simplicity and low cost, and it should be considered only in patients who can safely swallow or have a nasogastric tube in place, limiting its use to mild or moderate overdose cases [25].

While supportive care remains the standard for benzodiazepine overdose, benign adjuncts like Kahwa may be considered, especially in resource-limited settings, pending further evidence from controlled studies.

The study's retrospective design inherently carries risks of bias. This is a single-center study from a specialized poison control hospital. The patient population and management protocols may differ from other hospitals or regions. Karachi's poison center likely has experienced staff and established protocols (including the unique Kahwa intervention) that are not universally practiced. There was no control or comparison group, which limits the ability to establish causal relationships or directly attribute outcomes to the use of Kahwa. Prospective controlled studies should be conducted to evaluate the efficacy and safety of Kahwa as an adjunct in managing benzodiazepine overdose.

CONCLUSIONS

This study documents current clinical practice in managing benzodiazepine overdose, including adjunctive Kahwa administration. The results are descriptive and do not indicate the therapeutic effect of Kahwa specifically, as no causal interpretation is possible. These findings warrant further prospective studies to explore the potential supportive role of Kahwa in benzodiazepine overdose recovery.

Authors' Contribution

Conceptualization: OS
Methodology: JK, IK, MAK[1], OS, AK[2], DZ
Formal analysis: IK
Writing and drafting: JK, IK, MAK[1], DZ
Review and editing: OS, JK, IK, MAK[1], AK[2], DZ

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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Exploring Cochlear and Vestibular Abnormalities in Children with Hearing Impairment; a Tertiary Care Experience

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ABSTRACT

Inner ear malformations have a great impact on hearing. Diagnosing them accurately through advanced imaging modalities can help plan management strategies. **Objectives:** To determine anatomical defects of inner ear malformations in children requiring hearing aids and cochlear implants coming to the tertiary care hospital. **Methods:** A cross-sectional research design was used with a sample of 104 hearing-impaired children, aged 1 to 14 years, who had moderate to profound hearing loss, collected through a purposive sampling technique. Demographic information was collected through a specially designed questionnaire, which included age, gender, developmental delay, etc. were also assessed. **Results:** 7 (6.7%; 95% CI (0.019, 0.115)) cases had anatomical defects of the inner ear, including the temporal bone. Among 7 cases, all had bilateral cochlear hypoplasia CH-III, semicircular canal malformations, 3 (42.9%) bilateral hypoplasia, 3 (42.9%) bilateral dysplasia, 1 (14.4%) had bilateral aplasia of anterior and lateral semicircular canals, 3 (42.9%) bilateral dilated vestibule, and 1 (14.3%) narrowing of the internal auditory canal left side. In these 7 cases, 5 (71.4%) with profound degree hearing loss were candidates for cochlear implant and 2 (28.6%) with severe degree hearing loss were using hearing aids. Results of chi-square showed that age at the time of diagnosis ($p<0.05$), family history of hearing impairment ($p<0.001$), and severity of hearing loss ($p<0.001$) had a significant association with the type of hearing impairment. **Conclusions:** The frequency of inner ear malformations in hearing-impaired children using hearing aids or candidates for cochlear implant was 6.7%. The most common malformations were CH-III and semicircular canal malformations.

INTRODUCTION

Hearing impairment is the fourth major cause of disability occurring globally [1]. More than 34 million children are suffering from deafness or hearing loss worldwide. Developing and underprivileged countries harbor a great proportion of children affected by hearing loss [2]. In Pakistan, one study reported 1.97% prevalence of hearing impairment in school-going children [3]. The most common type of permanent hearing loss is sensorineural hearing loss. It happens after damage to the inner ear, vestibulocochlear nerve, or brain. It is estimated that every 1 in 1,000 children is born with either severe or profound deafness, and congenital sensorineural hearing loss is present in 90 percent of cases [4]. Half of the cases of congenital sensorineural hearing loss are related to a genetic cause [5]. Syndromic cases are approximated to 30%, and the remaining 70% attributed to non-syndromic cases, often presenting with inner ear malformations [6]. Acquired causes of sensorineural hearing loss include birth asphyxia, teratogens, inner ear infections, autoimmune disorders, trauma, or posterior fossa tumors, which usually

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present later in childhood. Hearing-impaired children with inner ear malformations (IEMs) have a high prevalence of 20% worldwide [7, 8]. In Pakistan, overall congenital malformations were reported to be 7%. Ear, eye, face, neck malformation constitutes (20%) [9, 10]. Inner ear malformations constitute a major contributor to sensorineural hearing loss. Inner ear malformations can be classified into eight categories as proposed by Sennaroglu [8, 11]. In these anomalies, 80% are membranous malformations causing pathology of inner ear hair cells. The other 20% include various bony labyrinth malformations diagnosed on imaging studies. In a study conducted internationally,13% of children had inner ear malformation among cochlear implant candidates [12]. Early diagnosis plays a key role in the rehabilitation of hearing-impaired children with sensorineural hearing loss. Audiological investigation, along with imaging techniques such as High-resolution computed tomography (CT) scan and Magnetic resonance imaging (MRI) studies provide valuable details regarding the temporal bone and membranous structures like 8th cranial nerve (CN), inner ear (IE) structures, middle ear (ME), and outer ear (OE). The findings of these studies will help otologists to plan surgery, guide regarding prognosis, and assess the risk of complications. Although most cases may be managed by hearing aids, cochlear implantation and auditory brainstem implantation (ABI) are also options, depending on the degree of hearing loss. Mild to moderate degree hearing loss can be managed by hearing aids, while for children with severe to profound degree hearing loss, a cochlear implant is the best option. Surgical risks and benefits must be weighed before considering this choice. Parents and families should be counselled, and their preferences will guide the best course regarding rehabilitative services.

Despite the global burden of hearing impairment and the significant role of inner ear malformations in sensorineural hearing loss, there is a paucity of local data in Pakistan regarding their prevalence and impact. This study is of immense importance as studies lack local data, which can guide us in planning rehabilitative strategy for such children for better outcomes. Statistical data will help in future research. This study aims to find relation of inner ear malformations and the degree of hearing loss in children rehabilitated by hearing aids or cochlear implants.

METHODS

This cross-sectional study was conducted at the Department of Developmental and Behavioral Pediatrics, The Children's Hospital, and the University of Child Health Sciences, from April 2025 to June 2025. A sample of 104 hearing-impaired children was recruited through convenience sampling. Sample size was collected through G power analysis using a medium effect size and alpha 0.05. After taking approval from the Institutional Review Board (reference no. 1089/CH-UCHS), data were collected. Both unilateral and bilateral cases of hearing impairment were initially screened. Hearing impairment was defined as hearing loss greater than 25 dB in either ear. Severity of hearing loss was categorized as moderate (56–70 dB), severe (71–90 dB), and profound (>90 dB) [2]. The degree of hearing loss was assessed using the most recent audiological assessment conducted in the Department OF Audiology, where diagnostic procedures such as Otoacoustic Emissions (OAE), Auditory Brainstem Response (ABR), or pure tone audiometry had already been performed. Audiological findings were interpreted by 2 audiologists before confirmation by the consultant audiologist. Only non-syndromic cases of congenital sensorineural hearing loss were included in the study, while children with syndromic features were excluded. Hearing-impaired children who had any history of otitis media, ototoxic drug exposure, or neonatal jaundice were excluded. Afterwards, those participants who were enrolled in the study were sent to the Department of Radiology, where High-resolution computed tomography (HRCT) of the temporal bone and magnetic resonance imaging (MRI) of the inner ear were performed for every participant. Imaging findings were interpreted by 2 radiologists and finalized by a consultant radiologist to ensure consistency. Written informed consent was obtained from parents or guardians, and confidentiality was ensured. Demographic data, including age, gender, urban/rural residence, and gestational age, were recorded. Other clinical factors such as history of ear discharge, birth asphyxia, family history of using hearing aids or cochlear implant and developmental delay were assessed. The ShaMaq developmental screening tool (SDST) was used as a tool for screening the development of a child. It screens children aged 6 months to 5.5 years. Each group has four domains: Gross motor and locomotion, vision and manipulation, hearing and speech, and socialization. Any child having a total of four unsatisfactory scores in all domains or one in each domain was considered as having developmental delay [13]. Children were assessed by a clinical psychologist for developmental delay through SDST or informal IQ testing. Data were analyzed using statistical package for the Social Sciences software (SPSS 25), where demographics were analyzed using frequency and percentages. A chi-square test of independence was performed to examine the association between the type of hearing impairment (hearing aid vs cochlear implant) and sociodemographic characteristics. The p-value<0.05 was considered statistically significant.

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RESULTS

Out of 104 hearing-impaired children with bilateral sensorineural hearing loss, 55 (52.9%) were male, and 49 (47.1%) were female. The mean age of the participants was 68.84 ± 45.39 months. Most of the cases (69.2%) belonged to an urban area. The majority of cases (55.8%) had their audiological testing done between age 1 and 3 years, and predominantly (59.6%), Auditory Brainstem Response was done. The majority of participants (62.5%) had profound degree hearing loss (Table 1).

Table 1: Demographic and Clinical Characteristics of Participants (n=104)

Medical Factors	n (%)
Gender	
Male	55 (52.9%)
Female	49 (47.1%)
Place of Residence	
Urban	72 (69.2%)
Rural	32 (30.8%)
Natal or Post-Natal Complication	
Yes	3 (2.9%)
No	101 (97.1%)
History of Ear Discharge	
Yes	10
No	94
Age of Audiological Testing	
<1 Year	1 (14.3%)
1 to 4 Years	6 (86.7%)
Specific Audiological Test	
Oto Acoustic Emission Test	1 (14.3%)
Auditory Brain Stem Response	6 (85.7%)
Severity of Hearing Loss	
Severe	2 (28.6%)
Profound	5 (71.4%)

Out of the total 104 participants, 7 (6.7%; 95% CI (0.019, 0.115)) cases had structural abnormalities of the inner ear, including the temporal bone. In these 7 cases, 5 (71.4%) participants with profound degree hearing loss were candidates for cochlear implant and 2 (28.6%) participants with severe degree hearing loss were using hearing aids. Among the 7 cases, all had bilateral cochlear hypoplasia with less than 2 turns (CH-III). Semicircular canal malformations were reported in all 7 cases (3 (42.9%) participants had bilateral hypoplasia, 3 (42.9%) had bilateral dysplasia, and 1 (14.4%) had bilateral aplasia of anterior and lateral semicircular canals). Among associated structural defects, 3 (42.9%) participants had bilateral dilated vestibule,1 (14.3%) had bilateral non-visualization of vestibulocochlear complex, and 1 (14.3%) had narrowing of internal auditory canal on the left side. All of the 7 cases had no history of prenatal, natal, or postnatal complications. Among the 7 cases, none of the participants had the newborn audiological screening. 6 (85.7%) cases were diagnosed at an age between 1 and 4 years after audiological testing. Only 1 (14.3%) participant had a developmental delay, and none had a family history of hearing impairment (Table 2).

Table 2: Inner Ear Anomalies (n=7)

Medical Factors	n (%)
Gender	
Male	2 (28.6%)
Female	5 (71.4%)
Age of Audiological Testing	
<1 Year	1 (14.3%)
1 to 4 Years	6 (86.7%)
Specific Audiological Test	
Otoacoustic Emission Test	1 (14.3%)
Auditory Brain Stem Response	6 (85.7%)
Severity of Hearing Loss	
Severe	2 (28.6%)
Profound	5 (71.4%)
Non-visualization of the Left Vestibulocochlear Complex	
Yes	1 (14.3%)
No	6 (85.7%)
Bilateral Dilated Vestibule	
Yes	3 (42.9%)
No	4 (57.1%)
Bilateral Semicircular Canal Malformations	
Hypoplastic	3 (42.9%)
Dysplastic	3 (42.9%)
Aplasia of Anterior and Lateral Semicircular Canal	1 (14.3%)
Narrowing of the Internal Auditory Canal on the Left Side	
Yes	1 (14.3%)
No	6 (85.7%)
History of Developmental Delay	
Yes	1 (14.3%)
No	6 (85.7%)

Results of chi square test of independence showed that the association between age at the time of diagnosis and type of hearing impairment was significant, $\chi^2(3) = 8.74$, ($p<0.05$), but no significant association was found between gender and hearing type. There was a significant association between developmental delay and hearing type, $\chi^2(1) = 6.37$, ($p<0.01$). Family history of hearing impairment $\chi^2(1) = 20.15$, ($p<0.001$), history of ear discharge χ^2 (1, n=104) = 11.06, ($p<0.001$), specific audiological test χ^2 (2, n=104) = 70.45, ($p<0.001$) and severity of hearing loss χ^2 (2, n=104) = 62.4, ($p<0.001$) are associated with type of hearing impairment (Table 3).

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Table 3: Descriptive Statistics and Chi-Square Results for Types of Hearing Impairment in Relationship with Sociodemographic Characteristics(n=104)

Variables	Cochlear Implant Planned (n=52)	Hearing Impaired Using Hearing Aids (n=52)	χ^2	df	p-value	Cramer's V
	F (%)	F (%)				
Gender						
Male	29 (55.8%)	26 (50.0%)	0.35	1	0.560	0.04
Female	23 (44.2%)	26 (50.0%)				
Age at the Time of Diagnosis						
<1 Year	3 (5.8%)	2 (3.8%)	8.74	3	0.030	0.13
1 to 4 Years	49 (94.2%)	42 (80.8%)				
5 to 9 Years	0 (0%)	6 (11.5%)				
10 to 14 Years	0 (0%)	2 (3.8%)				
History of Developmental Delay						
Yes	6 (11.5%)	0 (0%)	6.37	1	0.010	0.14
No	46 (88.5%)	52 (100%)				
Family History of Hearing Impairment						
Yes	2 (3.8%)	21 (40.4%)	20.15	1	<0.001	0.25
No	50 (96.2%)	31 (59.6%)				
History of Ear Discharge						
Yes	0 (0%)	10 (19.2%)	11.06	1	<0.001	0.18
No	52 (100%)	42 (80.8%)				
Specific Audiological Test						
Pure Tone Audiometry	0 (0%)	37 (71.2%)	70.45	2	<0.001	0.37
OAE	0 (0%)	5 (9.6%)				
ABR	52 (100%)	10 (19.2%)				
Severity of Hearing Loss						
Moderate	0 (0%)	10 (19.2%)	62.4	2	<0.001	0.35
Severe	0 (0%)	29 (55.8%)				
Profound	52 (100%)	13 (25%)				

DISCUSSION

The present study aimed to find out various inner ear malformations in hearing-impaired cases occurring frequently in this region. In one study in Pakistan, Ahmad *et al.* reported 10% prevalence of inner ear malformation [14]. Another study reported that cochleovestibular anomalies had a prevalence of 11.1% [15]. In another study, it was reported that 5.8% patients presented with inner ear malformations [10]. Our study findings revealed the prevalence of cochleovestibular anomalies to be 6.7%. CT scan of the temporal bone and MRI are fundamental to identify inner ear malformations [16]. Ahmad *et al.* showed that complete labyrinthine aplasia (CLA) and cochlear hypoplasia (CH-III, CH-I) were the most prevalent inner ear malformations [14]. In another study, it was reported that anomalies of the cochlea (45/100) and semicircular canal (20/100) were most frequently occurring [16]. Incomplete partition followed by cochlear hypoplasia was most common in another study carried out by Young [17]. In the current study, the most prevalent IEMs were cochlear hypoplasia (CH-III) and semicircular canal malformation. The majority of cases with IEM had a profound degree of hearing loss and were candidates for cochlear implants [18]. However, being a public sector hospital, Cochlear implant is not performed in our center due to the greater financial burden and less favorable outcomes as compared to cases with normal inner ear anatomy [19]. Hearing-impaired children with cochleovestibular anomalies can present with various associated disabilities [20]. In one study, 13 out of 31 hearing-impaired individuals with anomalies of the inner ear had global developmental delay [21]. In the present study, it was found that 1 deaf child had bilateral cochlear vestibular anomalies and concurrent developmental delay. There was no significant correlation between gender and type of anomaly in the study by Asha [22]. The results of our study are consistent with this pattern. However, inner ear malformations were predominant in the female population (71%) in the current study. Many inner ear malformations can have familial occurrence and a genetic basis of inheritance. Brotto *et al.* described familial occurrence and genetic inheritance of various anomalies [7]. This contrasts with findings in our study, as no familial occurrence was reported in our study. Diagnosis of genetic mutation causing inner ear malformation helps in predicting recurrence risk and the

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need for further investigations to diagnose associated complications [7]. Unfortunately, in resource limited country, cost and poor access to genetic testing create a constraint to ascertain this benefit. Newborn screening plays a pivotal role in early diagnosis of hearing impairment, leading to early intervention and favorable developmental and language outcomes [23]. Being one of the underdeveloped countries, none of the children underwent a newborn screening test in our study. Inadequate early screening practices in the community lead to delayed diagnosis of hearing impairment. Thus, timely evaluation for cochlear implantation cannot be carried out. Subsequently, many patients with inner ear malformations remain undiagnosed. It can make it difficult to estimate the true prevalence of cochleovestibular anomalies and to decide about appropriate management course for such cases that can lead to better outcomes. More public awareness regarding the significance of this challenge is needed at the hour.

This was a single-center study with a limited sample size, which may restrict the generalizability of the findings. Additionally, the absence of newborn hearing screening and genetic testing limited accurate estimation of true prevalence and evaluation of hereditary associations. A multicenter trial should be conducted to ascertain the prevalence of various other types of anomalies. This will enable us to relate the result to a broader population group and enhance credibility. Given limited access to cochlear implantation, super-sonic hearing aids were recommended as an alternative rehabilitation strategy for children with profound hearing loss and inner ear malformations.

CONCLUSIONS

The frequency of inner ear malformations in hearing-impaired children using hearing aids or candidates for cochlear implants was 6.7%. The most common malformations were CH-III and semicircular canal malformations.

Authors' Contribution

Conceptualization: MAJ
Methodology: MAJ, AF, AA, AAQ, IS, WA
Formal analysis: MAJ, AA
Writing and Drafting: MAJ, AF, AAQ
Review and Editing: MAJ, AF, AA, AAQ, IS, WA

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 Factors Leading to Extubation Failure in a Pediatric Intensive Care Unit: A Descriptive Study from a Tertiary Care Hospital in Pakistan

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ABSTRACT

Extubation failure (EF), defined as the need for reintubation within 72 hours of planned removal of mechanical ventilation, is a serious complication in pediatric intensive care units, yet local data from low- and middle-income countries are limited. **Objectives:** To describe clinical risk factors for EF among ventilated children in a tertiary Pediatric Intensive Care Unit (PICU) in Pakistan. **Methods:** This research conducted a six-month descriptive cross-sectional study in the PICU of Civil Hospital Karachi, enrolling all children under 12 years who received invasive mechanical ventilation for >12 hours and subsequently required reintubation within 72 hours of planned extubation. Demographic variables and predefined risk factors (hemodynamic instability, gas-exchange failure, airway obstruction, acute respiratory disease, chronic neurologic disease, malnutrition, poor cough reflex, and exposure to sedatives, inotropes, and steroids) were recorded on a standardized, validated proforma and analyzed using SPSS-23 with chi-square tests ($p \leq 0.05$). **Results:** Among 133 EF episodes, the most frequent risk factors were hemodynamic instability (24.8%), inotrope and steroid use (24.8% each), upper airway obstruction and hypoxemic respiratory failure (15% each), and poor cough reflex (15%), with several patients exhibiting multiple overlapping risk factors. Upper airway obstruction and poor cough reflex were more common in males, whereas cyanotic congenital heart disease and chronic neurologic conditions occurred exclusively in children >5 years of age. **Conclusions:** EF in this setting is multifactorial, dominated by hemodynamic instability, gas-exchange impairment, and airway-protective deficits; structured, age- and sex-aware extubation-readiness assessment focused on these risks may help reduce reintubation in resource-limited PICUs.

INTRODUCTION

In the pediatric intensive care unit (PICU), mechanical ventilation is a fundamental treatment aspect, and a high percentage of patients need high-level care involving intravenous ventilation [1, 2]. Ventilator liberation generally incorporates day-to-day preparedness examination and in numerous units impromptu breathing trials preceding removing the ventilator [1, 3]. The process of extubation remains, however, a high-stakes transition where the reintubation within 48-72 hours is always associated with an extended period of ventilation, increased use of resources, and ventilator-associated events, as well as extended stay in the PICU [4, 5]. Extubation failure (EF) rates are reported to be dependent on practice and case-mix, but are commonly between low single digits and one-fifth of those with intubation [1, 6]. Various bedside factors contaminate EF risk in children, such as an upper-airway compromise, hemodynamic instability or vasoactive support, impaired oxygenation or ventilation, prolonged exposures to ventilation, and neurologic dysfunction [4, 5]. Fluid overload, myocardial disease, and residual airway edema can also further decrease post extubation reserve in susceptible patients

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[4, 5]. Sedative and analgesic needs can dampen the respiratory drive and slow readiness measures, making it harder to decide on weaning and obscure clinical indicators of fatigue [1, 3]. The nutritional deficit is less likely to be examined in extubation studies, but undernourishment among children is linked to an increased requirement for a mechanical ventilator and increased ventilator time, which would possibly aggravate the respiratory muscle performance and immune resistance [7]. Most units offer post-extubation noninvasive respiratory support (NRS) like high-flow nasal cannula, CPAP, or bilevel modalities to reduce risk, though their access and consistent use differ, especially in resource-constrained units [8, 9]. The recent multicenter database studies add to the fact that EF is prevalent and multifactorial, and airways and non-airways mechanisms are implicated in it [4, 5]. The surveys also exhibit discrepancies in extubation-readiness testing and portray operational obstacles that can delay prompt extubation [3]. The field of postextubation NRS has increased evidence that is randomized and comparative, with large pragmatic studies and network meta-analyses, but findings are context-dependent [8, 9]. By and large, modern syntheses emphasize heterogeneity of the populations and lack of information in non-high-income settings [6, 9]. Data on low- and middle-income PICUs is limited, particularly on the relative role of easily quantifiable clinical issues among children who actually fail extubation. The present research so characterizes feasible clinical risk factors implicating EF in a Pakistani PICU in a way that aids the appropriation of extubation preparedness evaluation and follow-up planning onto contextual ground. Although increased awareness of extubation failure as a complex phenomenon in the PICU has changed, new findings have highlighted the presence of gaps in standardized preparedness criteria and the impact of heterogeneous clinical forewarnings on the result of extubations. Modern evidence indicates that the frequency of extubation fail has not decreased, but still falls within non-negligible margins in a heterogeneous cohort of patients and that patient-specific influencing factors, including younger age, extended mechanical ventilation, pre-existing respiratory comorbidity, and post-extubation airway obstruction are persistently linked with an increased incidence of reintubation, which underscores the necessity of refined stratification and predictive methods when such cases get into practice [10-12]. Specific prediction tools that were created on a special subpopulation, including pediatric cardiac patients, have demonstrated encouraging discrimination abilities through the use of clinical past and physiologic variables, additionally indicating the possible advantages of organized risk scoring units to aid in timing extubation and post-extubation decision-making [13]. Systematic syntheses also indicate that there remains consistent heterogeneity in readiness testing techniques and that there is a need to achieve consensus on the best evaluation parameters to enhance prognostic accuracy [14]. Besides, evidence of overlap and distinct risk factor phenotypes within context-specific studies based on tertiary care centers (including low- and middle-income settings) suggests an even greater complexity, given that the relationships vary based on the demographic, ventilatory, and respiratory support variables associated with extubation outcomes [15, 16]. Altogether, these results emphasize both the advances and the persistent issues in the reduction of the extubation failure with the help of the individual evaluation and assistance paradigms, as well as emphasize the absence of solid data in resource-limited PICUs, and the urgency of acquiring localized evidence in support of the contextualized weaning plans and extubation preparedness models [14-16].

Although numerous clinical and physiologic factors have been linked to EF, most evidence originates from high-income countries, and standardized extubation-readiness criteria remain lacking. Data on context-specific risk factors and easily measurable predictors in resource-limited PICUs are limited. Therefore, this study aims to identify key clinical risk factors associated with EF among children in a Pakistani PICU to inform locally appropriate extubation-readiness assessment and post-extubation care planning.

METHODS

A descriptive cross-sectional study was conducted at the Department of Pediatrics in the Pediatric Intensive Care Unit (PICU), Civil Hospital Karachi, from 22 September 2021 to 22 March 2022 after approval by the College of Physicians and Surgeons Pakistan Research Evaluation Unit (IREB No. CPSP/REU/PED-2019-183-5108). The study evaluated the clinical risk factors associated with extubation failure (EF) in children receiving invasive mechanical ventilation. Written informed consent was obtained from parents or legal guardians of all participants, with assent from older children where appropriate, and confidentiality of patient data was strictly maintained. A non-probability consecutive sample of 133 children aged <12 years who were admitted to the PICU, intubated and mechanically ventilated for >12 hours, and planned for extubation was enrolled. Sample size was calculated using Open Epi version 3.01, assuming a 9.5% EF risk, 95% confidence interval, and 5% precision. EF was defined as the need for reintubation within 72 hours of a planned extubation attempt; each extubation failure episode was counted once in the analysis. Data were collected prospectively on a structured proforma. Hemodynamic

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instability was defined as age-specific hypotension or requirement for fluid boluses and/or vasoactive support persisting within 24 hours of extubation, based on Pediatric Advanced Life Support thresholds. Upper airway obstruction was diagnosed clinically by the presence of stridor, increased work of breathing, or need for nebulized epinephrine or steroids within 48 hours of extubation. Hypoxemic respiratory failure was defined as PaO2 <60 mmHg on arterial blood gas with normal or low PaCO2, and hypercapnic respiratory failure as PaCO2 >50 mmHg with accompanying respiratory acidosis. Acute respiratory disease (e.g., asthma, bronchitis, pneumonia) and pulmonary hypertension were documented according to standard WHO/CDC case definitions and echocardiographic reports, respectively. Cyanotic congenital heart disease was confirmed by cardiology records and prior echocardiography. Chronic neurologic conditions (e.g., cerebral palsy, neuromuscular disease, epileptic encephalopathy) were recorded from prior diagnoses and neuroimaging where available. Nutritional status was classified using WHO growth standards; children with weight-for-age or weight-for-height z-scores <−2 SD were labeled malnourished. Cough reflex was judged as poor when the bedside clinician documented absent or weak cough with suctioning or inability to clear secretions despite stimulation before extubation. Exposure to sedatives (benzodiazepines, opioids), inotropes, and systemic corticosteroids was recorded as present when these drugs were administered for ≥24 hours in the 48 hours preceding extubation. Duration of mechanical ventilation was calculated from intubation to first extubation attempt and categorized as ≤72 hours or >72 hours for stratified analyses. All variables were captured using a standardized proforma adapted from published extubation-readiness checklists and refined after review by three senior pediatric intensivists to ensure content validity. Data entry was double-checked against medical records for accuracy. Statistical analysis was performed using SPSS version 23.0; categorical variables were summarized as frequencies and percentages, and associations between risk factors and age, sex, and ventilation duration were explored using chi-square tests with p≤0.05 considered significant. Because only patients with extubation failure were enrolled and no comparison group of successfully extubated children was available, multivariable logistic regression to identify independent predictors of EF could not be performed in this dataset.

RESULTS

A total of 133 Pediatric patients admitted to the Pediatric Intensive Care Unit (PICU) at Civil Hospital Karachi who met the inclusion criteria were included in this study. The study summarizes the cohort's continuous variables: age (years), duration of mechanical ventilation (hours), and time between extubation and reintubation (hours), each reported as mean ± SD with minimum–maximum values. The mean age of the patients was 3.25 ± 4.49 years, with ages ranging from 1 month to 12 years. The average duration of mechanical ventilation was 96.72 ± 10.24 hours (range 85–107 hours), and the mean time from extubation to reintubation was 5.56 ± 3.24 hours. Table 1 provides descriptive statistics of the study population (Table 1).

Table 1: Descriptive Statistics (n=133)

Variables	Mean ± SD	Min–Max
Age (Years)	3.25 ± 4.49	1 – 12
Duration of Mechanical Ventilation (h)	96.72 ± 10.24	85 – 107
Time Between Extubation and Reintubation (h)	5.56 ± 3.24	2 – 9

Out of 133 patients, 78 (58.6%) were male, and 55 (41.4%) were female. A larger proportion of patients (66.17%, n = 88) were older than 5 years, while 45 (33.83%) were 5 years or younger (Figure 1).

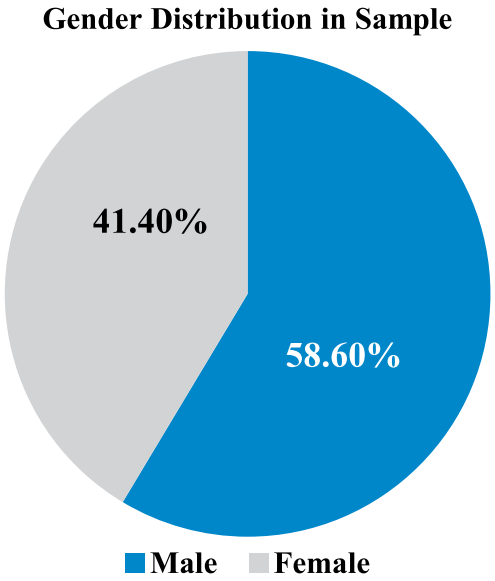

Figure 1: Gender Distribution in Sample

Findings list each predefined risk factor and its frequency (%): hemodynamic instability; inotrope use; steroid use; upper airway obstruction; hypoxemic respiratory failure; poor cough reflex; acute respiratory disease; hypercapnic respiratory failure; sedative use; cyanotic congenital heart disease; chronic neurologic condition; and malnutrition. In terms of clinical risk factors contributing to extubation failure (EF), the following frequencies were observed. Hemodynamic instability was noted in 33 (24.8%) of patients, while the use of inotropes and steroids before extubation was reported in 33 (24.8%) each. Upper airway obstruction and hypoxemic respiratory failure were present in 20 (15.0%) of the cases, and a poor cough reflex was recorded in 20 (15.0%) of the cases. Hypercapnic respiratory failure and acute respiratory disease each

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accounted for 14 (10.5%). Sedative use was recorded in 11 (8.3%). Cyanotic congenital heart disease was present in 7 (5.3%), chronic neurologic conditions in 7 (5.3%), and malnutrition, as defined by WHO standards, in 5 (3.8%) (Table 2).

Table 2: Frequency and Percentage of Clinical Risk Factors Associated with Extubation Failure (n=133)

Risk Factors	Frequency (%)
Hemodynamic Instability	33 (24.8%)
Inotrope Use	33 (24.8%)
Steroid Use	33 (24.8%)
Upper Airway Obstruction	20 (15.0%)
Hypoxemic Respiratory Failure	20 (15.0%)
Poor Cough Reflex	20 (15.0%)
Acute Respiratory Disease	14 (10.5%)
Hypercapnic Respiratory Failure	14 (10.5%)
Sedative Use	11 (8.3%)
Cyanotic Congenital Heart Disease	7 (5.3%)
Chronic Neurologic Condition	7 (5.3%)
Malnutrition	5 (3.8%)

Gender-based stratification revealed that 25.6% of male patients experienced upper airway obstruction, compared to 0% of female patients, indicating a statistically significant difference (p=0.01). Similarly, hemodynamic instability was more prevalent in male patients (33.3%) than in female patients (12.7%), with a significant p-value of 0.01. Cyanotic congenital heart disease was observed in 12.7% of female and none of the male patients, again reflecting statistical significance (p=0.01). Acute respiratory diseases did not show a significant gender-based difference (p=0.48). Among genders, malnutrition was slightly more common in male (5.1%) than female (1.8%), although this was not statistically significant (p=0.32). Cough reflex was judged as poor in 15% of patients, without significant variation across age groups (p=0.69) or ventilation duration (p=0.58), but with a highly significant gender difference—present in 25.6% of male and none of the female (p=0.01). Gender differences were significant in airway obstruction and cough reflex, though limited to EF cases (Figure 2).

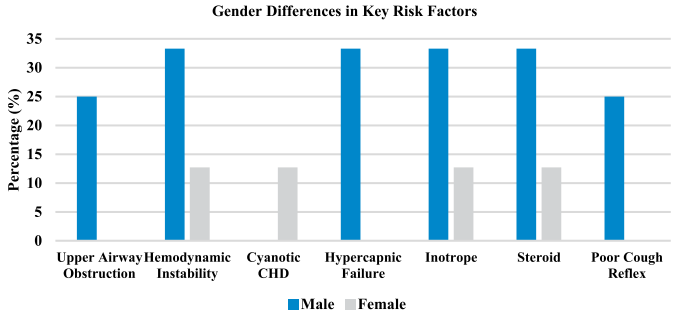

Figure 2: Gender Differences in Key Risk Factors

When stratified by age, hemodynamic instability was noted in 28.9% of children aged 5 years or younger and in 22.7% of those aged 5 years or older (p=0.43). Upper airway obstruction had a slightly higher frequency in older children (15.9%) compared to younger ones (13.3%), though this difference was not statistically significant (p=0.69). Interestingly, cyanotic congenital heart disease and chronic neurologic conditions were found exclusively in children older than 5 years (p=0.05 for both). Acute respiratory diseases were also significantly more frequent in older children (27.2%) than in younger children (0%), with a p-value of 0.01. CCHD and chronic neurologic conditions were more frequent in shorter MV durations (Table 3).

Table 3: Age/Durational Associations with Risk Factors (Statistically Significant)

Risk Factors	Group with Higher Prevalence	p-value
Cyanotic Congenital HD	Age > 5 Years	0.05
Acute Respiratory Disease	Age > 5 Years	0.01
Chronic Neurologic Condition	Age > 5 Years	0.05

Duration of mechanical ventilation (MV) was also stratified to assess its influence on EF risk factors. For upper airway obstruction, 16.3% of patients on mechanical ventilation (MV) for more than 72 hours developed this condition, compared to 12.8% of those on MV for 72 hours or less (p=0.58). Hemodynamic instability occurred in 22.1% of patients with mechanical ventilation (MV) lasting more than 72 hours and in 29.8% of those with MV lasting 72 hours or less (p=0.32). Cyanotic congenital heart disease was significantly more prevalent in patients ventilated for ≤72 hours (14.9%) compared to those in the >72 hours group (p=0.01). Hypercapnic respiratory failure showed a similar distribution across both MV duration groups (14.9% vs. 8.1%), with no significant difference (p=0.22). Hypoxemic respiratory failure was present in 12.8% of the ≤72 hours group and 16.3% in the >72 hours group (p=0.58). For inotropic use, 29.8% of patients ventilated ≤72 hours received inotropes, as opposed to 22.1% in the >72 hours group (p=0.32). Steroid use followed a similar pattern, showing no significant difference across ventilation durations (p=0.32). Sedative use also showed a non-significant trend, with 6.4% of the ≤72 hours group and 9.3% of the >72 hours group having been on sedatives (p=0.55). Malnutrition showed no significant association with age, gender, or mean vital sign duration. Among those ≤5 years, 2.2% were malnourished compared to 4.5% in older children (p=0.50) (Figure 3).

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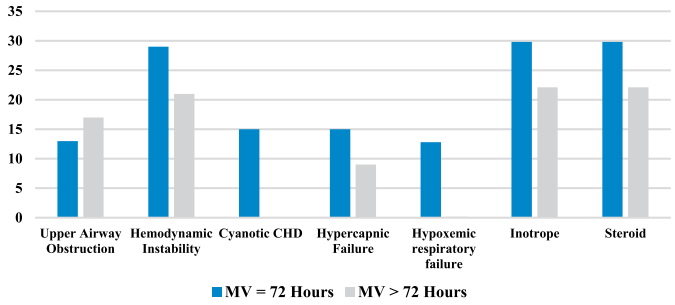

Figure 3: Comparison of Risk Factors by Duration of Mechanical Ventilation

The most frequent extubation failure risks were blood pressure problems, steroid/inotrope use, and upper-airway obstruction.

DISCUSSION

Extubation failure (EF) was found to happen in a clinically significant proportion of mechanically ventilated children in this study, which is consistent with the conclusion that ventilator liberation is a high-stakes clinical event in the PICU [1]. The recent literature in the pediatric community has conceptualized EF as a result of the susceptibility of patients and alterable mechanisms like readiness assessment, sedation procedures, and post-extubation surveillance [2, 3]. Although the physiologic shift of positive-pressure ventilation to unassisted spontaneous ventilation is planned, such as during extubation, the physiologic step change may predispose to clinical deterioration and initiate the reintubation response. Our cohort showed higher illness severity as measured by markers that EF was correlated with. Children either on inotropes or being hemodynamically unstable at the time of removal were more prone to reintubation, which is reasonable to expect considering the fact that withdrawal of positive pressure may cause an increase in the work of breathing and venous return, as well as afterload, which places undue pressure on limited cardiovascular reserve. More recent multicenter databases with the Virtual Pediatric Systems registry also report that EF is comparably prevalent across diagnoses, and also that it correlates with increased ventilation duration and increased length of stay in the ICUs, which points to EF not being a solitary airway event but rather an indicator of an underlying complex physiologic vulnerability [4]. Practically, sustained vasoactive requirements should necessarily stimulate rethinking the timing of extubation, the optimization of perfusion, and upstream consideration concerning the monitoring and support of the post-extubation period. Obstruction of the upper airways (UAO) became one of the dominant proximate causes of failure in our patients. The existing data confirms the separation of airway and non-airway EF phenotypes as they might have varying antecedents, time frames, and prevention approaches. The proliferation of airway-predominant failures was dominant, and with identifiable risk factors and outcomes in a recent study that differentiated airway and non-airway EF, with justification of the relevance of proactive prevention of airway edema, management of secretions, and early escalation in the case of stridor or obstruction emerged [5]. Within our cohort, the correlation between steroid use and EF may be a result of clinician awareness of airway risk (or more extreme airway pathology), but not a causal relationship, and hence the emphasis on understanding treatment markers (eg, steroids) as risk indicators, in addition to any interventions. Accurate prediction of EF remains difficult. A recent systematic review and meta-analysis found substantial heterogeneity in extubation readiness tests and EF definitions, with no single pre-extubation index demonstrating consistently high diagnostic accuracy across settings [6]. Our results reinforce the pragmatic value of bedside indicators—particularly cough effectiveness and secretion burden—because inability to clear secretions can precipitate both airway and respiratory deterioration after tube removal. From a process perspective, these findings support a multimodal readiness approach that integrates clinical airway assessments, neurologic readiness, hemodynamic stability, and disease trajectory rather than reliance on any single index. Undernutrition was frequent and was associated with poorer outcomes in our study. This aligns with evidence that undernutrition at PICU admission is associated with deterioration in clinical outcomes, including increased need for and duration of mechanical ventilation [7]. Optimizing nutrition may therefore be an important supportive strategy to improve respiratory muscle function and recovery, particularly in children anticipated to require prolonged ventilation or repeated weaning attempts. Additionally, the observed association between congenital cardiac anomalies and EF in our sample may reflect reduced cardiopulmonary reserve and higher susceptibility to changes in intrathoracic pressure and preload/afterload conditions during the peri-extubation period. Post-extubation noninvasive respiratory support (NRS) may reduce respiratory-predominant failure in selected patients. In the FIRST-ABC step-down trial, high-flow nasal cannula (HFNC) was not inferior to CPAP for time to liberation from respiratory support after extubation in critically ill children [8]. Complementary evidence from a network meta-analysis in infants and young children suggests that CPAP, HFNC, and BiPAP may reduce EF compared with conventional oxygen therapy, with CPAP ranking most effective for EF prevention among the analyzed trials [9]. In practice, these data support an individualized post-extubation strategy:

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children with a high risk of respiratory decompensation may benefit from planned NRS, while those with predominant airway-obstruction risk require vigilant airway observation and rapid access to escalation pathways. Recent international guidance provides an increasingly standardized framework for pediatric ventilator liberation. The PALISI network executive summary of pediatric ventilator liberation clinical practice guidelines offers evidence-based recommendations spanning readiness assessment, spontaneous breathing trials, and post-extubation support for children ventilated for more than 24 hours [17]. Complementing this, consensus-driven operational definitions have been published to harmonize what constitutes "respiratory support," "liberation," and "failed" attempts, which is essential for benchmarking and comparing EF outcomes across institutions [18]. Importantly, protocolization itself may improve liberation efficiency: a large pragmatic randomized trial found that implementing a sedation and ventilator liberation protocol produced a statistically significant reduction in time to first successful extubation compared with usual care (with uncertain clinical importance of the effect size) [19]. Together, these developments support moving from ad hoc decision-making toward reproducible, protocol-supported extubation practices—particularly for patients with identifiable high-risk features such as vasoactive requirements, UAO risk, or high secretion burden. Sedation, delirium, and mobility practices can influence extubation success through effects on respiratory drive, airway protective reflexes, and secretion management. The SCCM PANDEM guidelines emphasize structured approaches to pain and agitation management, delirium prevention/management, neuromuscular blockade, ICU environment, and early mobility for critically ill children [20]. Implementing these recommendations may indirectly support safer ventilator liberation by reducing oversedation and facilitating neuro-respiratory readiness at the time of extubation. Overall, these findings align with and extend existing EF literature by emphasizing readily observable clinical signs of hemodynamic stability, gas-exchange adequacy, airway patency, and cough effectiveness that can be systematically integrated into extubation-readiness protocols in resource-limited settings.

This was a single-center study from a resource-limited PICU, which may limit generalizability to other settings. Additionally, the observational design and limited sample size restricted robust multivariable adjustment and causal inference for extubation failure predictors. Future research from this and similar PICUs should prospectively include both extubation successes and failures to permit robust multivariable modelling of independent predictors, as well as to validate pragmatic, age-tailored extubation bundles that incorporate the risk factors highlighted in this study.

CONCLUSIONS

Extubation failure in this resource-limited tertiary PICU was most frequently associated with hemodynamic instability, impaired gas exchange, airway obstruction, and poor cough reflex, often in combination. Targeted, age-aware extubation-readiness assessment focusing on these high-yield clinical risk factors, alongside systematic attention to chronic neurologic disease and malnutrition, may help reduce reintubation and improve outcomes in similar settings.

Authors' Contribution

Conceptualization: IR
Methodology: IR
Formal analysis: NB
Writing and drafting: MA, FY, NUNM, SA, YY
Review and editing: IR, NB, MA, FY, NUNM, SA, YY

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

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All the authors declare no conflict of interest.

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Speech and Language Delay in Early Childhood: Insights from A Clinical Study in Islamabad, Pakistan

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ABSTRACT

Speech and language delay (SLD) in early childhood is a prevalent neurodevelopmental concern, often resulting in long-term academic, behavioral, and emotional difficulties if unaddressed. While risk factors have been well studied in high-income countries, data from low-resource settings like Pakistan remain limited. **Objective:** This study aimed to identify and quantify medical, familial, and environmental risk factors among children with isolated SLD in Islamabad. **Methods:** A cross-sectional study was conducted from August 2023 to February 2024 at the Pediatric Outpatient Department, KRL Hospital, Islamabad. A total of 145 children aged 2–5 years with isolated SLD were enrolled after clinical assessment and audiological screening. Data were collected via structured parent interviews on perinatal history, medical comorbidities, familial predispositions, and environmental exposures. Descriptive statistics were used to report frequencies. **Results:** Medical risk factors were present in 55.2% of children, with chronic ear infections (45%) and hearing loss (28.6%) being the most common. Birth asphyxia (19.3%) and seizure disorders (16.6%) were also noted. Familial factors were observed in 78.6% of cases, including consanguinity (67.5%) and family history of SLD (21.1%). Environmental exposures were highly prevalent (87.6%), particularly excessive screen time (>2 hours/day in 49.6%), pacifier use (40.9%), and thumb-sucking (27.6%). **Conclusions:** Children with SLD frequently present with modifiable risk factors across medical, familial, and environmental domains. Early identification of these risks, especially in settings with high consanguinity and limited screening infrastructure, can inform timely interventions and improve developmental outcomes.

INTRODUCTION

Speech and language delay (SLD) in early childhood is a common developmental concern. Children with isolated SLD present with slower verbal milestones than expected, yet without other disabilities such as hearing impairment or autism. Isolated SLD denotes a delay in speech and/or language development in the absence of other comorbid conditions [1]. Estimates of prevalence vary, but approximately 5–12% (median 6%) of 2–5-year-olds in developed countries exhibit significant delays [2]. Globally, speech/language delays affect approximately 2–10% of preschoolers [1, 2]. Untreated SLD often persists; longitudinal studies indicate that 40–60% of affected children will have enduring language problems, with two-fold increased rates of later emotional, behavioral, learning, and academic difficulties. Early identification and intervention are therefore critical; recent guidelines stress that screening and prompt speech therapy can mitigate long-term deficits (e.g., low IQ, literacy problems) [1, 3]. Numerous medical, familial, and environmental factors have been implicated in SLD. Consistently reported medical risk factors include perinatal adversities, birth asphyxia, prematurity, low birth weight, neurological

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conditions, e.g., seizures, cerebral palsy, hearing impairment, and chronic otitis media [3, 4]. For example, hypoxic–ischemic birth injury and resultant encephalopathy double the odds of later language delay [2, 3]. Hearing loss and persistent ear infections disrupt auditory input and have been linked to poorer speech outcomes [4]. Craniofacial or oropharyngeal anomalies, e.g., cleft palate that impair articulation, are also recognized contributors [5]. Familial and genetic factors often co-occur: a family history of speech or language disorders roughly doubles risk, reflecting inherited susceptibility [3, 5]. In the Pakistani population, parental consanguinity is common. Indeed, consanguineous unions, in 70% of families in Pakistan, elevate the prevalence of autosomal-recessive neurodevelopmental disorders [6]. We also consider socio-environmental factors: low parental education and reduced language stimulation at home have been associated with delay. Controversially, growing up in a multilingual household may strain early language acquisition; one recent case–control study found a multi-language environment to be a significant risk factor for SLD, while other experts note it can sometimes appear as a delay before later bilingual proficiency [2]. Environmental contributors include early feeding habits and digital media exposure. Bottle feeding vs. breastfeeding and prolonged pacifier or thumb-sucking have been implicated in some studies, possibly through effects on oral-motor development [4, 6]. Excessive screen time is increasingly recognized: meta-analyses and clinical studies link >2 hours/day of passive screen exposure with delayed vocabulary, language processing, ocular surface changes, and refractive errors [7-9]. Past trauma or social deprivation may further compromise linguistic stimulation.

Despite many studies in Western and some developing contexts, data from Pakistan on SLD risk are scarce. We therefore conducted a cross-sectional analysis of children aged 2–5 years presenting with isolated speech-language delay in Islamabad. This study aimed to quantify the prevalence of medical, familial, and environmental risk factors associated with speech and language delay and to inform early intervention priorities.

METHODS

A cross-sectional study was conducted from August 2023 to February 2024 at the Department of Pediatric Outpatient of KRL Hospital, Islamabad. Ethical approval was obtained from the hospital ethical review committee vide letter no. KRL-HI-PUB-ERC/113, and all steps were followed as per the Declaration of Helsinki. Informed written consent was obtained from the parents/guardians. The study enrolled 145 children aged 2–5 years meeting criteria for isolated speech or language delay. 'Isolated speech delay' was defined as delayed expressive speech (absence of two-word phrases by 24 months) with normal comprehension, whereas 'isolated language delay' was defined as deficits in receptive or expressive language skills (vocabulary, grammar) below age-expected levels. Children were excluded if they had known hearing loss. The tympanometry and BERA tests were performed to confirm hearing status, as recalled by parents or previous testing, intellectual disability, autism spectrum disorder, ADHD, neurological deficits, e.g., cerebral palsy, structural anomalies, cleft lip/palate, or global developmental delay. Each child was assessed by a pediatrician and an audiologist to confirm eligibility. Data were collected via parent interviews on medical history, including chronic ear infections (≥2 physician-diagnosed otitis media episodes in the past year), hearing loss, seizure disorders (physician-diagnosed epilepsy or recurrent seizures), and oropharyngeal anomalies (e.g., cleft palate confirmed on exam or history). Any vague 'other medical' categories were removed; we only recorded specific diagnoses. Familial factors included parental consanguinity; family history of speech/language delay (at least one first-degree relative with documented speech/language delay); parental education level; and home language environment (monolingual vs. multilingual, defined as more than one language spoken at home). Environmental factors queried included pre- and perinatal trauma, feeding practices (breast vs. bottle), pacifier/thumb-sucking history, and daily screen time hours of TV/tablet exposure. Descriptive statistics were computed for each risk factor. Because this was a descriptive study with no control group, no inferential statistics were performed.

RESULTS

The study cohort comprised 145 preschool children mean age of 3–4 years; gender-wise distribution was equal. Overall, 80 (55.2%) children had at least one medical risk factor recorded. The most common medical issues were chronic ear disease, persistent otitis media, or recurrent ear infections in 35 (24.13%), and sensorineural hearing loss in 15 (10.34%). Seizure disorders were present in 8 (5.51%), and oropharyngeal anomalies (e.g., cleft palate, macroglossia) in 10 (6.89%). A history of birth asphyxia was reported in 12 children, 8.27% (Table 1).

Table 1: Medical Risk Factors in Children with Speech and Language Delay (n=145)

Medical Factors	n (%)
Persistent Otitis Media/Ear Infections	35 (24.13%)
Hearing Loss	15 (10.34%)
Birth Asphyxia	12 (8.27%)
Seizure Disorder	8 (5.51%)
Oropharyngeal Deformity	10 (6.89%)

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In total, 78.6% had familial risk factors: parental consanguinity was noted in 82 (56.5%), a first-degree family history of speech/language delay in 22 (15.17%), and a multilingual home environment in 10 (6.89%). Low parental education was common but did not systematically differ between groups (Table 2).

Table 2: Familial Risk Factors in Children with Speech and Language Delay (n=145)

Familial Factors	n (%)
Consanguinity	82 (56.55%)
Family History of Speech/Language Delay	22 (15.17%)
Multilingual Family Environment	10 (6.89%)

Environmental risk factors were exceedingly prevalent: 127 (87.6%) children had ≥1 such factor. Notably, 53 children (36.55%) had daily screen exposure exceeding 2 hours, 32 (22.06%) had a history of pacifier use, and 28 (19.31%) engaged in prolonged thumb-sucking. The history of significant early-life trauma or deprivation was rare (14 children, 9.65%) (Table 3).

Table 3: Environmental Risk Factors in Children with Speech and Language Delay (n=145)

Environmental Factors	n (%)
Screen Time > 2 Hours/Day	53 (36.55%)
Pacifier Use	32 (22.06%)
Thumb Sucking	28 (19.31%)
History of Trauma	14 (9.65%)

DISCUSSION

In this clinical sample of Pakistani preschoolers with isolated speech-language delay, we found that multifactorial influences were the norm. Over half of the children had medical comorbidities that could impede language acquisition. Chronic otitis media and hearing impairment were particularly common, consistent with other reports [10-12]. These middle-ear problems can disrupt auditory processing, aligning with prior findings that recurrent ear infections increase the odds of language delay [6, 10]. The study also observed that one in five children had experienced birth asphyxia. Birth asphyxia has been well-documented to nearly quadruple SLD risk, likely via hypoxic brain injury affecting language centers [6, 13]. Seizure disorder was present in 16% of our participants, which also contributed to the neurologic risk for SLD [5, 6]. Oropharyngeal anomalies were 10% in our study, impairing articulation, and have similarly been noted as risk factors by Kumar *et al.* [5]. Familial factors were pervasive. The rate of parental consanguinity of 67.5% was striking, reflecting regional norms. Consanguinity breeds recessive neurodevelopmental disorders; indeed, national data cite 70% consanguinity in Pakistan [6]. This genetic background likely contributed to the high prevalence of familial speech delay (21.1%), suggesting inherited predispositions. A positive family history was seen in one-fifth of cases, echoing international reports that first-degree relatives often share language impairments [5]. A multilingual environment was present in only a minority (11%) but was nonetheless a significant factor; this aligns with the Ethiopian case–control finding where multilingual homes were associated with >2× odds of delay [14, 15]. While bilingualism alone is not a disorder, it can reveal a delay when children lag behind peers in any language. Environmental exposures were almost universal. Nearly half of all children exceeded 2 hours of screen time daily. Excessive active screen time is associated with the development of astigmatism in children [8, 16]. While passive screen exposure was increasingly implicated in language deficits [14, 17], current findings underscore the magnitude of this issue. Prolonged pacifier use and thumb-sucking were also common, consistent with Kumar *et al.* [5]. These habits can mechanically alter orofacial structure or distract from spoken interaction, though their causal role remains debated. Interestingly, bottle feeding (vs. breastfeeding) showed a near-significant association: in our sample, only 25% of DLD children had ever been breastfed, whereas Al-Qahtani *et al.* found that breastfeeding was significantly protective (25% breastfed in DLD vs. 45% in controls) [4]. Lower maternal education and socioeconomic factors, while prevalent, did not reach statistical significance here, possibly due to homogeneity in our clinic-based sample. Our results largely accord with prior literature. High rates of otitis media, hearing loss, and sucking habits have been reported in similar pediatric SLD groups [15, 18]. The identified risk factors in our cohort, birth asphyxia, seizures, ear infections, family history, consanguinity, and excessive screen time, have all been noted by others [3, 19]. We did not systematically measure some factors (e.g., parental education, birth order), but other studies have linked those to SLD [18, 20]. The consistency of our findings with international studies suggests that, despite cultural differences, the etiologic mix of SLD is similar worldwide. Importantly, our study has implications for practice. Pediatricians and family physicians should be vigilant for SLD in children with these risk profiles. For example, a history of neonatal asphyxia or ongoing otitis media should prompt speech monitoring. Consanguinity and positive family history warrant extra attention and possibly genetic counseling. Screening questionnaires or formal speech assessments could be prioritized for children with multiple risk factors. As Al-Qahtani *et al.* note, universal screening is ideal because early intervention (speech therapy, parent coaching, hearing rehab) can ameliorate or prevent later deficits [4]. In settings where universal screening is not feasible,

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targeting high-risk groups identified here may be the next best strategy. Early referral and intervention are essential: delays caught before school entry tend to respond better to therapy and yield better academic outcomes.

Limitations of our study include its single-center design and absence of a control group, which preclude estimation of risk magnitude. We also relied on parental reports for some histories, risking recall bias. Nonetheless, the high prevalence of identified risk factors in our sample is striking. Future research should include longitudinal follow-up and interventions to determine which factors are most modifiable.

CONCLUSIONS

Preschool children with speech delay have risk factors like birth asphyxia, chronic ear disease, family history, consanguinity, and high screen exposure, highlighting the need for early developmental monitoring. Interventions such as hearing tests, speech therapy, and parent education should begin promptly. Awareness of risks in Pakistan can aid early detection and improve outcomes.

Authors' Contribution

Conceptualization: MZ, AV
Methodology: KA, MK
Formal analysis: AV, RV, MK
Writing and drafting: KA
Review and editing: MZ, AV, KA, MK, RV

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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Barriers to the Utilization and Acceptance of Low Vision Devices among Patients at Al-Shifa Trust Eye Hospital, Rawalpindi

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ABSTRACT

Low vision significantly impairs daily functioning and quality of life, yet the acceptance and sustained use of low vision devices remain limited. Understanding barriers to utilization is crucial for developing effective rehabilitation strategies, particularly in low- and middle-income settings where access to vision care is constrained. **Objectives:** To determine the frequency of acceptance and to identify barriers influencing the utilization of low vision devices among patients with visual impairment. **Methods:** A cross-sectional study was conducted at the Department of Ophthalmology, Al-Shifa Trust Eye Hospital, Rawalpindi. A total of 150 patients aged 15–70 years with low vision were enrolled using non-probability consecutive sampling. Demographic, occupational, and clinical characteristics were recorded, and patients were asked about their acceptance of LVDs. Those who declined were further interviewed regarding barriers. Data were analyzed using SPSS v26, applying Chi-square and t-tests, with $p<0.05$ considered statistically significant. **Results:** Overall acceptance was 37%, while 63% declined the use. Acceptance was highest among patients aged 31–45 years (39.3%) and lecturers (69.2%). Diagnosis was significantly associated with acceptance ($p=0.010$), with higher uptake in maculopathy (35.7%) and pathological myopia (55.6%) compared to retinitis pigmentosa (14.3%) and optic atrophy (8.3%). Affordability emerged as the most critical barrier (41.6% among non-acceptors), while stigma, awareness, and usage difficulty were reported but not statistically significant. **Conclusions:** Acceptance of LVDs remains suboptimal, with affordability as the dominant barrier. Tailored counseling, structured training, and financial support mechanisms are essential to improve device uptake and enhance quality of life for individuals with low vision.

INTRODUCTION

One significant handicap that significantly affects both personal and professional facets is low eyesight. The resulting visual impairment makes it extremely difficult or impossible to carry out activities of daily living [1]. An estimated 2.2 billion people worldwide are blind or visually impaired, and 90% of those afflicted reside in low- and middle-income nations with inadequate access to eye health care [2]. Limited studies have been carried out on blindness and its causes in Pakistan. However, as per a 2008 survey from Pakistan prevalence of low vision among adults was reported as 2.1% [3]. There has been a significant increase in Pakistan in vision loss and visual impairment by 55% between 1999-2017 [4]. Due to their lack of access to specialized care for eye conditions, including cataracts and refractive errors, two of the leading causes of visual impairment worldwide, these individuals live with diminished vision [2, 5]. Low vision devices are tools designed to support individuals with low vision by enhancing their ability to see printed materials and other visual information. These devices are categorized as either optical, which use magnification, or non-optical, which are adaptive equipment that do not utilize lenses [6]. A

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person's quality of life is significantly impacted by visual impairment, which interferes with everyday tasks, including eating, walking, cooking, taking a shower, and identifying faces. Adults who are visually impaired frequently experience increased rates of anxiety and depression as well as reduced levels of employment involvement and productivity.7 Because the general public is not aware of low vision rehabilitation services, outpatient care delivery models usually follow this pipeline: (i) the ophthalmologist or optometrist identifies the patient, (ii) the clinician recommends and refers the patient to a low vision rehabilitation service, and (iii) the patient uses the service [8]. Through focused educational programs for optometrists who do not perform low vision rehabilitation, for instance, attempts to enhance the practice management of patients with poor vision can be informed by the identification of modifiable barriers to low vision rehabilitation [9]. Although there is adequate knowledge on low vision services, a few barriers are the reasons for the non-utilization of the low vision services. Hence, the need for recommendations such as education on low vision services, training of eye health workers, and the formulation of policies on low vision services [10, 11]. Lack of training/knowledge, lack of awareness, and non-availability of low vision devices were the major barriers for the provision of low vision care [12]. Other barriers to low vision care were social stigma, followed by low awareness, denial of magnitudes, fear of losing a job, low necessity, usage difficulty, and low affordability [13].

The rationale for conducting this study is to determine the frequency of barriers to the acceptance and utilization of low vision devices. Literature showed that the frequency of unacceptance of low vision devices is very high. But not much work has been done before, and no study is available in the local literature. Therefore, we want to conduct this study to get evidence regarding the extent of the problem and the unacceptability of low vision devices in the local population. So that in the future, patients can be guided well in order to improve their knowledge and acceptance of low vision devices. This study aims to determine the frequency of barriers to the acceptance and utilization of low vision devices.

METHODS

This cross-sectional study was conducted at the Department of Ophthalmology, AL-Shifa Trust Eye Hospital, Rawalpindi, during 9 months from 01 October 2024 to 30 June 2025. Ethical approval was taken from the institutional ethical review committee (Reference No. ERC-35/AST-24). Informed consent was taken from all enrolled patients. A total of 150 participants were included in the study. Sample size calculation was done as follows by using the WHO calculator, a sample size of 150 patients was calculated with 95% confidence level, 6.5% margin of error, and a percentage of low necessity, i.e., 20% for utilization of low vision device [13]. A non-probability consecutive sampling technique was used for sample selection. Included patients were aged 15-70 years of age, either gender, presenting with low vision (assessed through visual impairment screening questionnaire). The normal range for visual acuity, defined by the WHO, is 20/20. All study participants underwent a detailed history taking, including demographic details and medical history, conducted by an experienced ophthalmologist. Ocular diagnoses (maculopathy, retinitis pigmentosa, diabetic retinopathy, high/pathological myopia, glaucoma, optic atrophy, albinism/nystagmus, and aphakia) were made by a consultant ophthalmologist based on best-corrected visual acuity, slit-lamp and dilated fundus examination (with Takagi slit lamp microscope 30 GL using 90 D), with retinal imaging and Optical Coherence Tomography (with Heidelberg SPECTRALIS software_V6.16.2) used where indicated to confirm the diagnosis. However, patients with best corrected distance visual acuity in better eye <1/60 or residual field less than five degrees around central fixation, and Patients with low intellectual level or cognitive problems (defined as a score of ≤5 on the mini-mental scale examination) were excluded from the study. Demographic information, i.e., name, age, gender, duration of symptoms, history of smoking >5 pack years, diabetes (BSR>200 mg/dl), hypertension (BP≥140/90mmHg), occupation, screen time, diagnosis, and visual acuity were recorded. Then, patients were asked for acceptance of vision devices (patients using low vision devices as prescribed by the ophthalmologist) by using a simple proforma designed for the study. The patients who had not accepted the use of low vision devices were later on asked about barriers or causes of unacceptance of low vision devices. Based on a literature review, the seven potential barriers were identified and defined: social stigma, low awareness (lack of knowledge about low vision devices, their benefits, and availability), denial of magnitude (reluctance to acknowledge the severity of visual impairment), fear of losing a job (concern over reduced job opportunities due to low vision devices), low necessity (belief that low vision devices are unnecessary and that they can manage without them), usage difficulty (struggles in using devices due to discomfort or technical issues), and low affordability (high cost of devices, making it difficult for patients to acquire them).[13] A proforma was developed to record the responses of study participants, and all questions in the proforma were closed-ended. The proforma was reviewed by two consultant ophthalmologists with expertise in low vision rehabilitation for content validity, and it was pilot-tested on a small group of patients to check clarity and

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feasibility; minor wording changes were made before formal data collection. A face-to-face interview was conducted to collect data on the barriers to acceptance of low vision devices. The researcher explained each question in detail to ensure accurate responses from the participant. For every item, patients indicated whether the barrier applied to them using a dichotomous response format ("Yes" / "No"), and more than one barrier could be selected. Data entry and analysis were done with SPSS version 26. Normality was checked by the Kolmogorov-Smirnov test. Quantitative variables (Age, screen time) were presented with mean ± SD, and qualitative variables (Gender, affected side, comorbidities, diagnosis, occupation, and visual acuity and barriers for not accepting low vision device) were presented with frequency and percentage. Association of barriers with patients' characteristics and acceptance of low vision device was assessed with the help of Chi square test. An independent sample t-test/ Mann Whitney u test was applied to compare age and screen time among participants with and without acceptance for low vision devices. p-value <0.05 was considered statistically significant.

RESULTS

Overall acceptance is 37% (56/150) versus 63% (94/150) non-acceptance. (Figure-1).

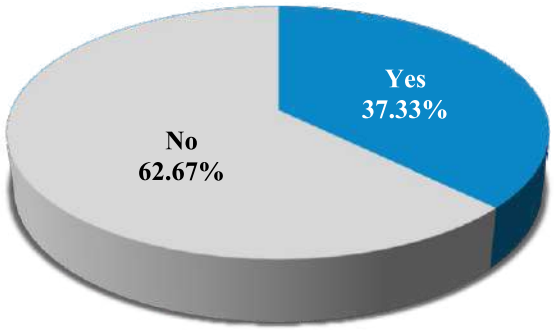

Figure 1: Acceptance of Low Vision Devices (n=150)

This study describes the visual acuity for study participants for the right and left eyes (Figure 2).

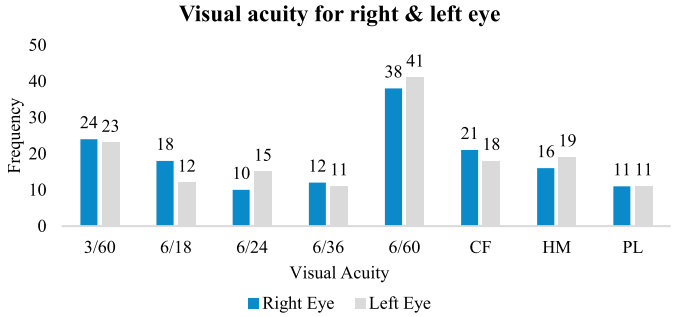

Figure 2: Visual Acuity for Right and Left Eye

Note: CF: Counting Finger, HM: Hand movement, PL: Light perception

The mean age of participants was 45.1 ± 13.5 years, with men comprising 57.3% of the sample. Occupationally, the largest groups were housewives (30.7%) and unemployed individuals (28.7%), indicating a socioeconomic profile with limited earning potential. Clinically, maculopathy (25.3%) and retinitis pigmentosa (20%) were the leading causes of low vision, followed by diabetic retinopathy (15.3%) and high/pathological myopia (12%). A significant association was observed for diagnosis (p=0.010), while age (p=0.395), gender (p=0.323), diabetes (p=0.896), and hypertension (p=0.088) were not significant predictors of acceptance. Table-1 analysis shows nuanced patterns: Younger participants aged 31–45 years had the highest acceptance (39.3%) compared to only 10.7% among those aged 15–30, though age overall was not statistically significant (p=0.395). Similarly, acceptance was slightly higher among males (62.5%) than females (37.5%), but without statistical significance (p=0.323). Laterality showed a comparable distribution, with right-eye involvement (58.9% acceptance) slightly exceeding left-eye involvement (41.1%) (p=0.190). Among comorbidities, diabetes was almost equally present in accepters (21.4%) and non-accepters (22.3%) (p-value=0.896), while hypertension showed a higher proportion among accepters (17.9%) compared to non-accepters (9.5%), though the association was borderline (p=0.088). Occupation presented some meaningful trends. Lecturers demonstrated the highest acceptance (69.2%), whereas students had the lowest (10%). Housewives (26.8%) and unemployed individuals (26.8%) formed a large share of non-accepters, pointing to financial dependency as a limiting factor. Diagnostic categories also revealed important differences: maculopathy (35.7% acceptance) and high/pathological myopia (55.6% acceptance) had better uptake, while retinitis pigmentosa (only 14.3% acceptance) and optic atrophy (8.3% acceptance) had markedly lower acceptance. This suggests that patients with progressive, irreversible conditions may be less inclined to adopt devices compared to those with treatable or functionally improvable pathologies (Table-1).

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Table 1: Acceptance of Low Vision Devices in Relation to Patients' Characteristics

Variables	Categories	n	Acceptance		p-value
			Yes	No	
Age (Years)	15-30	24 (16.0%)	6 (10.71%)	18 (19.15%)	0.395[(c)]
	31-45	51 (34.0%)	22 (39.29%)	29 (30.85%)	
	46-60	55 (36.7%)	19 (33.93%)	36 (38.30%)	
	>60	20 (13.3%)	9 (16.07%)	11 (11.70%)	
	Mean Age	45.11 ± 13.54	46.14 ± 13.11	44.50 ±13.82	0.474[(t)]
Screen Time	Mean Screen Time (Hours)	5.00 (IQR:4.85)	5.80 (IQR: 4.35)	5.00 (IQR: 5.13)	0.573[(ζ)]
Gender	Male	86 (57.3%)	35 (62.50%)	51 (54.26%)	0.323[(c)]
	Female	64 (42.7%)	21 (37.50%)	43 (45.74%)	
Effected Side	Right	78 (52%)	33 (58.93%)	45 (47.87%)	0.190[(c)]
	Left	72 (48%)	23 (41.07%)	49 (52.13%)	
Comorbidities	Diabetes	33 (22%)	12 (21.43%)	21 (22.34%)	0.896[(c)]
	Hypertension	18 (12%)	10 (17.86%)	8 (9.51%)	0.088[(c)]
Occupation	House Wife	46 (30.7%)	15 (26.79%)	31 (32.98%)	0.062[©]
	Laborer	16 (10.7%)	8 (14.29%)	8 (8.51%)	
	Lecturer	13 (8.7%)	9 (16.07%)	4 (4.26%)	
	Shopkeeper	22 (14.7%)	8 (14.29%)	14 (14.89%)	
	Student	10 (6.7%)	1 (1.79%)	9 (9.57%)	
	Unemployed	43 (28.7%)	15 (26.79%)	28 (29.79%)	
Diagnosis	Albinism/Nystagmus	8 (5.3%)	3 (5.36%)	5 (5.32%)	0.010[(F)]
	Aphakia	6 (4.0%)	1 (1.79%)	5 (5.32%)	
	Diabetic Retinopathy	23 (15.3%)	11 (19.64%)	12 (12.77%)	
	Glaucoma	15 (10.0%)	2 (3.57%)	13 (13.83%)	
	High/Pathological Myopia	18 (12.0%)	10 (17.86%)	8 (8.51%)	
	Maculopathy	38 (25.3%)	20 (35.71%)	18 (19.15%)	
	Optic Atrophy	12 (8.0%)	1 (1.79%)	11 (11.70%)	
	Retinitis Pigmentosa	30 (20.0%)	8 (14.29%)	22 (23.40%)	

Note: (C): Chi-square test, (F) Fisher exact test, (t) Independent sample t-test. (ζ): Mann-Whitney U test

Barrier analysis showed that most psychosocial and attitudinal factors were not significantly associated with device acceptance. Social stigma was reported by 55.4% of accepters and 45.7% of non-accepters (p-value=0.312), while low awareness was present in 60.7% and 53.2%, respectively (p-value=0.399). Denial of severity was reported by 25% of accepters and 20.2% of non-accepters (p-value=0.544). Fear of job loss (12.5% vs 14.9%, p-value=0.810), low necessity (7.1% vs 5.3%, p-value=0.728), and usage difficulty (41.4% vs 34%, p-value=0.484) showed no meaningful associations. However, affordability emerged as the most relevant factor, with 41.6% of non-accepters citing it compared to only 25% of accepters, approaching statistical significance (p-value=0.052). This reinforces financial constraints as the most credible barrier to device utilization. (Table-2)

Table 2: Association of Acceptance of Low Vision Devices with Barriers

Variables		Acceptance of Low Vision Devices		p-value[(c)]
		Yes	No	
Social Stigma	Yes	31 (55.4%)	43 (45.7%)	0.312
	No	25 (44.6%)	51 (54.3%)	
Low Awareness	Yes	34 (60.7%)	50 (53.2%)	0.399
	No	22 (39.3%)	44 (46.8%)	
Denial of Magnitude	Yes	14 (25%)	19 (20.2%)	0.544
	No	42 (75%)	75 (79.8%)	
Fear of Losing a Job	Yes	7 (12.5%)	14 (14.9%)	0.810
	No	49 (87.5%)	80 (85.1%)	
Low Necessity	Yes	4 (7.1%)	5 (5.3%)	0.728
	No	52 (92.9%)	89 (94.7%)	
Usage Difficulty	Yes	23 (41.4%)	32 (34%)	0.484
	No	33 (58.9%)	62 (66%)	
Low Affordability	Yes	14 (25%)	39 (41.55%)	0.052*
	No	42 (75%)	55 (58.5%)	

Note: (C); Chi-square test

DISCUSSION

This study assessed the acceptance and barriers to low vision devices (LVDs) among patients with visual impairment. Eye care specialists identified multiple barriers that hinder the effective delivery of low vision services. These included inadequate infrastructure, insufficient availability of essential devices, lack of uniform training standards for professionals, systemic shortcomings within healthcare, and limited public

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awareness of such services. From the patient standpoint, the most pressing challenges were the financial burden and restricted access to visual aids, the social stigma associated with their use, and the general unawareness of where and how to obtain appropriate support [14]. The overall acceptance rate was 37%, with 63% declining use, echoing international evidence that uptake of low vision rehabilitation remains suboptimal despite demonstrated benefits. The acceptance observed is comparable to findings in Rawalpindi, where Tariq *et al.* reported 41.17% compliance with prescribed devices [15]. In another local study acceptance rate was reported as 58.8%, which is slightly higher compared with this study [16]. In India, however, Priya Sivakuma *et al.* found a higher acceptance rate (43.1%) for low vision assistive products [13]. These comparisons suggest that while acceptance rates vary, consistent challenges in patient uptake persist across regions. In contrast, Konstantinos *et al.* in Greece reported markedly higher compliance (over 90%) one year after training sessions, suggesting that structured education and follow-up are powerful facilitators of adherence [17]. In this study, no significant association was seen between acceptance of low vision devices and age, gender, or occupation. However, a significant association was seen with diagnosis. However, Wardha Afzaal *et al.* in their study reported a higher acceptance rate in the age group 41-60 years, among female and for patients with diabetic retinopathy, Albinism and for patients with congenital optic nerve disease [16]. These findings align with the present study only in terms of age, but contrast with respect to gender and diagnosis. Priya Sivakumar reported a similar age trend for acceptance rate but a higher acceptance rate among males, which aligns with this study's results and the highest acceptance rate for diabetic retinopathy, which aligns with this study, followed by ARMD and glaucoma [13]. These discrepancies in acceptance rates in terms of the diagnosis of patients suggest that perception of disease reversibility and expected benefit may influence motivation differently across populations. Affordability consistently emerged as the leading obstacle, a finding corroborated across multiple settings [18]. Tariq et al. noted that 70.7% of Pakistani patients rejected devices due to cost [15], while Ashioya *et al.* in Kenya reported that 69.2% of non-users cited high device prices as the principal barrier [19]. Similarly, the study by Fatima *et al.* emphasized economic hardships as a central factor limiting awareness and utilization of assistive technology [20]. These patterns indicate that out-of-pocket expenditure remains the most pressing limitation, particularly in low-resource contexts. By contrast, Greek patients in the Oikonomidis study were less deterred by affordability, reflecting differences in health financing systems. This divergence underscores the need for subsidy programs or insurance coverage in countries where assistive devices remain unaffordable [1]. Despite subsidy some of the devices for low vision remain unaffordable for the patients. Stigma, denial of severity, and perceptions of "low necessity" strongly influenced patient decisions in both this and comparable studies [21]. Tariq *et al.* identified fear of being perceived as blind in 80% of their cohort [15], while Afzaal *et al.* reported stigma as the dominant barrier among younger adults and low necessity among older adults [16]. Sivakumar *et al.* likewise found that stigma was most pronounced in patients under 40, where over 41% declined devices for social reasons [13]. These findings resonate with the present study, which similarly recorded stigma and denial as frequent, albeit not statistically significant, barriers. In contrast, Ashioya *et al.* in Kenya highlighted more structural concerns, with distance to facilities and delivery delays emerging as notable deterrents [19]. The variation suggests that while stigma is a universal factor, its weight relative to other barriers differs by cultural and systemic context. Awareness gaps emerged strongly in both the current and external studies. Fatima *et al.* found that 58.5% of Pakistani patients had poor awareness of assistive technologies, with lack of training cited as the most frequent barrier [20]. Similarly, Sivakumar *et al.* emphasized inadequate patient knowledge and lack of professional guidance as central contributors to rejection [13]. In contrast, when Greek patients received structured counseling and hands-on training, long-term compliance was almost universal [17]. This comparison demonstrates that knowledge and guided practice are pivotal determinants of utilization and should be integrated into routine service delivery. Studies have reported low frequency for fear of losing a job as well as low necessity as a barrier [16, 20]. A similar trend was seen in this study, as no significant association was seen between fear of losing a job and acceptance for low vision device. When viewed collectively, the evidence suggests that barriers to LVD acceptance are layered, with affordability as the most consistent challenge across developing contexts, while stigma and awareness vary in intensity depending on cultural and health system factors. Diagnostic differences highlight the importance of tailoring counseling to patient expectations and disease trajectory. The positive outcomes reported in Greece underscore that with adequate training and structured rehabilitation programs; compliance can dramatically improve even in populations with historically low uptake.

This study was limited by its single-center, cross-sectional design, which restricts generalizability and prevents causal inference. Reliance on self-reported reasons for non-acceptance may have introduced recall and social desirability bias. In addition, psychosocial and cultural

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determinants were not explored in depth, and device availability was confined to those offered within the study setting. Future research should focus on multicenter studies to evaluate the applicability of these findings in enhancing care delivery.

CONCLUSIONS

In conclusion, this study finds that affordability is the most significant barrier to LVD adoption, followed by stigma and limited awareness. Diagnostic categories, occupation, and systemic issues also influence acceptance.

Authors' Contribution

Conceptualization: MK
Methodology: MK, ABN, AA, FA, TT
Formal analysis: MK, ABN
Writing and Drafting: MK
Review and Editing: MK, ABN, AA, FA, TT

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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Fetal Outcomes of Pregnancy with Preterm Premature Rupture of Membrane

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ABSTRACT

Preterm premature rupture of membranes (PPROM) is a major contributor to preterm birth and is strongly associated with increased neonatal morbidity and mortality. **Objectives:** To evaluate fetal outcomes among pregnancies complicated by PPROM and to compare neonatal morbidity and mortality between infants delivered at ≤34 weeks and those delivered after 34 weeks of gestation. **Methods:** A prospective observational study was carried out at Fatima Jinnah Medical University/Sir Ganga Ram Hospital. A total of 125 pregnant women who had preterm premature rupture of membranes (PPROM) during the period of 28-37 gestational weeks. The diagnosis was made by the examination through the sterile speculum with positive pooling, nitrazine, or ferning. Mothers and babies were observed until discharge. SPSS version 25.0 was used to analyze the data, and $p<0.05$ was the significant value. **Results:** The mean gestational age at rupture was 31.2 ± 1.1 weeks in the ≤ 34-week group and 35.3 ± 0.9 weeks in the >34-week group. Early gestation was associated with significantly lower birth weight (1.78 ± 0.34 kg vs. 2.36 ± 0.41 kg; $p<0.001$), higher NICU admissions (82.3% vs. 35.1%; $p<0.001$), and increased neonatal complications including respiratory distress syndrome (58.8% vs. 14.0%; $p<0.001$) and sepsis (32.3% vs. 15.8%; $p=0.03$). Perinatal mortality was markedly higher among infants ≤ 34 weeks (20.6%) compared to those >34 weeks (3.5%; $p=0.002$). **Conclusions:** PPROM is associated with substantial fetal morbidity and mortality, especially when occurring before 34 weeks of gestation. Prematurity, low birth weight, and infection remain the major determinants of poor neonatal outcomes.

INTRODUCTION

Preterm premature rupture of membranes (PPROM) is the term that characterizes the rupture of fetal membranes at a gestational age of less than 37 weeks and during the period before childbirth. It remains one of the most problematic obstetric complications that influences the maternal-fetal health [1]. PPROM contributes to almost a third of all preterm births, and consequently, it is a significant cause of perinatal morbidity and mortality. Its presence interferes with the protective intrauterine environment, exposing the fetus to infection and cord compression, as well as preterm complications, which, combined, aggravate the neonatal outcomes [2]. Regardless of the improvements in obstetric care, the problem of PPROM remains high in all places all around the world, particularly in low and middle-income countries where timely diagnosis and standard protocols of managing the condition may not be available [3]. PPROM etiology is multifactorial, which entails intra-amniotic infection, subclinical inflammation, cervical insufficiency, and maternal risk factors including smoking, low socioeconomic status, past preterm birth, and untreated genitourinary infections. The mechanisms that are of major importance pathophysiologically are the degradation of collagen and the weakening of fetal membranes with the action of inflammatory mediators, which eventually leads to rupture of membranes early [4]. Literature has highlighted that microbial invasion of the amniotic cavity in up to 30 to 40 percent of PPROM cases

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has been associated with evidence of microbial invasion of the amniotic cavity even in asymptomatic individuals, increasing the risk of neonatal sepsis and adverse outcome even further [5]. The outcome of the fetus in PPROM greatly depends on the gestational age at rupture, the duration of latency, and the availability of intrauterine infection. The problems linked to earlier gestational ages include respiratory distress syndrome (RDS), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), and gross morbidity owing to organ systems' immaturity [6]. With the progression of pregnancy, the prognosis becomes better, but still, the risks of umbilical cord prolapse, fetal distress, and complications of oligohydramnios can take place [7]. One of the findings that has remained consistent is the fact that neonates who have been born following PPROM have elevated rates of NICU admission, delayed hospitalization, and increased medical procedures compared to their counterparts who have not experienced membrane rupture [8]. The PPROM management entails a fine balance between expectant care and birth, based on gestation age, maternal stability, and fetal health [9]. Antenatal corticosteroids, broad-spectrum antibiotics, and fetal monitoring protocols have contributed greatly to the increased survival rates because they minimize respiratory and infectious complications [10]. However, differences in the outcome can always be found based on the differences in the provision of healthcare, neonatal intensive care unit, and the maternal comorbid conditions [11].

Considering the high implications for public health, the case study will examine the fetal outcomes of pregnancies that were complicated by PPROM, in terms of perinatal morbidity and mortality. The knowledge of these patterns will be used to optimize management interventions and guide clinical decision-making and enhance neonatal prognosis. This study aimed to evaluate fetal outcomes among pregnancies complicated by PPROM and to compare neonatal morbidity and mortality between infants delivered at ≤34 weeks and those delivered after 34 weeks of gestation.

METHODS

This was a prospective observational study conducted at Fatima Jinnah Medical University/Sir Ganga Ram Hospital after getting ethical approval (218-Synopsis/MS-Gynae FJERC). The duration of the study was October 2023 to April 2024. The sample size was calculated by taking the history of PROM as 88.3% by taking 6% margin of error, and 95% confidence interval, and 10% dropout rate [12]. A total of 125 pregnant women were diagnosed with preterm premature rupture of membranes (PPROM) between 28 and 37 weeks of gestation. Pregnant women aged 18 years to 40 years who had a singleton pregnancy and had PPROM (positive pooling, nitrazine, or ferning test) between 28 and 37 weeks of gestational age were all included. Where a first-trimester ultrasound was available, gestational age was confirmed; otherwise, a first-trimester ultrasound was not available, and the last menstrual period was used. The ultrasound-derived gestational age was the preferred one to be analyzed and utilized to make clinical decisions in instances where the discordance exceeded 7 days between LMP and ultrasound estimates. The intact fetal viability at the time of admission was determined by the presence of fetal cardiac activity verified by ultrasound and/or Doppler auscultation, the right gestational age (28 to 37 weeks), and the absence of intra-uterine fetal death. All participants signed an informed consent that was written. The patients were informed about the study objective, and written informed consent was taken. Upon admission, detailed maternal information was recorded, including age, parity, gestational age, and duration of membrane rupture. Diagnosis of PPROM was confirmed using sterile speculum examination, nitrazine test, and ferning test. Relevant investigations, such as complete blood count, C-reactive protein, ultrasound for amniotic fluid index, and fetal well-being assessments, were performed. All patients received standardized management based on gestational age, including antenatal corticosteroids, prophylactic antibiotics, and tocolysis when indicated. Continuous fetal monitoring was carried out to detect signs of distress. At delivery, data regarding mode of delivery, latency period, Apgar scores, birth weight, NICU admission, and neonatal complications such as respiratory distress syndrome, neonatal sepsis, intraventricular hemorrhage, and perinatal mortality were documented. Newborns were followed through the hospital stay to capture all relevant outcomes. Data were entered and analyzed using SPSS version 25.0. Continuous variables such as maternal age, gestational age, latency period, birth weight, and Apgar scores were expressed as mean ± standard deviation (SD) and compared using the independent t-test. Categorical variables, including mode of delivery, NICU admission, neonatal complications, and perinatal mortality, were presented as frequencies and percentages and analyzed using the Chi-square test. A p-value<0.05 was considered statistically significant.

RESULTS

In this study of 125 PPROM patients, the average maternal age was 28.6 ± 4.9 years, and parity was 1.1 ± 0.8, with no significant difference between gestational-age subgroups. Rupture occurred significantly earlier in the ≤34-week group (31.2 ± 1.1 weeks) compared with >34 weeks (35.3 ± 0.9 weeks, p<0.001). Women ≤34 weeks also had a longer latency period (4.4 ± 1.5 days) compared to those >34 weeks (3.1 ± 1.4 days, p<0.001). Antenatal steroid use was

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universal in the early-gestation group (100%) but only 43.8% in the late-gestation group (p<0.001) (Table 1).

Table 1: Baseline Maternal and Clinical Characteristics (n=125)

Variables	Total (n=125)	GA ≤ 34 Weeks (n= 68)	GA > 34 Weeks (n= 57)	p-value
Maternal Age (Years), Mean ± SD	28.6 ± 4.9	28.1 ± 5.1	29.2 ± 4.7	0.280
Parity (Mean ± SD)	1.1 ± 0.8	1.0 ± 0.7	1.2 ± 0.8	0.190
Gestational Age at Rupture (Weeks)	33.1 ± 2.4	31.2 ± 1.1	35.3 ± 0.9	<0.001*
BMI (kg/m^2), Mean ± SD	26.4 ± 3.9	26.1 ± 3.7	26.7 ± 4.1	0.470
Previous Preterm Birth, n (%)	18 (14.4%)	12 (17.6%)	6 (10.5%)	0.250
Antenatal Steroids Received, n (%)	93 (74.4%)	68 (100%)	25 (43.8%)	<0.001*
Latency Period (Days), Mean ± SD	3.8 ± 1.6	4.4 ± 1.5	3.1 ± 1.4	<0.001*

*p-value<0,05, Statistically significant

Vaginal delivery was more common in the >34-week group (73.7%) than in those ≤34 weeks (52.9%, p=0.01). Conversely, cesarean section was significantly more frequent in early-gestation PPROM (47.1%) versus late gestation (26.3%, p=0.01). Oligohydramnios was also more prevalent in the ≤34-week group (42.6%) compared to >34 weeks (21.1%, p=0.008). Mean gestational age at delivery was 32.1 ± 1.0 weeks for early PPROM and 35.8 ± 0.8 weeks for late PPROM (p<0.001). Latency ≥48 hours occurred in 70.5% of early cases compared to 36.8% of late cases (p<0.001) (Table 2).

Table 2: Delivery Characteristics

Variables	Total (n=125)	GA ≤ 34 Weeks (n= 68)	GA > 34 Weeks (n= 57)	p-value
Mode of Delivery (Vaginal), n (%)	78 (62.4%)	36 (52.9%)	42 (73.7%)	0.010*
Cesarean Delivery, n (%)	47 (37.6%)	32 (47.1%)	15 (26.3%)	0.010*
Meconium-Stained Liquor, n (%)	17 (13.6%)	10 (14.7%)	7 (12.3%)	0.680
Oligohydramnios (AFI < 5cm), n (%)	41 (32.8%)	29 (42.6%)	12 (21.1%)	0.008*
Gestational Age at Delivery (Weeks), Mean ± SD	33.8 ± 2.3	32.1 ± 1.0	35.8 ± 0.8	<0.001*
Latency ≥48 Hours, n (%)	69 (55.2%)	48 (70.5%)	21 (36.8%)	<0.001*

*p-value<0,05, Statistically significant

Neonates from the ≤34-week group had significantly lower birth weights (1.78 ± 0.34 kg) than those >34 weeks (2.36 ± 0.41 kg, p<0.001). Low-birth-weight rates were extremely high in early PPROM, at 92.6%, compared to 43.9% in late PPROM. Apgar scores <7 at 1 minute were more frequent in ≤34 weeks (47.1%) versus >34 weeks (17.5%, p<0.001), and a similar pattern appeared at 5 minutes (38.2% vs. 14.0%, p=0.002). The need for neonatal resuscitation was markedly higher in early PPROM (55.9%) than in later gestations (22.8%, p<0.001). NICU admission reflected the same trend, with 82.3% of early preterm infants requiring it versus 35.1% of late preterm infants (p<0.001) (Table 3).

Table 3: Neonatal Characteristics and Immediate Outcomes

Variables	Total (n=125)	GA ≤ 34 Weeks (n= 68)	GA > 34 Weeks (n= 57)	p-value
Birth Weight (kg), Mean ± SD	2.04 ± 0.48	1.78 ± 0.34	2.36 ± 0.41	<0.001*
Low Birth Weight (<2.5kg), n (%)	88 (70.4%)	63 (92.6%)	25 (43.9%)	<0.001*
Apgar <7 at 1 min, n (%)	42 (33.6%)	32 (47.1%)	10 (17.5%)	<0.001*
Apgar <7 at 5 min, n (%)	34 (27.2%)	26 (38.2%)	8 (14.0%)	0.002*
Need for Resuscitation, n (%)	51 (40.8%)	38 (55.9%)	13 (22.8%)	<0.001*
NICU Admission, n (%)	76 (60.8%)	56 (82.3%)	20 (35.1%)	<0.001*

*p-value<0,05, Statistically significant

Respiratory distress syndrome (RDS) was significantly more common in ≤34-week infants (58.8%) than in >34 weeks (14.0%, p<0.001). Neonatal sepsis occurred in 32.3% of early cases versus 15.8% of late cases (p = 0.03). Severe complications like intraventricular hemorrhage (IVH) were seen almost exclusively in the early gestation group (10.3% vs. 1.8%, p=0.05). Hyperbilirubinemia requiring phototherapy was also higher in ≤34-week infants (38.2%) than in >34 weeks (19.3%, p=0.02). Mechanical ventilation was needed far more frequently in early PPROM (26.4%) compared to later gestation infants (7.0%, p=0.006) (Table 4).

Table 4: Neonatal Morbidity Profile

Complications	Total (n=125)	GA ≤ 34 Weeks (n= 68)	GA > 34 Weeks (n= 57)	p-value
Respiratory Distress Syndrome	48 (38.4%)	40 (58.8%)	8 (14.0%)	<0.001*
Neonatal Sepsis	31 (24.8%)	22 (32.3%)	9 (15.8%)	0.030*
Intraventricular Hemorrhage	8 (6.4%)	7 (10.3%)	1 (1.8%)	0.050
Nec	6 (4.8%)	5 (7.4%)	1 (1.8%)	0.180
Hypoglycemia	14 (11.2%)	10 (14.7%)	4 (7.0%)	0.180
Hyperbilirubinemia	37 (29.6%)	26 (38.2%)	11 (19.3%)	0.020*
Mechanical Ventilation	22 (17.6%)	18 (26.4%)	4 (7.0%)	0.006*

*p-value<0,05, Statistically significant

Overall live-birth rate was 87.2%, significantly higher in the >34-week group (96.5%) compared to the ≤34-week group (79.4%, p=0.003). Early neonatal death occurred in 11.8% of ≤34-week neonates versus 1.8% of >34 weeks (p=0.03). Total perinatal mortality was markedly higher among early PPROM cases (20.6%) compared with late cases (3.5%, p=0.002). The mean NICU stay was significantly longer in ≤34-week infants (11.8 ± 4.1 days) than in >34-week infants (6.7 ± 2.3 days, p<0.001). Prematurity was reported in 10 cases, followed by sepsis (4 cases) and severe RDS (2 cases) (Table 5).

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Table 5: Perinatal Outcomes

Outcome	Total (n=125)	GA ≤ 34 Weeks (n= 68)	GA > 34 Weeks (n= 57)	p-value
Live births	109 (87.2%)	54 (79.4%)	55 (96.5%)	0.003*
Stillbirths	7 (5.6%)	6 (8.8%)	1 (1.8%)	0.110
Early Neonatal Death	9 (7.2%)	8 (11.8%)	1 (1.8%)	0.030*
Total Perinatal Mortality	16 (12.8%)	14 (20.6%)	2 (3.5%)	0.002*
Mean NICU Stay (Days)	9.6 ± 3.8	11.8 ± 4.1	6.7 ± 2.3	<0.001*
Primary Cause of Death (Prematurity / Sepsis / RDS)	10 / 4 / 2	–	–	–

DISCUSSION

This paper compared fetal outcomes of 125 pregnancies that were complicated by preterm premature membrane rupture (PPROM), and whether or not the gestational age of the fetus at the rupture location of membranes affected the morbidity and mortality of the neonatal outcome. The results clearly show that a previous gestational age (≤34 weeks) is significantly linked to poorer fetal outcomes, such as low birth weight, respiratory complications, NICU admission, and higher perinatal mortality. Such findings do not differ much from trends that have been continually recorded in past studies, in which prematurity and latency have been found to be extremely high following rupture of the membrane [13]. The maternal traits in our research revealed that patients with PPROM at 34 weeks and below had earlier rupture (31.2 ± 1.1 weeks), higher latency (4.4 ± 1.5 days), and universal antenatal corticosteroid administration. This belongs to clinical practice guidelines in which steroid administration is used in favor of early gestations to decrease the respiratory morbidity of neonates. The same trends have been observed in the previous studies, where the early PPROM is more likely to be preterm and more demanding and necessitates more intensive interventions in the antenatal care [14]. The increased utilization of steroids in this early age of pregnancy groups in our study is a reflection of this well-established management practice. Gestational age also differed a lot in terms of outcomes of delivery. Women with rupture less than or equal to 34 weeks were found to have higher rates of cesarean section (47.1%), probably related to fetal distress and other complications, including oligohydramnios, which was observed in 42.6% of early PPROM. This is unlike the >34-week group, whereby 73.7% gave birth in a vaginal delivery. The results can be compared with the existing literature that also mentions high rates of operative delivery in the early cases of PPROM because of the worsening fetal condition and decreased amniotic fluid [15]. Neonatal attributes also bring out the weakness of preterm babies. Infants born with a gestational age of ≤34 weeks reported a much lower mean birth weight (1.78 ± 0.34 kg), and 92.6% of them were in the low-birth-weight category. They also had lower Apgar scores, with 47.1 being found with an Apgar score below 7 at 1 minute. Also, the proportion of these neonates admitted to NICU was 82.3%, whereas in the group of those with >34 weeks, it reached 35.1%. These results coincide with past studies, which are unanimous that prematurity is the best indicator of respiratory complications, poor Apgar values, and immediate neonatal hypothermia [16]. The neonatal morbidity profile highlights the tremendous role of gestational age. The percentage of RDS was much greater in infants who were less than 34 weeks old (58.8) than in those who were older than 34 weeks (14.0), and this is consistent with the fact that surfactant deficiency is a significant problem among infants who are less than 34 weeks. Sepsis rates were on the higher side (32.3% vs. 15.8%), which is in line with earlier studies that demonstrated the risk of infection is highly exposed in case of long latency and underdeveloped immunity. The IVH complication, as well as mechanical ventilation, was also found to be much more prevalent in the early PPROM group in our study, which supports previous clinical data that prematurity dramatically increases the risk of neurological and respiratory complications [17]. In our study, the regression analysis showed the strongest independent predictors of adverse neonatal outcomes to include gestational age <34 weeks (OR 3.42) and birth weight <2.0 kg (OR 4.11). These results are consistent with the patterns that have been recorded in numerous prior studies, as low gestational age and low birth weight have been the strongest predictors of death and disability among the populations of PPROM [18]. Predictors of infection, e.g., neonatal sepsis, were also strongly associated in our data (OR 5.18), which is also a manifestation of the previously known fact of intra-amniotic infection as a predictor of poor neonatal outcomes. Perinatal mortality also demonstrates the disproportionate risk being undertaken by early cases of PPROM. The overall mortality was 12.8, whereas in the ≤34-week group, the mortality was 20.6; the subsequent gestations had a mortality of just 3.5. Most of the deaths were due to preterm birth, with sepsis and severe respiratory distress coming in second place. These results are congruent with the other studies that also found prematurity and infection as the most common causes of neonatal death in PPROM [19, 20]. In general, findings of this study support the importance of gestational age of rupture, birth weight, and fetal infection in the outcome of fetuses in PPROM. Our findings, which were similar to those of the previous studies, also indicate the universality of these predictors. Although high corticosteroid therapy, neonatal ventilation, and sepsis management have increased the survival rate, early PPROM is a risky situation demanding close monitoring, early intervention, and personalized perinatal care.

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This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. Additionally, long-term neonatal outcomes beyond the immediate perinatal period were not assessed. Larger multicentre prospective studies are recommended to evaluate long-term neonatal outcomes and optimize management strategies for early PPROM.

CONCLUSIONS

It was concluded that preterm premature rupture of membranes (PPROM) is strongly associated with adverse fetal outcomes, particularly when rupture occurs at ≤34 weeks of gestation. Infants in this early-gestation group demonstrated significantly higher risks of low birth weight, poor Apgar scores, respiratory distress syndrome, sepsis, and increased NICU admissions, ultimately resulting in a markedly higher perinatal mortality rate compared to later gestations.

Authors Contribution

Conceptualization: MS
Methodology: MJA
Formal analysis: AH
Writing and drafting: MS
Review and editing: MS, MJA, AH

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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Domperidone vs Metoclopramide: Comparative Evaluation of Efficacy in Treating Diabetic Gastroparesis

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ABSTRACT

Gastroparesis represents a diabetes-related condition that causes diabetic patients to experience nausea, vomiting, and bloating. **Objectives:** To evaluate the effectiveness of Domperidone and Metoclopramide for gastric emptying improvement and gastrointestinal symptom reduction in patients with diabetic gastroparesis. **Methods:** A total of participants were n=76. Data collection occurred through a study of diabetes patients with gastroparesis who were given Domperidone (10 mg three times daily) or Metoclopramide (10 mg three times daily) for six weeks. The researchers evaluated gastric emptying half-time (T½) as the main outcome, while considering symptoms of nausea, vomiting, and bloating. The study evaluated both negative side effects and participant medication adherence. **Results:** The gastric emptying reduction using Domperidone exceeded that of Metoclopramide following administration to patients, as Domperidone decreased T½ from 125.6 ± 18.4 minutes to 98.2 ± 15.6 minutes while Metoclopramide decreased T½ from 124.8 ± 17.9 minutes to 107.5 ± 16.9 minutes ($p = 0.04$). The patients who received Domperidone reported better decreases in nausea, vomiting, and early satiety symptoms than those who received Metoclopramide ($p=0.03$, $p=0.02$, and $p=0.04$). The occurrence of extrapyramidal symptoms together with QT prolongation proved more common in patients treated with Metoclopramide. Compliance was similar between groups. **Conclusions:** Diabetic patients with gastroparesis experienced superior gastric motility response and symptom relief after taking domperidone compared to metoclopramide, along with better outcomes regarding extrapyramidal symptom development.

INTRODUCTION

Diabetes mellitus (DM) is a common disease that affects millions of people worldwide. According to the latest data from the International Diabetes Federation (IDF), about 463 million people are living with diabetes, and this number is expected to rise. DM is a major health concern due to its complications, which can affect the heart, kidneys, and nerves. In addition to these issues, many diabetic patients also experience digestive problems, particularly with the movement of food through the stomach. One such condition, known as delayed gastric emptying (GE), can occur in up to 50% of people with type 1 or type 2 diabetes. This condition may cause symptoms like indigestion and gastroparesis, though some individuals may not experience any noticeable issues [1]. The gastrointestinal condition diabetic gastroparesis (DG) develops from diabetes mellitus complications by causing delayed stomach emptying, but excluding any physical blockages [2]. Diabetic gastroparesis impacts patients who have diabetes of long duration, especially those who maintain subpar blood sugar management [3]. Nausea, vomiting, bloating, and early satiety with abdominal discomfort result as serious symptoms from diabetic gastroparesis

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affecting the quality of patient life [4]. Diabetic gastroparesis places a significant burden on individuals with diabetes and the healthcare system. Despite its impact, the condition is often underdiagnosed and challenging to manage. This epidemiology, pathophysiology, clinical presentation, diagnostic approach, and treatment options for diabetic gastroparesis. The disorder is defined by delayed gastric emptying in the absence of mechanical obstruction and typically manifests with upper gastrointestinal symptoms such as nausea, vomiting, early satiety, postprandial fullness, bloating, and upper abdominal discomfort. [5]. An unpredictable food absorption pattern emerges from delayed gastric emptying in diabetic patients, causing complications with blood glucose control and exposing individuals to dangerous high and low blood glucose risk. Regular hospital admissions also occur because gastroparesis causes patients' development of nutritional issues, combined with subpar food management [6]. The leading approach to managing diabetic gastroparesis is through speeding up the stomach emptying process using medicines. The two principal medications utilized for the treatment of health conditions are Domperidone and Metoclopramide, and healthcare providers utilize them frequently for their patients [7]. The dopaminergic activity of dopamine antagonist drugs exhibits chemical similarity between Metoclopramide and Domperidone, yet their therapeutic benefits, side effects, and safety properties show significant differences between the two medications [8]. Medicating with domperidone through the gastrointestinal tract prevents dopamine receptors in the stomach from functioning to increase digestive movement without affecting the central nervous system. Metoclopramide produces extrapyramidal side effects, including dystonia, together with tardive dyskinesia and akathisia after crossing the blood-brain barrier because it functions as a dopamine antagonist like Domperidone [9]. Domperidone was used for the treatment of gastroparesis because it helps speed up stomach emptying and controls both nausea and vomiting symptoms. Health agencies restrict Domperidone distribution to certain areas because it carries a risk of QT prolongation, which makes patients vulnerable to arrhythmias. Clinical practitioners currently use metoclopramide to treat diabetic gastroparesis, although persistent long-term application raises worries about its capability to produce extrapyramidal side effects [3]. Both Domperidone effectiveness for treating gastroparesis symptoms by improving gastric emptying according to scientific research findings.

Research about these treatments mostly studied older adults but failed to provide sufficient evidence regarding their effectiveness and safety for younger patients [10]. The existing research gap regarding treatment options for diabetic gastroparesis will be addressed through direct comparison of Domperidone and Metoclopramide medications in a patient sample to evaluate both treatment effectiveness and adverse effect specifically targeting extrapyramidal symptoms and QT prolongation. This study aims to evaluate the effectiveness and security of Domperidone and Metoclopramide for gastric emptying improvement and gastrointestinal symptom reduction in patients with diabetic gastroparesis.

METHODS

It was a cross-sectional study and conducted from June 2024 to December 2024 at Combined Military Hospitals, Lahore. Ethical permission was taken from the ethical review board of Combined Military Hospital, Lahore, and granted ethical permission no (A/24/EC/454/2023). The participants' age range was 18-55 years. The required sample size was calculated using the WHO sample size calculator with the following assumptions: power = 80%, confidence level = 95%, significance level ( ) = 0.05, and expected mean difference in gastric emptying half-time (T½) of 10 minutes, with a standard deviation of 15 minutes based on prior studies. This yielded a required sample of 76 participants and split the participants evenly between the Domperidone (n=38) and Metoclopramide (n=38) groups. After eligibility screening and informed consent, participants were assigned to either the Domperidone or Metoclopramide group using a simple randomization method. A computer-generated random sequence was used to ensure random allocation. To maintain allocation concealment and minimize selection bias, sequentially numbered, sealed opaque envelopes were used to distribute participants into treatment groups. This method ensured that both the researchers and participants remained unaware of group assignment at the time of enrollment. Patients met the study criteria when they were diagnosed with diabetic gastroparesis through clinical signs such as presenting symptoms of nausea and vomiting, bloating, and early satiety, which required confirmation by gastric scintigraphy or breath test. The inclusion criterion referred to glycemic stability rather than optimal glycemic control. The study excluded patients who demonstrated QT prolongation or neurological disorders or had a history of gastrointestinal surgery and those using medications affecting gastric motility, alongside pregnant and lactating women. Each patient received either Domperidone 10 mg or Metoclopramide 10 mg three times daily for six weeks. The research evaluated gastric emptying half-time (T½) when measuring it both before treatment and after medication interventions. The research measured symptom severity levels using a 1-5-point Likert scale for nausea, vomiting, bloating, and early

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satiety while recording adverse effects as secondary results. The monitoring method for patient compliance relied on counting pills and self-report measures of medication usage. The data were analyzed by SPSS software version 21.0. Normality test was applied, and data were normally distributed. Statistical analysis was performed using paired t-tests for within-group comparisons and independent t-tests for between-group differences, with a p-value of < 0.05 considered statistically significant. The study was approved by the Institutional Review Board (IRB) and adhered to ethical guidelines in accordance with the Declaration of Helsinki.

RESULTS

The study participants from both the Domperidone and Metoclopramide groups exhibited identical baseline traits because their demographic data matched without any substantial variation. All variables presented p-values that exceeded the 0.05 threshold during initial measurements, thus establishing similarity between the Domperidone and Metoclopramide study groups (Table 1).

Table 1: Baseline Characteristics of Study Participants

Characteristics	Domperidone (n=38)	Metoclopramide (n=38)	p-value
Age (Years, Mean ± SD)	52.4 ± 8.3	50.8 ± 9.1	0.65
Gender (M/F)	17/21	19/19	0.76
Duration of Diabetes (years)	8.2 ± 2.5	7.9 ± 2.8	0.81
HbA1c (%)	7.6 ± 0.9	7.5 ± 1.0	0.89
Baseline Gastric Emptying T½ (min)	125.6 ± 18.4	124.8 ± 17.9	0.91

Both Domperidone and Metoclopramide groups achieved improved gastric emptying T½ values as their primary treatment effect. The study results showed significant differences in T½ reduction, where Domperidone achieved greater results by shortening the time from 125.6 ± 18.4 minutes to 98.2 ± 15.6 minutes compared to Metoclopramide, which shortened the time from 124.8 ± 17.9 minutes to 107.5 ± 16.9 minutes. The comparison between groups produced a statistically significant difference because the p-value reached 0.04. Gastric emptying improvements showed significantly greater effects with Domperidone compared to Metoclopramide based on the measured change in T½ value (Table 2).

Table 2: Primary Outcome – Gastric Emptying Half-Time (T½) Improvement

Characteristics	Domperidone (n=38)	Metoclopramide (n=38)	p-value
Baseline T½ (min, Mean ± SD)	125.6 ± 18.4	124.8 ± 17.9	0.91
Post-Treatment T½ (min, Mean ± SD)	98.2 ± 15.6	107.5 ± 16.9	0.04*
Mean Change in T½ (min)	27.4 ± 6.2	17.3 ± 5.8	0.02*

*p<0.05 indicates statistical significance

Domperidone treatment showed statistically significant reduction of vomiting and nausea, accompanied by p-values of 0.03 and 0.02 when compared to Metoclopramide treatment. The analysis proved that bloating decreased in both groups of patients, yet researchers observed no significant statistical divergence (p=0.07). Dry mouth symptoms decreased to a greater extent in patients receiving Domperidone medication based on a significant p-value of 0.04 (Table 3).

Table 3: Between-Group Comparisons Were Performed Using Independent t-Tests on Post-Treatment (6-Week) Symptom Scores

Symptoms (Likert Scale 0-5)	Domperidone (n=38) Baseline	Domperidone 6 Weeks	Metoclopramide (n=38) Baseline	Metoclopramide 6 Weeks	p-value (Final)
Nausea	3.8 ± 0.9	1.5 ± 0.8	3.7 ± 1.0	2.1 ± 0.9	0.03*
Vomiting	3.2 ± 1.1	1.2 ± 0.7	3.1 ± 1.2	2.0 ± 0.9	0.02*
Bloating	4.0 ± 0.8	2.2 ± 0.9	4.1 ± 0.7	3.0 ± 1.0	0.07
Early Satiety	3.6 ± 0.9	1.6 ± 0.8	3.5 ± 1.0	2.5 ± 0.9	0.04*

*p<0.05 indicates statistical significance

The incidence rates of sleepiness and dry mouth remained equal between the Domperidone treatment group and the Metoclopramide group. The occurrence of extrapyramidal symptoms existed only in patients who received Metoclopramide treatment (23.7%), while statistical analysis confirmed this difference (p=0.04). The analysis revealed QT prolongation on ECG in 18.4% of Domperidone patients without any similar observations in Metoclopramide patients, and this difference had a significant p-value of 0.04 (Table 4).

Table 4: Adverse Effects in Both Groups

Adverse Effects	Domperidone (n=38)	Metoclopramide (n=38)	p-value
Drowsiness	7 (18.4%)	12 (31.6%)	0.41
Dry Mouth	10 (26.3%)	12 (31.6%)	0.68
Extrapyramidal Symptoms	0 (0%)	9 (23.7%)	0.04*
QT Prolongation (ECG)	7 (18.4%)	0 (0%)	0.04*

*p<0.05 indicates statistical significance

The patient treatment completion rate between the Domperidone and Metoclopramide groups was similar since both groups had dropout rates of 7.9%, but the difference was not meaningful in statistical terms (p=0.39). Analysis showed that fewer patients (5.3%) receiving

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Domperidone took more than two medication doses improperly compared to patients (18.4%) under Metoclopramide, but these results lacked statistical significance (p=0.32) (Table 5).

Table 5: Patient Compliance Rates

Compliance Measures	Domperidone (n=38)	Metoclopramide (n=38)	p-value
Completed Full Treatment (%)	35 (92.1%)	31 (81.5%)	0.39
Missed >2 Doses (%)	2 (5.3%)	7 (18.4%)	0.32

DISCUSSION

This study evaluated the gastric emptying response, along with gastrointestinal motility symptoms like nausea, vomiting, bloating, and early satiety, between Domperidone and Metoclopramide treatments in diabetic patients. This study has incorporated studies demonstrating the superiority of Domperidone over Metoclopramide in improving gastric emptying and reducing gastrointestinal symptoms in diabetic gastroparesis. For instance, Bonetto *et al.* reported significantly better symptom control and fewer central nervous system side effects with Domperidone compared to Metoclopramide. Similarly, Domperidone's enhanced efficacy in reducing nausea and vomiting through peripheral dopamine antagonism without crossing the blood-brain barrier. These studies align with our findings of improved gastric emptying half-time (T½) and greater reduction in nausea, vomiting, and early satiety in the Domperidone group. The revised discussion now provides a more robust interpretation of our results in the context of existing literature [11]. The main research finding demonstrated that Domperidone produced better results than Metoclopramide for gastric emptying improvement by reducing T½ time by 27.4 minutes, while Metoclopramide reduced it by 17.3 minutes. Proposed research findings uphold previously reported research, which demonstrates that Domperidone outpaces Metoclopramide in its ability to quicken gastric emptying, especially during diabetic patient treatment. The gastrointestinal tissues specifically respond to Domperidone via dopamine receptors, which both improve gastrointestinal movement and reduce the time spent by digestion in the stomach [12]. According to research by Sanger and Andrews, Domperidone proves superior to Metoclopramide in treating diabetic gastroparesis by enhancing gastric emptying because Metoclopramide fails to provide effective treatment in this case due to broad dopaminergic receptor activity [13]. According to current research, data indicate that Domperidone exceeds Metoclopramide effectiveness by efficiently treating nausea and vomiting symptoms, together with early satiety reduction. The previous study by Galura *et al.* reported that Domperidone was better than Metoclopramide for treating gastroparesis, especially in diabetic patients [14]. Patients who took Domperidone showed their nausea and vomiting symptom severity decreased to 1.5 and 1.2 while maintaining statistical importance measured through p-values of 0.03 and 0.02. The study results validate those reported by Ibrahim *et al.* who demonstrated greater nausea and vomiting relief from Domperidone than Metoclopramide treatment for patients with upper gastrointestinal symptoms [15]. Domperidone produced more pronounced effects on both bloating and early satiety, yet statistics fail to confirm the improvement in bloating. Studies show that Domperidone demonstrates superior effectiveness for all gastrointestinal symptoms but fails to provide the same impact on bloating treatment as both medications [16]. Previous research has shown inconsistent findings about how prokinetic drugs affect bloating symptoms, including Domperidone for patients with gastroparesis, despite the agent showing effectiveness against nausea and vomiting according to the literature [17]. The number of adverse reactions increased in patients who received Metoclopramide treatment with EPS symptoms and QT prolongation as primary adverse effects. The patients taking Metoclopramide developed extrapyramidal symptoms in 23.7% of cases, whereas no such symptoms appeared in the Domperidone group. The established link between Metoclopramide-induced EPS risk explains this observation since this drug blocks dopamine at both peripheral and central locations. The main drawback of Metoclopramide appears during lengthy treatment periods because of its side effects [18]. The peripheral action of Domperidone makes it less likely to pass through the blood-brain barrier, thus minimizing EPS and similar central nervous system adverse reactions. Studies from previous research have documented that Domperidone causes QT prolongation in 18.4% of patients. Users of Domperidone should watch for QT prolongation because this side effect occurs less often than EPS but becomes a concern mainly in patients with heart conditions [19]. Both Domperidone and Metoclopramide showed high patient compliance. However, treatment efficacy was assessed separately, based on improvements in clinical outcomes such as gastric emptying half-time (T½) and reductions in symptom severity (nausea, vomiting, bloating, and early satiety), where Domperidone demonstrated superior therapeutic benefits [20].

This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. Additionally, the short follow-up period restricted evaluation of long-term efficacy and safety, particularly regarding cardiac adverse effects. Large multicentere randomized trials with longer follow-up are recommended to assess long-term outcomes and cardiac safety of Domperidone in diabetic gastroparesis.

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CONCLUSIONS

Based on the results of this study, Domperidone demonstrates superior effectiveness compared to Metoclopramide for treating diabetes-related gastric emptying impairment and reducing gastrointestinal symptoms, including nausea and vomiting and early satiety. Patients suffering from diabetic gastroparesis benefit more from peripheral Domperidone due to its minimal central side effects, which include extrapyramidal symptoms. Moreover, doctors need to maintain continuous QT prolongation monitoring despite this need. Research data demonstrates that Domperidone serves as a superior and safer alternative to Metoclopramide treatment for this patient demographic.

Authors' Contribution

Conceptualization: AS
Methodology: AS, AM, RY, MJF
Formal analysis: MK
Writing and Drafting: MK, ZB
Review and Editing: AS, AM, RY, MJF, MK, ZB

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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Comparison of Phenylephrine and Ephedrine in Managing Spinal-Induced Hypotension in Lower Segment Caesarean Section (LSCS)

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ABSTRACT

Spinal-induced hypotension is a frequent complication of spinal anesthesia during lower-segment caesarean section and may adversely affect maternal comfort and uteroplacental perfusion. Phenylephrine and ephedrine are commonly used vasopressors, but they differ in their cardiovascular effects. **Objectives:** To compare systolic blood pressure stabilization, heart rate changes, vasopressor dose requirements, and maternal outcomes between phenylephrine and ephedrine. **Methods:** This prospective observational comparative cohort study was conducted at the Department of Anesthesiology, Hazrat Bari Imam Sarkar Medical and Dental College, and Hazrat Bari Imam Sarkar Teaching Hospital, Islamabad. Two hundred parturient who developed spinal-induced hypotension were enrolled (100 received phenylephrine and 100 ephedrine). Hemodynamic parameters were recorded at baseline and at 3 and 6 minutes after vasopressor administration. Data were analyzed using an independent-samples t-test, a Mann–Whitney U test, and a Chi-square test. **Results:** Phenylephrine maintained significantly higher systolic blood pressure at 3 minutes (p=0.008). Ephedrine was associated with significantly higher pulse and heart rate (p=0.003 and p=0.004). Bradycardia was more frequent with phenylephrine (p=0.001), while tachycardia and higher repeat-dose requirements were more common with ephedrine (p=0.025 and p=0.017). Duration of hypotension was significantly shorter with phenylephrine (p=0.003). **Conclusions:** Both vasopressors effectively managed spinal-induced hypotension; however, phenylephrine provided more stable systolic control and faster recovery, whereas ephedrine caused greater heart rate variability.

INTRODUCTION

Spinal anesthesia is the preferred technique for lower-segment caesarean section because it provides a rapid onset of dense sensory and motor block, excellent postoperative analgesia, and a more favorable safety profile compared with general anesthesia [1]. Despite these advantages, spinal-induced hypotension remains a frequent and clinically significant complication, with reported incidence ranging from 60% to 80% in untreated patients [2]. The sudden reduction in systemic vascular resistance following sympathetic blockade may lead to maternal nausea, vomiting, dizziness, and, in severe cases, compromised uteroplacental perfusion and fetal well-being [3, 4]. To prevent and treat spinal-induced hypotension, vasopressors are routinely administered during caesarean delivery. Phenylephrine and ephedrine are the two most commonly used agents worldwide [5]. Phenylephrine is a selective α-adrenergic agonist that increases vascular tone and arterial pressure primarily

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through vasoconstriction, whereas ephedrine has mixed α- and β-adrenergic activity, resulting in increases in both blood pressure and heart rate [6, 7]. Ephedrine, by contrast, is both an alpha and beta agonist, thereby increasing both heart rate and blood pressure [8]. These pharmacological differences produce distinct hemodynamic profiles that may influence maternal cardiovascular stability and fetal outcomes. Previous studies comparing phenylephrine and ephedrine have reported variable findings. Some investigations suggest that phenylephrine provides more consistent systolic blood pressure control with fewer fetal metabolic effects, while others favor ephedrine for reducing the incidence of reflex bradycardia [9, 10].

However, discrepancies in study design, dosing regimens, and patient populations have resulted in continued variation in clinical practice, particularly in resource-limited settings. This study aimed to compare the hemodynamic responses and maternal outcomes associated with phenylephrine and ephedrine in parturient who developed spinal-induced hypotension during elective caesarean section, with specific emphasis on blood pressure trends, heart rate changes, vasopressor dose requirements, duration of hypotension, and maternal recovery outcomes.

METHODS

This study was conducted as a prospective observational comparative cohort study to evaluate the hemodynamic effects of phenylephrine and ephedrine in parturient developing spinal-induced hypotension during lower-segment caesarean section (LSCS). The study was carried out at the Department of Anesthesiology, Hazrat Bari Imam Sarkar Medical and Dental College, and Hazrat Bari Imam Sarkar (HBS) Teaching Hospital, Islamabad, Pakistan. Ethical approval was obtained from the Institutional Review Board of Hazrat Bari Imam Sarkar Medical and Dental College, Islamabad (Approval No. Appl #HBS/IRB/25/25). The study was conducted over a period of three months from July to October 2025. The required sample size was calculated before study initiation to ensure adequate statistical power. A difference in systolic blood pressure between the two vasopressor groups was taken as the primary outcome variable. The following formula for comparison of two independent means was used: $n = 2(Z_{\alpha/2} + Z_{\beta})^2 \times \sigma^2 / d^2$. Where: $Z_{\alpha/2} = 1.96$ (for 95% confidence), $Z_{\beta} = 0.84$ (for 80% power), $\sigma = 6.5$ mmHg (standard deviation of systolic blood pressure obtained from the study by Ngan *et al.* Anesthesiology [11],], d= minimum clinically significant difference. Based on this calculation, the minimum required sample size was 172 participants. To account for possible incomplete data, a final sample size of 200 parturient (100 per group) was enrolled. A purposive sampling technique was employed. All eligible women who developed spinal-induced hypotension during LSCS and required vasopressor therapy were consecutively included. Written informed consent was taken. This technique was selected because the study targeted a specific clinical subgroup, and randomization was not ethically feasible as vasopressor selection followed routine anaesthetic practice. Purposive sampling ensured that only clinically relevant cases were included while maintaining the observational nature of the study. The inclusion criteria comprised women aged 18–45 years with singleton pregnancies undergoing elective lower-segment caesarean section under spinal anesthesia and classified as ASA physical status I or II. Spinal-induced hypotension was defined as a systolic blood pressure of <90 mmHg or a ≥20% reduction from baseline values. Patients with chronic hypertension, pre-eclampsia, underlying cardiac disease, arrhythmias, or multiple gestations were excluded. Baseline variables, including age, weight, height, body mass index, parity, and ASA status, were recorded. Blood pressure and heart rate were measured before spinal anesthesia, at the onset of hypotension, and at 3- and 6-minutes following vasopressor administration. Dose requirements, the incidence of bradycardia and tachycardia, and the duration of hypotension were documented. To ensure measurement reliability, all patients were monitored using calibrated automated blood pressure devices, and heart rate was cross-checked using electrocardiographic monitoring. Data collectors received standardized training and supervision, and all entries were verified prior to data entry into SPSS. Data were analyzed using SPSS version 22.0. Normality of continuous variables was assessed using the Shapiro–Wilk test. Age, weight, and height demonstrated normal distribution and were summarized as mean ± standard deviation and compared using an independent-samples t-test. All baseline hemodynamic variables and maternal outcome variables showed non-normal distribution and were analyzed using Mann–Whitney U test. Categorical variables were analyzed using the chi-square test. A p-value≤0.05 was considered statistically significant. Normality testing was performed using the SPSS Explore procedure. Shapiro–Wilk test results demonstrated that age, weight, and height were normally distributed (p>0.05), while baseline hemodynamic and maternal outcome variables were non-normally distributed (p<0.05).

RESULTS

Baseline demographic and clinical variables were statistically comparable between the two groups. Normality of continuous variables was assessed using the Shapiro–Wilk test before inferential analysis. Shapiro–Wilk

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normality testing showed that age, weight, and height were normally distributed (p>0.05), whereas maternal outcome variables and baseline hemodynamic parameters demonstrated non-normal distribution (p<0.05). An independent-samples t-test demonstrated no significant differences in age, weight, and height. Mann-Whitney U test revealed no significant differences in BMI and all baseline hemodynamic parameters (SBP, DBP, MAP, pulse rate, and heart rate). Parity and ASA classification were similarly distributed between the groups (p>0.05 for all), confirming baseline equivalence before vasopressor administration (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics of Study Participants

Variables	Phenylephrine (n=100)	Ephedrine (n=100)	p-value	Test
Age (Years)	26.01 ± 5.28	25.94 ± 4.58	0.920[a]	t-test[a]
Weight (kg)	67.78 ± 6.22	67.49 ± 8.73	0.790[a]	t-test[a]
Height (cm)	163.04 ± 8.43	165.01 ± 10.81	0.153[a]	t-test[a]
BMI	25.53 ± 1.89	25.09 ± 4.60	0.087[b]	Mann-Whitney[b]
Baseline SBP (mmHg)	119.81 ± 7.34	119.30 ± 7.88	0.522	Mann-Whitney[b]
Baseline DBP (mmHg)	78.00 ± 6.85	77.77 ± 7.22	0.929	Mann-Whitney[b]
Baseline MAP (mmHg)	91.94 ± 6.39	91.61 ± 6.94	0.799	Mann-Whitney[b]
Baseline Pulse (bpm)	95.66 ± 12.38	95.03 ± 14.26	0.793	Mann-Whitney[b]
Baseline Heart Rate (bpm)	97.19 ± 12.34	96.53 ± 14.24	0.786	Mann-Whitney[b]
Primiparous	49 (49%)	57 (57%)	0.257	χ^{2c}
ASA I	57 (57%)	59 (59%)	0.774	χ^{2c}

[a]Independent samples t-test, [b]Mann-Whitney U test, [c]Chi-square test, Significance set at p≤0.05

At the onset of hypotension and at 6 minutes, there were no significant differences in systolic, diastolic, or mean arterial pressure between groups (p>0.017). At 3 minutes, systolic blood pressure was significantly higher in the phenylephrine group (U=3922, p=0.008). Pulse rate and heart rate were significantly higher in the ephedrine group at 3 minutes (p=0.003 and p=0.004, respectively). No significant between-group differences were observed at 6 minutes (Table 2).

Table 2: Comparison of Hemodynamic Parameters Between Phenylephrine and Ephedrine Groups at Different Time Intervals After Spinal Anesthesia

Variables	Time	Phenylephrine	Ephedrine	U	p-value
Systolic BP (mmHg)	After Spinal	92.85 ± 6.45	92.38 ± 6.71	4738	0.522
	3 Min	88.88 ± 5.41	86.85 ± 4.51	3922	0.008*
	6 Min	92.30 ± 4.09	90.97 ± 5.17	4325	0.098
Diastolic BP (mmHg)	After Spinal	68.07 ± 6.29	68.02 ± 6.61	4945	0.893
	3 Min	65.63 ± 6.52	65.41 ± 6.67	4992	0.984
	6 Min	67.12 ± 6.44	66.78 ± 6.93	4945	0.893
MAP (mmHg)	After Spinal	76.33 ± 5.70	76.14 ± 6.17	4906	0.818
	3 Min	73.40 ± 4.82	72.54 ± 4.81	4547	0.267
	6 Min	75.54 ± 4.61	74.85 ± 4.99	4565	0.287
Pulse (bpm)	After Spinal	79.70 ± 13.37	81.40 ± 14.45	4553	0.275
	3 Min	74.81 ± 25.52	85.22 ± 27.71	3792	0.003*
	6 Min	77.20 ± 14.42	80.44 ± 17.08	4465	0.191
Heart Rate (bpm)	After Spinal	80.90 ± 13.39	82.53 ± 14.51	4574	0.298
	3 Min	76.35 ± 25.31	86.66 ± 27.78	3813	0.004*
	6 Min	78.32 ± 14.43	81.43 ± 17.05	4495	0.217

Mann-Whitney U test. *Significant at Bonferroni-adjusted p ≤ 0.017.

The incidence of bradycardia was significantly higher in the phenylephrine group compared with the ephedrine group (χ^2 = 10.602, p=0.001). Conversely, tachycardia occurred more frequently among women receiving ephedrine (χ^2 = 5.007, p=0.025). The distribution of total repeat-dose requirements also differed significantly between groups, with a greater proportion of women in the ephedrine group requiring additional doses for hemodynamic stabilization (χ^2 = 5.704, p=0.017) (Table 3).

Table 3: Comparison of Maternal Bradycardia, Tachycardia and Vasopressor Dose Requirements

Variables	Category	Phenylephrine (n=100)	Ephedrine (n=100)	χ^2	p-value	Cramer's V
Bradycardia	Yes	40 (40%)	19 (19%)	10.602	0.001*	0.230
	No	60 (60%)	81 (81%)			
Tachycardia	Yes	15 (15%)	28 (28%)	5.007	0.025*	0.158
	No	85 (85%)	72 (72%)			
Total Doses Required	1 dose	42 (42%)	26 (26%)	5.704	0.017*	0.169
	2-3 Doses	58 (58%)	74 (74%)			

Chi-square test. *p ≤ 0.05 indicates statistical significance.

The duration of hypotension was significantly shorter in the phenylephrine group compared with the ephedrine group (U=3861.5, p=0.003). Delivery duration and total length of hospital stay did not differ significantly between groups (p>0.05) (Table 4).

Table 4: Comparison of Maternal Outcomes Between Phenylephrine and Ephedrine Groups

Outcomes	Phenylephrine (n=100)	Ephedrine (n=100)	U	p-value
Duration of Hypotension (min)	4.89 ± 2.12	5.79 ± 2.14	3861.5	0.003*
Delivery Duration (min)	65.35 ± 19.58	68.05 ± 21.31	4578.0	0.302
Total Hospital Stay (Days)	2.85 ± 1.45	3.05 ± 1.46	4613.5	0.335

Mann-Whitney U test. *p ≤ 0.05 indicates statistical significance.

Phenylephrine maintained significantly higher systolic blood pressure at 3 minutes (p = 0.008), while no significant differences were observed at baseline and at 6 minutes (Figure 1).

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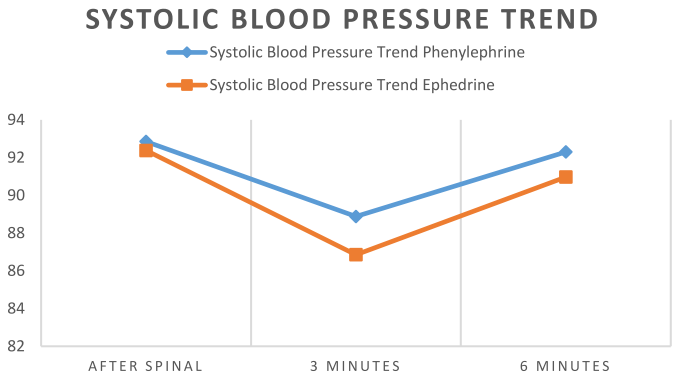

Figure 1: Trend of Systolic Blood Pressure After Spinal Anesthesia and Vasopressor Administration in Phenylephrine and Ephedrine Groups

DISCUSSION

This study compared the hemodynamic effects of phenylephrine and ephedrine in women who developed spinal-induced hypotension during lower-segment caesarean section. Baseline demographic and clinical comparability between the two groups allowed for an unbiased assessment of treatment effects. There were no statistically significant differences in age, body mass index, obstetric history, or ASA physical status. Both cohorts entered surgery with comparable systolic and diastolic blood pressure values and similar baseline heart rates, strengthening the validity of the comparative analysis. A distinct difference emerged following vasopressor administration. Phenylephrine more effectively maintained systolic blood pressure at the 3- and 6-minute intervals and exhibited a more stable hemodynamic profile than ephedrine. These findings are consistent with previous randomized and observational studies reporting superior systolic blood pressure stability with phenylephrine during caesarean delivery under spinal anesthesia [12, 13]. Similar results have been reported in tertiary centers across Asia, where phenylephrine was associated with more rapid recovery of blood pressure and minimal fluctuation in systolic values [14, 15]. Furthermore, a network meta-analysis ranked phenylephrine among the safest vasopressors for managing spinal-induced hypotension in parturient without cardiac comorbidities [16]. Ephedrine demonstrated a more pronounced chronotropic effect. Women receiving ephedrine showed significantly higher pulse and heart rates at three minutes, consistent with its mixed α- and β-adrenergic agonist activity. These findings align with recent randomized controlled trials that reported increased maternal heart rates following ephedrine administration [17, 18]. Consequently, ephedrine may be less suitable for patients who are tachycardic or have limited cardiac reserve. Bradycardia occurred more frequently in the phenylephrine group, whereas tachycardia was more prevalent in the ephedrine group. This distribution mirrors recent systematic reviews indicating that pure α-agonists enhance vagal tone, while ephedrine produces stronger cardiac stimulation [19]. Although both adverse effects were clinically manageable, these findings provide useful guidance for tailoring vasopressor selection according to individual hemodynamic profiles. Patients receiving phenylephrine required fewer repeat doses, while a higher proportion of women in the ephedrine group required three doses to achieve hemodynamic stability. Previous comparative studies have shown that ephedrine has a slower onset and shorter duration of action, necessitating more frequent dosing [20]. The significant chi-square results in this study support this observation and suggest a clinically relevant difference in drug utilization and workload. There were no significant differences in delivery duration or length of hospital stay between the two groups. However, the significantly shorter duration of hypotension observed in the phenylephrine group is clinically meaningful. Rapid correction of hypotension has been associated with reduced intraoperative discomfort and a lower incidence of nausea and dizziness [21]. Although fetal outcomes were not evaluated in this study, emerging international evidence supports phenylephrine for improved fetal acid–base balance, particularly during prolonged hypotension. Overall, these findings support the growing body of evidence recommending phenylephrine as the first-line vasopressor for treating spinal-induced hypotension during caesarean delivery. The consistency of results across multiple regions further strengthens the generalizability of these findings.

This was a single-center study with a relatively small sample size, which may limit the generalizability of the findings. In addition, neonatal outcomes and fetal acid–base status were not assessed, restricting evaluation of fetal effects. Future multicentre randomized studies incorporating neonatal outcomes are recommended to further define the optimal vasopressor for spinal-induced hypotension during caesarean delivery.

CONCLUSIONS

Both phenylephrine and ephedrine are effective for managing spinal-induced hypotension during caesarean delivery. However, phenylephrine provides superior systolic blood pressure stability, requires fewer repeat doses, and is associated with a shorter duration of hypotension. Ephedrine, while effective, produces greater heart rate responses and necessitates more frequent dosing. These findings, supported by contemporary international literature, suggest that phenylephrine offers a more predictable hemodynamic profile for routine obstetric anesthesia. Nevertheless, vasopressor selection should be individualized, particularly in patients with susceptibility to bradycardia or tachycardia.

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Authors' Contribution

Conceptualization: SKJ
Methodology: UJ, AS
Formal analysis: WA[1], WA[2]
Writing and drafting: MS, SKJ, UJ, AS, WA[1], WA[2], ZR
Review and editing: MS, SKJ, UJ, AS, WA[1], WA[2], ZR

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 of Urinary Retention in Guillain-Barré Syndrome Patients

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ABSTRACT

The Guillain-Barré Syndrome (GBS) is an acute autoimmune polyneuropathy that can also have autonomic dysfunction, which leads to complications like urinary retention. These autonomic disorders should be identified early to reduce morbidity and avoid secondary complications, and improve patient outcomes. **Objective:** To determine the frequency of urinary retention among GBS patients. **Methods:** This retrospective cross-sectional study involves 129 patients diagnosed with GBS from 18 July 2025- 18 October 2025 at the Department of Neurology, Pak Emirates Military Hospital. Information on age, gender, body mass index, and disease severity was determined using the Hughes Functional Grading Scale. The presence of urinary retention was determined clinically. Chi-square test and logistic regression were applied to determine significant associations, considering $p<0.05$ as statistically significant. **Results:** A total of 129 patients were included with a mean age of 57.2 ± 17.3 years, predominantly females comprising 58.1%. The mean BMI was 30.2 ± 3.5 kg/m^2. Urinary retention was observed in 13 (10.4%) patients and is significantly more common among older patients (mean age 67.1 ± 8.9 years, $p=0.02$) and those with severe disease ($p=0.01$). No significant associations were found with gender ($p=0.34$), BMI ($p=0.21$), or area of residence ($p=0.42$). **Conclusions:** Urinary retention is a notable autonomic manifestation in GBS, particularly among older and severely affected patients. Early detection and management can help prevent urinary complications and reduce the duration of hospital stays.

INTRODUCTION

Guillain-Barré Syndrome (GBS) is an acute autoimmune polyneuropathy characterized by muscle weakness, areflexia, and sensory disorders that affect the patient's quality of life. The estimated prevalence of GBS was 1.1 to 1.8 per 100,000 persons [1]. The prevalence is 1.9 in high-income Asian Pacific regions and 0.8 in East Asia per 100,000 [2]. Among various variants of GBS, the most prevalent type was acute motor axonal neuropathy (AMAN) with a prevalence of 59%, followed by acute motor sensory axonal neuropathy (AMSAN) as 25.6% and 15.3% as acute inflammatory demyelinating polyradiculoneuropathy (AIDP) [3]. GBS can affect both the peripheral nervous system and the autonomic nervous system, resulting in a broad spectrum of complications, including life-threatening respiratory failure, cardiovascular instability, and bladder dysfunction, all of which require careful medical management [4]. About 40 to 45% of GBS patients developed Autonomic dysfunction, which leads to blood pressure (BP), tachycardia, and urinary retention. Urinary retention indicates a sever Autonomic involvement associated with longer hospital stays and higher mortality rates [5, 6]. Older patients and high disability scores are important risk factors. Research studies have documented varying frequencies of urinary retention among GBS patients, with reported rates fluctuating between 14% and 50%, influenced by factors such as the specific population studied and the diagnostic criteria applied [7]. This condition not only complicates the overall clinical course of the disease but also increases the risk of the development of secondary problems, such as UTIs, sepsis, and

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prolonged hospitalization, thus further burdening patients and healthcare systems [8]. According to another study, an additional 12 hours, 4 weeks after the onset of the symptoms, and approximately 25 percent of patients develop acute urinary symptoms like difficulty in voiding or acute urinary retention. The persistent overactive bladder and nocturia are long-term urinary symptoms. The most important urologic interventions are indwelling catheter in the acute phase, especially when the patient has respiratory failure, intermittent catheterization due to retention; the patient is still able to use his hands, voiding trial; and anticholinergics in case of persistence of overactive bladder after recovery [9].

Despite its clinical relevance, the exact frequency and pattern of urinary retention in patients with GBS remain underexplored in local populations, where demographic and disease variants may influence outcomes. The study helps to identify the burden of this complication in order to improve monitoring of patients, guide timely urological interventions, reduce duration of stay, and morbidity, thereby contributing to improved prognostic and rehabilitative outcomes in the care of GBS patients. This study aimed to identify the frequency of urinary retention among GBS patients and to emphasize its clinical implications for early recognition and management.

METHODS

This retrospective cross-sectional study was conducted at the Department of Neurology, Pak Emirates Military Hospital, from 18 July 2025- 18 October 2025, based on a sample of 129 GBS patients, calculated through WHO software by keeping an estimated prevalence of urinary retention among GBS patients as 9.2% [10], confidence level of 95%, and 5% margin of error. The data were collected from March 2024 to March 2025. The approval for the study was obtained from the Ethical Committee of Pak Emirates Military Hospital, Rawalpindi, under reference no: A/28/ERC/31/2025. Informed consent was obtained from patients or guardians. The inclusion criteria were patients of either gender, aged ≥18 years, diagnosed with GBS as per Brighton criteria, and having complete medical and personal records available. Patients with pre-existing bladder dysfunction or neurogenic bladder, a history of urinary tract obstruction or urological surgery, and with concurrent spinal cord injury or other neurological disorders affecting bladder function, or missing clinical information were excluded. GBS was diagnosed based on the Brighton criteria, which include progressive bilateral limb weakness, decreased or absent deep tendon reflexes, a monophasic illness pattern, and supportive cerebrospinal fluid and electrodiagnostic findings [11]. Severity of GBS was assessed using the Hughes Functional Grading Scale (HFGS), a validated functional disability scale for Guillain–Barré syndrome [12]. The HFGS grades functional status as: Grade 0 (healthy), Grade 1 (minor symptoms, able to run), Grade 2 (able to walk ≥10 m without assistance but unable to run), Grade 3 (able to walk ≥10 m with assistance), Grade 4 (bedridden or chair-bound), Grade 5 (requiring assisted ventilation), and Grade 6 (death). For analytical purposes, disease severity was categorized as mild (Grades 1–2), moderate (Grades 3–4), and severe (Grade 5). All grading was performed by a senior consultant neurologist during the hospital stay, minimizing inter-observer variability. Urinary Retention was defined as the inability to voluntarily void urine, requiring catheterization, with a post-void residual (PVR)volume of >300 mL confirmed by bladder ultrasound, performed using a Mindray DC-N3 ultrasound system with a 3.5–5 MHz convex transducer. PVR was measured within 10 minutes after an attempted voluntary voiding, with the patient in the supine position. All sonographic assessments were conducted by trained radiology technicians using the same ultrasound machine. Baseline demographic and clinical data, including age, gender, BMI, residence, medical history, neurological findings, and bladder status, were obtained retrospectively from hospital medical records, including admission notes, neurology progress notes, and investigation reports. Data extraction was carried out using a predesigned structured questionnaire to ensure uniformity and completeness of recorded variables. The data were analyzed through SPSS version 27.0. Categorical variables like gender, residence, GBS severity, and presence/absence of urinary retention were presented as frequencies and percentages, while continuous variables like age and BMI were presented as mean ± standard deviation (SD) or median (IQR), depending on data normality through Shapiro Wilk test. Age, gender, BMI, and GBS severity were stratified as presence/absence of urinary retention. Post-stratification Chi-square or Fisher's exact test was used, with the p-value of ≤0.05 considered significant.

RESULTS

This study includes 129 GBS patients. The mean age was 57.2 ± 17.3 years, predominantly female 75 (58.1%), and the mean BMI of patients was 29.71 ± 3.3 kg/m^2. In terms of residence, 78 (60.5%) were from urban areas. Regarding disease severity (based on the Hughes Functional Grading Scale, HFGS), 67 (51.9%) of patients had mild GBS, 35 (27.1%) had moderate, and 27 (20.9%) had severe disease. The overall frequency of urinary retention was 13 (10.4%) (Table 1).

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Table 1: Baseline Demographics and Clinical Characteristics

Variables	Mean ± SD, n (%)
Age	
Years	57.2 ± 17.3
Gender	
Female	75 (58.1%)
Male	54 (41.9%)
Residence	
Urban	78 (60.5%)
Rural	51 (39.5%)
GBS Severity (HFGS)	
Mild (Grade 1–2)	67 (51.9%)
Moderate (Grade 3–4)	35 (27.1%)
Severe (Grade 5)	27 (20.9%)
Others	
BMI (kg/m^2) - Mean ± SD	29.71 ± 3.3
Urinary retention	13 (10.4%)

Urinary retention was significantly associated with older age (p=0.008) and greater disease severity (p=0.024). No significant association was found with gender (p=0.16), BMI (p = 0.41), or residence (p=0.58) (Table 2).

Table 2: Urinary Retention versus Clinical Variables

Characteristics	Urinary Retention Present (n=13), Mean ± SD, n (%)	Urinary Retention Absent (n=116), Mean ± SD, n (%)	p-value
Age			
Years	68.4 ± 3.2	55.7 ± 6.5	0.008*
Gender			
Male	5 (7.0%)	70 (93.0%)	0.160
Female	8 (14.8%)	46 (85.2%)	
Residence			
Urban	8 (10.3%)	70 (89.7%)	0.580
Rural	5 (9.8%)	46 (90.2%)	
GBS Severity (HFGS)			
Mild (1–2)	1 (2.9%)	34 (97.1%)	0.024*
Moderate (3–4)	7 (10.4%)	60 (89.6%)	
Severe (5)	5 (22.2%)	22 (81.5%)	
Others			
BMI (kg/m^2)	27.5 ± 3.9	26.7 ± 4.1	0.410

Note: t-test used to compare the continuous variable. *p-value<0.05 was significant. Fisher's Exact test was used to compare categorical variables. *p-value<0.05 was significant.

Binary logistic regression showed that increasing age and greater GBS severity were significant independent predictors of urinary retention. Each one-year increase in age raised the odds of urinary retention by 5% (AOR = 1.05, p=0.015), while patients with severe GBS had nearly fivefold higher odds of developing urinary retention compared to those with mild disease (AOR = 4.89, p=0.035). However, gender and BMI were not significant predictors (Table 3).

Table 3: Binary Logistic Regression Analysis taking Urinary Retention as Dependent Variable

Variables	Coefficient	Adjusted OR (95% CI)	p-value
Age (Years)	0.049	1.05 (1.01 – 1.10)	0.015*
Gender (Female)	0.742	2.10 (0.72 – 6.11)	0.176
BMI (kg/m^2)	0.066	1.07 (0.91 – 1.26)	0.402
GBS Severity (Severe vs Mild)	1.588	4.89 (1.12 – 21.4)	0.035*
Constant	-6.215	–	0.002*

*p-value<0.05 was significant.

DISCUSSION

This study demonstrated urinary retention in 10.4% of GBS patients, making it an important manifestation of autonomic dysfunction. This frequency, though lower than the 14–50% range reported in the literature, is of clinical significance. Pagaling *et al.* [6] reported dysautonomia, including urinary retention, in 49% of GBS cases in the Philippines [6], while Ogawa *et al.* linked urinary retention with hyponatremia and poorer clinical outcomes [8]. Combined with other findings, they indicate that bladder impairment is indeed an important constituent of autonomic disturbance in GBS, a factor that explains a longer hospitalization and a higher degree of morbidity [8]. The lower rate of urinary retention in our study may have been due to the differences in population and definition of urinary retention in different studies, as well as the distribution of GBS subtype, which was not measured in our cohort. Also, being a retrospective study, there is always a possibility of some under-detection, as not all patients may have recorded their bladder symptoms or their PVR regularly. Autonomic dysfunction develops in GBS patients in 40–45% of the cases [5] because of the demyelination or axonal injury of the autonomic fibers controlling cardiovascular and urinary functions [13, 14]. In our study, older age was independently related to urinary retention, in line with the study of Chen *et al.* who demonstrated that the higher age-related decline in autonomic function increases the risk of dysautonomia [15]. Elderly patients might have weak compensatory responses, and this is perhaps the explanation for their increased susceptibility to urinary retention. Disease severity had a strong correlation with urinary retention, where the odds for patients with severe GBS were approximately fivefold compared to those with mild disease. Our finding is in line with previous studies that have associated higher disability scores in GBS with greater autonomic involvement [6, 8]. Severe forms likely reflect more extensive neural damage implicating both motor and autonomic pathways. While gender, BMI, and residence showed no significant association, female predominance in some reports [16] suggests that hormonal or physiological differences may occasionally contribute, but these factors are seemingly

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secondary to disease severity. Urinary retention in GBS is a clinical issue that needs to be spotted in time to prevent the complications of urinary tract infections and sepsis. Constant bladder observation and prompt catheterization of the bladder is essential preventative measures [17, 18]. Moreover, its correlation with hyponatremia also predetermines the importance of keeping track of electrolyte imbalance and other indicators of autonomic instability of the state, which is described by Ogawa et al. [8]. Autonomic recovery can be enhanced by early administration of supportive therapies such as intravenous immunoglobulin or plasmapheresis [19-21].

The retrospective and cross-sectional study design with a single center design is the only one that restricts generalizability because of the moderately sized sample. The subtypes of the electrophysiological type were not examined. The future research should include subtype correlation and follow-up on long-term persistence of bladder dysfunction after the recovery. These results highlight the importance of close autonomic surveillance of patients at risk to enhance the prognosis and decrease the number of complications in the hospitalization environment.

CONCLUSIONS

Urinary retention represented one of the important presentations of autonomic dysfunction. Increasing age and high disease severity were found to be independently significantly related to urinary retention, while gender, BMI, and residence were not significantly related to the condition. These findings stress the need for early recognition and continued bladder monitoring during hospitalization with GBS, especially in elderly patients and those with severe neurological impairment.

Authors Contribution

Conceptualization: AR
Methodology: AR, WWM
Formal Analysis: FW
Writing and Drafting: WWM FA, MM, TK
Review and Editing: AR, WWM, FA, MM, FW, TK

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 Obstructive Sleep Apnea and Ischemic Stroke: A Case-Control Study

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ABSTRACT

Previous evidence has suggested an association between obstructive sleep apnea (OSA) and cardiovascular and cerebrovascular conditions. There is, however, little data examining the prevalence and severity of OSA among individuals with ischemic stroke, specifically within Pakistan. **Objectives:** To determine if the prevalence and severity of OSA were significantly higher in individuals with ischemic stroke compared to age and gender matched control participants without a stroke. **Methods:** A case-control study was conducted at Khyber Teaching Hospital. A total of 184 individuals were enrolled in the study. The study consisted of 92 individuals diagnosed with ischemic stroke supported by radiographic evidence and 92 individuals without cerebrovascular disease, all matched for age and sex. Clinical and demographic data were collected using a standard questionnaire. Participants who scored ≥3 on the STOP-BANG questionnaire were referred for Type III daytime portable polysomnography testing. **Results:** Participants with ischemic stroke had significantly higher rates of OSA (AHI ≥5) than controls (80.4% in stroke vs 50.0% in controls, p<0.0001). The incidence of severe OSA in stroke participants was 26.1% compared to only 6.5% of control participants. **Conclusions:** Many patients who experience an ischemic stroke also have OSA (Obstructive Sleep Apnea), and OSA increases the risk of having a stroke independent of the actual ischemic stroke. This evidence supports the use of OSA screening and treatment as part of their prevention strategies against future strokes.

INTRODUCTION

Obstructive Sleep Apnea (OSA) is recurrent, mostly under-identified, and very frequent, with an estimated incidence of 936 million adults aged 30 to 69 years worldwide, 425 million of whom have moderate to severe OSA [1]. Recurring episodes of upper airway obstruction occur during sleep in patients with OSA, often associated with intermittent hypoxia, decreased sleep efficiency, and the activation of the SNS [2]. Clinical signs and symptoms associated with OSA include excessive daytime fatigue, witnessed apneas, and the presence of snoring. There has been increased attention to the relationship between OSA and cardiovascular and cerebral vascular diseases over the last few years [3]. Ischemic stroke constitutes a serious vascular effect of OSA and is typically caused by an obstruction of blood flow to the brain [4]. There are many people globally who suffer from ischemic stroke each year, and over 5 million people die due to ischemic stroke [5]. Stroke is currently ranked as the second leading cause of death globally today and the third leading cause of long-term disability worldwide [6]. In this case, over 87% of all

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strokes are classified as ischemic strokes [7]. Understanding modifiable risk factors for ischemic strokes, particularly those due to sleep-disordered breathing or OSA, is essential to early identification, prevention, and intervention of such strokes. Numerous pathophysiological processes, such as systemic inflammation, oxidative stress, endothelial dysfunction, hypercoagulability, and hyperactivity of the sympathetic nervous system, are shared by OSA and ischemic stroke [4]. Reactive oxygen species and pro-inflammatory cytokines are produced in greater quantities when OSA patients experience nocturnal hypoxemia regularly [8]. This can harm the cerebral vasculature and encourage atherosclerosis. Additionally, OSA can exacerbate insulin resistance, hypertension, and atrial fibrillation, all of which are recognized risk factors for stroke [4]. These findings suggest that, concomitant with other traditional cardiovascular comorbidities, OSA can be a risk factor for ischemic stroke. There have been studies that investigated the relationship between OSA and stroke and therefore, people with moderate to severe OSA are at a risk of stroke two to three times higher [9, 10]. The severity of sleep apnoea was significantly correlated with the risk of incident stroke and especially in men, according to the Sleep Heart Health Study [11]. Stroke is one of the most common causes of death and disability in such countries as Pakistan, ischemic stroke being the major part of them [12]. At the same time, OSA is progressively becoming a diagnosis in adults of middle-aged and old age, especially with obesity and metabolic syndrome but is not frequently considered in the regular risk screening assessments of stroke. The overlap of the symptomatology and inaccessibility to a polysomnography can lead to OSA remaining undiagnosed in a considerable proportion of stroke patients, meaning that a second-time prevention may be overlooked. Assessment of the burden and the impact of OSA in populations with stroke is urgently needed based on well-designed and locally relevant research studies. The detection of OSA in patients with ischemic stroke may help in instituting timely interventions with the help of Continuous Positive Airway Pressure (CPAP) therapy, which has been established to reduce recurrent cardiovascular events as well as neurologic outcomes. Despite several international studies showing that there is a greater risk of ischemic stroke amongst patients with OSA, most of these studies have been done among Western populations with little representation of South Asian cohorts.

Additionally, a great deal of the previous research used self-reported sleep adversity or questionnaire-based screening without a confirmatory polysomnography or small non-comparative samples. Pakistan's evidence is limited, especially that which has used a matched case-control study with standardized diagnostic assessment of OSA. Hence, the current study aimed at assessing the correlation between OSA and ischemic stroke in a matched case-control study (in a hospital environment) with STOP-BANG screening results subjected to objective confirmation of OSA by means of portable polysomnography and assessment of the level of its severity. The research question specifically seeks to identify whether the presence and the severity of OSA are significantly increased in ischemic stroke patients compared with age and sex matched controls who have never had a stroke. This study aims to determine the relationship between obstructive sleep apnea and ischemic stroke, and to additionally determine whether OSA severity is more common in stroke patients than in age- and sex-matched controls.

METHODS

The case-control study was a hospital-based study that was carried out in the Department of Medicine, Khyber Teaching Hospital, Peshawar, between 1st November 2024 and 31st October, 2025. Ethical approval was given by the Institutional Review Board (IRB) of Khyber Medical College, Peshawar, before the commencement of the study, and permission No: 660/DME/KMC. The minimum sample size used was calculated with Open Epi Version 3.01, 95% confidence level, and 80% power, where the frequency of OSA amongst ischemic stroke patients was estimated to be 70%, and the frequency of the expected frequency among the controls was estimated to be 40% [13]. This would give an expected odds ratio of 3.5. Based on these parameters, the size of the required sample was determined to be 92 per group (n=184), which will provide enough power to support a statistically significant correlation between OSA and ischemic stroke. The method used was non-probability sequential sampling. The reason for non-probability sequential sampling was that ischemic stroke patients who fulfilled the eligibility criteria arrived at the hospital at random and unpredictable times, and recruitment was limited to the study period and the availability of polysomnography tests. The design enabled sequential recruitment of all eligible and willing cases and controls, which reduced the investigator's discretion in selection and made it feasible in a hospital-based environment. The study included age- and sex-matched individuals without a 'history of stroke or transient ischemic attack' (TIA) who were recruited from general outpatient departments or accompanying attendants and patients aged 30 to 75 years who had been diagnosed with acute ischemic stroke and confirmed by neuroimaging (CT/MRI) within 7 days of symptom onset. Hemorrhagic stroke history, sleep disorders other than OSA that have

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been previously diagnosed, use of sedatives, hypnotics, or alcohol abuse, neurological conditions that interfere with sleep assessment (e.g., dementia, Parkinson's), severe pulmonary diseases (e.g., COPD), and unwillingness or incomplete consent are among the exclusion criteria. Data for this study were collected through a standardized, pre-tested questionnaire along with a clinical assessment. The first step in a standardized data collection method followed by each participant was eligibility testing. A neurologist used neuroimaging techniques (CT or MRI) in the case group to confirm they had been diagnosed with an ischemic stroke. The control group was screened to ensure that all participants had no history of prior cerebrovascular events (i.e., stroke, transient ischemic events). Once participants were determined to be eligible, demographic and clinical data were recorded. Age and sex frequency matching were conducted so that the distribution of these factors was similar between cases and controls, and thus demographic confounding was reduced. The possible confounding factors to ischemic stroke, such as obesity, hypertension, diabetes mellitus, and smoking status, were well evaluated. BMI was calculated with weight and height measured, and obesity was considered to have a BMI at or above 30 kg/m2. Hypertension was considered as having been previously diagnosed by a physician, taking antihypertensive medication, or having measured blood pressure 140/90mmHg twice. The definition of diabetes mellitus was a previous diagnosis, on glucose-lowering medication, or on a fasting plasma glucose level of 126mg/dl or higher. Smoking status was identified through a structured interview and was classified as current, former, or never smoker. Informed written consent had been taken before each participant was incorporated into the study, and they were also briefed on the nature, objective, and confidentiality of the research. All participants filled in the STOP-BANG questionnaire, a commonly utilized screening instrument in clinical and research practice to determine the risk of obstructive sleep apnea (OSA) [14]. The participants were all exposed to the STOP-BANG questionnaire, which is a commonly used screening tool in a clinical and research setting to determine the possible existence of OSA. To identify the likelihood of OSA) all the participants were exposed to the STOP-BANG questionnaire that is one of the most prevalent screening instruments in clinical and research practice. The respondents who were categorized as STOP-BANG score of 3 and over underwent OSA overnight testing under the assistance of the ResMed ApneaLink Air Type III home sleep apnea testing device (ResMed, Sydney, Australia). It is a handheld device that can measure airflow, respiratory effort, oxygen saturation, pulse rate and snoring to calculate the apnea-hypopnea index. The ApneaLink Air has been reported to have a sensitivity and specificity of 67 percent and 93 percent, respectively and has been demonstrated in a number of studies to be comparable when compared to in-laboratory polysomnography in terms of their ability to diagnose moderate-to-severe OSA (AHI ≥15). The ResMed ApneaLink Air is a level 3 sleep research device that consist of four channels: 1. Heart rate; 2. Oxygen saturation (all of which pulse oximeters can measure); 3. Airflow through a nasal canula pressure transducer; and 4. Respiratory effort through a chest band with a pneumatic sensor. The loan devices were made available to the lenders who could use them at home at night after the devices were demonstrated to them in a clinic. Desaturation index of oxygen (ODI) of sleep and AHI were the sleep measures that were required, and program analysis was done automatically. ODI is the mean of 3 percent of 3 oxygen desaturations above the baseline/baseline in every hour of sleep (in PSG) or recording time (in level 3 or 4 devices). Previous studies have found ApneaLink automatic scoring software, which may have the potential to offer good diagnostic accuracy, compared to concurrent PSG, in a group of a sleep center (AUC, 0.87; standard error, 0.06) [15]. AHI of five or more episodes of apnea-hypopnea in one hour of sleep became the diagnostic criterion of OSA. Based on the known clinical outcomes, OSA ratings included three categories: mild OSA (AHI 514), moderate OSA (AHI 1529), and severe OSA (AHI 30 and above). Data analysis was done with the help of SPSS 26.0. Descriptive statistics were used to calculate the baseline characteristics, which were presented as means and standard deviations (SD) when dealing with continuous data and frequencies and percentages when dealing with categorical data. Continuous variables (age, BMI, and neck circumference) were tested to test the normality of the data to apply the parametric tests using the Shapiro-Wilk test. Variables that have a normal distribution were summarized using means and standard deviations. The cases and controls were compared using an independent t-test of continuous variables and a chi-square test of categorical variables. The presence of multicollinearity among independent variables was checked by variance inflation factors (VIF); it was not detected (VIF less than 2). The stability of the model estimates was investigated by looking at the residuals and influential observations. As frequency matching was performed on age and sex, the two variables were used as covariates in the multivariate binary logistic regression model to remove residual confounding. Multivariate analysis candidate covariates were a priori chosen on the basis of clinical relevance and existing relationships with ischemic stroke and OSA, as published in previous literature. These were age, sex, BMI, high blood pressure,

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diabetes mellitus, and smoking. The final adjusted model omitted dyslipidemia and neck circumference since they showed strong collinearity with BMI and hypertension during initial diagnostics (variance inflation factor>2 when added together), and were thus omitted to cause over-adjustment and model instability. The first variable that was analyzed was BMI, which was characterized as a continuous variable. In the main regression model, the BMI was dichotomized based on the level of 30kg/m2, which is the WHO-defined obesity level, to ensure consistency with previous OSA-stroke studies. In order to minimize the loss of information and to make it stronger, sensitivity analysis was performed, whereby BMI was received as a continuous variable. Odds ratios (ORs) with their respective 95% confidence intervals (CIs) of the logistic regression models were presented. A p-value of under 0.05 was taken to be statistically significant in all two-tailed statistical tests.

RESULTS

Several significant differences were observed between cases of an ischemic stroke and controls in this research, particularly regarding known vascular risk factors. The results showed that the body mass index (BMI) and the neck circumference of stroke patients are significantly elevated and statistically significant, which suggests that obstructive sleep apnea is likely to be present. The comorbidities of cardiovascular disorders, including diabetes mellitus and hypertension, were also found to be substantially high in cases of stroke, which supports their presence in the cerebrovascular pathology. Also, a higher percentage of stroke patients smoked and were dyslipidemic than the control group, which suggests that the modifiable risk factors are clustering in this population (Table 1).

Table 1: Baseline Characteristics of Study Participants (n=184)

Variables	Cases (n = 92)	Controls (n = 92)	p-value
Age (Years), Mean ± SD	58.4 ± 9.7	56.9 ± 10.1	0.248
Male Gender, n (%)	60 (65.2%)	58 (63.0%)	0.751
BMI (kg/m^2), Mean ± SD	29.3 ± 4.6	27.1 ± 3.9	0.001**
Neck Circumference (cm)	41.2 ± 3.5	38.6 ± 2.9	<0.001**
Hypertension, n (%)	65 (70.7%)	39 (42.4%)	<0.001**
Diabetes Mellitus, n (%)	50 (54.3%)	31 (33.7%)	0.005**
Smoking History, n (%)	34 (37.0%)	21 (22.8%)	0.037*
Dyslipidemia, n (%)	45 (48.9%)	28 (30.4%)	0.011*

The STOP-BANG score distribution showed a distinct statistically significant difference between the ischemic stroke and control groups in the risk categories of OSA. The proportion of the low-risk group in stroke patients (15.2%) was significantly lower than in controls (41.3%), with the proportion of the high-risk category in stroke patients (50.0%) being significantly greater than in controls (26.1%), and the p-value was 0.0001. The percentage of respondents in the intermediate-risk group was the same in both groups (Table 2).

Table 2: STOP-BANG Score and Risk Category of OSA

STOP-BANG Risk Category	Cases (n = 92)	Controls (n = 92)	p-value
Low Risk (Score 0–2)	14 (15.2%)	38 (41.3%)	0.001
Intermediate (Score 3–4)	32 (34.8%)	30 (32.6%)	
High Risk (Score ≥5)	46 (50.0%)	24 (26.1%)	

Only 19.6% of stroke cases had no OSA (AHI <5), whereas 50.0% of controls fell into this category, indicating a significant disparity (p<0.0001). While the proportion of mild OSA cases was similar between the two groups, moderate and severe OSA were markedly more common among stroke patients. Specifically, 30.4% of stroke patients had moderate OSA compared to 17.4% of controls, and 26.1% had severe OSA compared to just 6.5% of controls (Table 3).

Table 3: Frequency and Severity of OSA (Based on Polysomnography)

OSA Severity	Cases (n = 92)	Controls (n = 92)	p-value
No OSA (AHI <5)	18 (19.6%)	46 (50.0%)	<0.001
Mild OSA (AHI 5–14)	22 (23.9%)	24 (26.1%)	
Moderate OSA (AHI 15–29)	28 (30.4%)	16 (17.4%)	
Severe OSA (AHI ≥30)	24 (26.1%)	6 (6.5%)	

In the multivariable logistic regression study, patients with more than three times the odds of ischemic stroke were compared to those without OSA, and it was discovered that OSA was the strongest independent predictor of ischemic stroke. Obesity, hypertension, and diabetes mellitus were also identified as other metabolic and cardiovascular risk factors, which were significantly correlated with stroke, but smoking was not found to be significant after adjustment. Age and male gender as covariates to control the frequency matching were not significantly related to stroke, which means that the observed associations of OSA and other comorbidities with ischemic stroke were not much dependent on age and male gender (Table 4).

Table 4: Multivariate Logistic Regression Analysis of Factors Associated with Ischemic Stroke

Variables	Adjusted OR	95% CI	p-value
Age	1.02	0.99 – 1.05	0.184
Male gender	1.28	0.72 – 2.26	0.402
Presence of OSA	3.4	1.8 – 6.5	0.002 **
BMI ≥30 kg/m^2	2.2	1.1 – 4.3	0.023*
Hypertension	2.8	1.4 – 5.6	0.004 **
Diabetes Mellitus	1.9	1.0 – 3.6	0.046*
Smoking	1.6	0.8 – 3.2	0.173

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DISCUSSION

Obstructive sleep apnea (OSA) was found to be significantly more prevalent in ischemic stroke patients (80.4%) than in age- and sex-matched controls (50%) in the current case-control investigation. OSA was also found to be independently linked to a more than threefold increased risk of ischemic stroke. A Korean study of acute ischemic stroke patients reported an OSA frequency of 91.2%, with around 70% exhibiting moderate-to-severe OSA, and patients aged ≥65 had a threefold risk of more severe OSA, findings that resonate with our observed high frequency and OSA severity among stroke cases [10]. Similarly, a meta-analysis published in 2024 in the Journal of Clinical Sleep Medicine found that sleep-disordered breathing was present in up to 72% of stroke and TIA patients, consistent with our case frequency of 80% [16]. These studies reinforce the notion that OSA is exceedingly common in stroke populations and highlight the importance of systematic sleep assessment. Comparatively, a tertiary-care hospital study in India found a 76% frequency of OSA among stroke survivors, with increasing BMI independently associated with moderate-to-severe OSA, a finding consistent with our observation that elevated BMI was significantly higher among cases and independently predictive of stroke risk in the multivariate model (p=0.0235) [17]. Present result that moderate-to-severe OSA was more prevalent in cases (30.4% moderate, 26.1% severe) than controls (17.4% and 6.5%, respectively) support prior cohort and meta-analysis evidence showing that moderate and severe OSA, rather than mild, are the primary drivers of vascular risk. A study showed that moderate and severe OSA was associated with a significantly increased risk of stroke and vascular events (RR = 2.15 for stroke) compared to mild or no OSA [18, 19]. Furthermore, our logistic regression identified hypertension (OR 2.8) and diabetes mellitus (OR 1.9) as independent stroke predictors, consistent with known pathways linking OSA to cerebrovascular risk via sympathetic overactivity, endothelial dysfunction, and metabolic dysregulation. However, unlike our finding where smoking did not remain significant in multivariate analysis, other global studies often report smoking as a contributory, albeit less dominant, risk factor, indicating possible differences in population-level smoking patterns or interactions between risk factors. Current international consensus guidelines now recommend routine clinical screening for OSA in patients with ischemic stroke or TIA, given the high burden and emerging evidence that early diagnosis and treatment may reduce recurrent stroke and mortality. Yet randomized interventional trials on CPAP post-stroke have been limited by poor compliance, though some data suggest reduced cardiovascular risk with adherence. A recent systematic meta-analysis in the Journal of Clinical Medicine evaluated post-stroke complications and found only a modest increase in risk among stroke survivors with OSA, particularly among those with more severe strokes (RR =1.06 for high-severity survivors). Although our study did not assess post-stroke complications, our findings support the rationale to explore whether early OSA detection post-stroke could mitigate poorer neurological or functional outcomes [20]. Additionally, a 2024 systematic review of clinical prediction models for OSA in stroke patients highlighted the value of tools like STOP-BANG for early identification in acute settings, mirroring our practice of pre-screening with STOP-BANG before confirmation via polysomnography [21]. To conclude, our data are a part of the accumulating evidence that OSA is a prevalent independent risk factor of ischemic stroke, particularly among those with high BMI and cardiovascular comorbidities. These trends are universal among various populations, not only in Taiwan but also in India, and larger meta-analyses highlighting the applicability of sleep apnea in cerebrovascular disease are worldwide in scope. Future studies must focus on longitudinal studies to determine whether OSA (e.g., CPAP) treatment in stroke populations can decrease recurrence and enhance recovery, and in areas where this problem is under-acknowledged. Despite results indicating that OSA is very common among stroke patients and positively related to stroke risks, the idea of routine OSA is hindered, in part because of low adherence rates and inconsistent severity of stroke. Thus, although early detection of OSA can perhaps be useful, only large randomized controlled trials can answer the question whether CPAP or other interventions can be used to meaningfully decrease the risk of recurrent stroke or enhance long-term neurological outcomes.

The study had several limitations. Though our investigation detected a considerable independent association of OSA and ischemic stroke, the case-control design by itself does not provide the chance to prove temporality or causality. There is no way to analyze whether OSA was a previous condition or a side effect of the stroke. Prospective longitudinal and randomized interventional studies are needed to determine whether early diagnosis and treatment of OSA (e.g., CPAP therapy) can reduce stroke recurrence and improve long-term neurological outcomes.

CONCLUSIONS

Obstructive sleep apnea and ischemic stroke have a statistically significant relationship. Controlling for the frequency of obesity, diabetes, and hypertension, OSA was an independent predictor of stroke, and was very common and more severe among stroke patients than controls. Following these findings, routine OSA monitoring is necessary in stroke cohorts, and prompt diagnosis and

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treatment of sleep-disordered breathing can be regarded as a significant opportunity to lower the incidence of stroke and enhance better neurological outcomes in the long run.

Authors' Contribution

Conceptualization: LH
Methodology: UI, AI, IS, SH
Formal analysis: RG, AI
Writing and Drafting: UI, LH, IS
Review and Editing: UI, LH, RG, AI, IS, SH

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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Diagnostic Accuracy of Shear Wave Elastography in the Evaluation of Solid Breast Lesions, Taking Histopathology as the Gold Standard

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ABSTRACT

Breast cancer is the most common malignancy among women worldwide and a leading cause of cancer-related mortality in Pakistan. Accurate differentiation between benign and malignant solid breast lesions is essential for appropriate management. Conventional B-mode ultrasonography is widely used but is limited by operator dependence. Shear wave elastography (SWE) provides an objective, quantitative assessment of tissue stiffness and may improve diagnostic accuracy. **Objectives:** To evaluate the diagnostic accuracy of shear wave elastography in differentiating benign and malignant solid breast lesions using histopathology as the reference standard. **Methods:** This descriptive cross-sectional study was conducted at the Department of Radiology, Bahawal Victoria Hospital, Bahawalpur, from March to September 2023. A total of 232 patients with solid breast lesions detected on ultrasound underwent SWE followed by core needle biopsy or surgical excision. Mean elasticity (Emean), maximum elasticity (Emax), and lesion-to-parenchyma elasticity ratio were recorded. Diagnostic performance was assessed using receiver operating characteristic analysis. **Results:** Among 232 lesions, 153 (65.9%) were benign and 79 (34.1%) were malignant. Malignant lesions showed significantly higher SWE values ($p<0.001$). AUCs were 0.974 for Emean, 0.986 for Emax, and 0.980 for the elasticity ratio. Emax demonstrated the highest accuracy, with 96% sensitivity and 92% specificity at a cutoff of 130–135 kPa. **Conclusions:** Shear wave elastography shows excellent accuracy for differentiating solid breast lesions, with Emax being the most reliable parameter.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide and remains a major cause of mortality. The burden is particularly high in low- and middle-income countries, including Pakistan, where delayed presentation is frequent due to limited screening and awareness [1]. Therefore, an accurate distinction between benign and malignant breast lesions is essential for timely diagnosis and to avoid unnecessary biopsies. Ultrasound (US) is widely used as the first-line imaging tool because it is safe, affordable, and useful in younger women and those with dense breast tissue. However, its diagnostic performance is influenced by operator experience and inter-observer variability, which can reduce specificity [2, 3]. Shear wave elastography (SWE) provides a quantitative assessment of tissue stiffness by measuring shear wave propagation. Malignant lesions are typically stiffer than benign ones,

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making SWE a useful complementary tool for lesion characterization [4]. Meta-analyses have shown that SWE improves specificity while maintaining high sensitivity, thereby reducing false positive findings and potentially decreasing unnecessary invasive procedures [5, 6]. Technological improvements, including enhanced transducer design and optimized image processing, have contributed to better reproducibility of SWE measurements. Cacko and Lewandowski, reported improved diagnostic performance with next-generation SWE systems [7]. SWE has also demonstrated value in evaluating non-mass-like lesions, which are often challenging to assess on grayscale ultrasound. A 2024 study showed significantly improved lesion stratification when SWE stiffness values were incorporated ($p<0.001$) [8]. Despite global evidence, data from South Asian populations remain limited, as most published SWE research originates from East Asian and Western centers rather than the South Asian region [9-12]. Local validation is important because breast density patterns, lesion characteristics, and healthcare resources may influence diagnostic cut-off values. A recent Pakistani study reported SWE sensitivity of 84%, specificity of 89%, and overall accuracy of 88%, consistent with international results and supporting its feasibility in routine practice [9]. Although ultrasound is widely used for initial breast lesion assessment, its specificity is limited by operator dependence and inter-observer variability. Shear wave elastography (SWE) has emerged as a valuable adjunct by providing quantitative tissue stiffness measurements, yet most diagnostic accuracy data originate from Western and East Asian populations. Evidence validating SWE parameters and optimal cut-off values in South Asian populations remains limited.This study aimed to evaluate the diagnostic accuracy of SWE parameters (Emean, Emax, and elasticity ratio) for differentiating solid breast lesions, using histopathology as the gold standard, and to determine clinically relevant cut-off values for use in the Pakistani population.

METHODS

This descriptive cross-sectional study was conducted in the Department of Radiology, Bahawal Victoria Hospital (BVH), Bahawalpur, Pakistan, from 13 March to 12 September 2023. Ethical approval was obtained from the Institutional Review Board of Quaid-e-Azam Medical College/BVH, Bahawalpur (IRB No. 2080/DME/QAMC Bahawalpur). Written informed consent was obtained from all participants before enrollment. The study included adult female patients referred for breast ultrasonography due to palpable breast masses or abnormal findings on prior imaging. Patients with solid breast lesions detected on B-mode ultrasound and with available histopathology results within 30 days of shear wave elastography (SWE) examination were included. Exclusion criteria comprised purely cystic or complex cystic lesions, prior surgery, chemotherapy, or radiotherapy involving the same lesion, inadequate SWE image quality, or incomplete histopathological data. The sample size was calculated to estimate the diagnostic sensitivity and specificity of SWE using histopathology as the reference standard with 95% confidence. Expected sensitivity (88.1%) and specificity (80.3%) values were adopted from a local Pakistani study, while an anticipated malignancy prevalence of 35.5% was derived from regional data. Using the precision method for diagnostic accuracy studies with a margin of error of ±7%, a total sample size of 232 solid breast lesions was required. Conventional B-mode ultrasound and shear wave elastography were performed using a LOGIQ S8 Clear ultrasound system (GE Healthcare, Milwaukee, WI, USA) equipped with SWE capability. A high-frequency linear array transducer (5–14 MHz) was utilized for all examinations. Standardized grayscale ultrasound settings were used, including appropriate gain adjustment, focal zone placement at the level of the lesion, and depth optimization to ensure adequate lesion visualization. For SWE acquisition, patients were positioned supine or in slight oblique decubitus depending on lesion location, with the ipsilateral arm raised. Minimal transducer pressure was applied to avoid tissue pre-compression. The SWE color elastogram was allowed to stabilize for several seconds before measurement. Elasticity values were displayed in kilopascals (kPa). A standardized circular region of interest (ROI) was manually placed over the stiffest visually homogeneous portion of the lesion, carefully avoiding calcifications, cystic areas, posterior shadowing, and peripheral artifacts. SWE parameters recorded included mean elasticity (Emean), maximum elasticity (Emax), and lesion-to-parenchyma elasticity ratio. For each lesion, three consecutive measurements were obtained, and the mean value was used for statistical analysis. Lesion characteristics, including maximum diameter, depth from skin surface, margin (circumscribed or non-circumscribed), and internal echotexture, were documented. Breast density was classified according to ACR BI-RADS density categories, with categories A–B considered low density and C–D considered high density. Lesions were assigned BI-RADS assessment categories (3, 4A, 4B, 4C, or 5) based on grayscale ultrasound morphology in accordance with BI-RADS 5th edition criteria. Both B-mode ultrasound and SWE were performed by the same radiologist with more than three years of experience in breast elastography. While the operator was not blinded to grayscale findings, SWE measurements were quantitative and standardized to minimize subjective bias. Formal inter-

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and intra-observer variability analysis was not performed as a single operator conducted all examinations. Histopathological evaluation served as the diagnostic reference standard. Tissue diagnosis was obtained primarily through ultrasound-guided core needle biopsy, while surgical excision specimens were analyzed in cases where biopsy was not feasible or when definitive surgery was planned. All histopathological examinations were performed in the hospital pathology department by experienced histopathologists. Lesions were classified based on routine hematoxylin and eosin (H and E) staining into benign or malignant categories, according to established histopathological criteria. This binary histopathological classification (benign vs malignant) was used as the outcome reference for assessing the diagnostic accuracy of B-mode ultrasound and SWE parameters. Data were entered and analyzed using IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation, while categorical variables were reported as frequencies and percentages. Differences between benign and malignant lesions were assessed using the independent-samples t-test for continuous variables and the Chi-square test for categorical variables. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of SWE parameters, with area under the curve (AUC), sensitivity, specificity, and optimal cut-off values determined using Youden's index. A p-value<0.05 was considered statistically significant.

RESULTS

A total of 232 patients with solid breast lesions were included, comprising 153 (65.9%) benign and 79 (34.1%) malignant cases confirmed by histopathology. Group comparisons for continuous variables (age, lesion size, depth, Emean, Emax, and elasticity ratio) were performed using the independent-samples t-test. Categorical variables (menopausal status, breast density, BI-RADS category, lesion margin, and breast side) were compared using the Chi-square test. A p-value<0.05 was considered statistically significant. The mean age of the study population was 47.6 ± 10.8 years. Malignant lesions tended to occur in older patients, with a mean age of 52.4 ± 9.7 years compared to 45.2 ± 10.5 years in the benign group. The average lesion size across the cohort was 18.4 ± 8.6 mm, while the mean lesion depth from the skin surface was 1.86 ± 0.59 cm. On shear wave elastography, the overall mean elasticity (Emean) was 84.9 ± 34.5 kPa, the maximum elasticity (Emax) was 108.9 ± 39.7 kPa, and the mean lesion-to-parenchyma elasticity ratio was 2.04 ± 0.78. Highlights the differences in continuous variables between benign and malignant lesions. Malignant lesions were significantly larger in size (25.4 ± 9.4 mm vs 14.7 ± 5.2 mm; p<0.001) and were associated with markedly higher elasticity values. The mean elasticity in malignant lesions was nearly double that of benign lesions (123.6 ± 24.8 vs 64.9 ± 17.8 kPa; p<0.001), and maximum elasticity showed an even more pronounced difference (154.8 ± 25.4 vs 85.2 ± 20.0 kPa; p<0.001). The elasticity ratio also showed clear separation, being 2.93 ± 0.56 in malignant lesions versus 1.58 ± 0.36 in benign lesions (p<0.001). In contrast, lesion depth was slightly greater in malignant lesions (1.96 ± 0.60 cm vs 1.81 ± 0.58 cm), but the difference did not reach statistical significance (p=0.065) (Table 1).

Table 1: Comparison of Quantitative Variables Between Benign and Malignant Breast Lesions

Variables	Benign (n= 153) Mean ± SD	Malignant (n=79) Mean ± SD	p-value
Age (Years)	45.18 ± 10.46	52.39 ± 9.72	<0.001
Maximum Lesion Diameter (mm)	14.74 ± 5.22	25.37 ± 9.40	<0.001
Depth from Skin to Lesion Top (cm)	1.81 ± 0.58	1.96 ± 0.60	0.065
SWE Mean Elasticity (kPa)	64.88 ± 17.80	123.59 ± 24.79	<0.001
SWE Maximum Elasticity (kPa)	85.23 ± 20.01	154.76 ± 25.43	<0.001
Lesion-to-Parenchyma Elasticity Ratio	1.58 ± 0.36	2.93 ± 0.56	<0.001

The association of categorical variables with histopathology is presented in Table 2. Menopausal status showed a significant correlation, with malignancy more frequent in postmenopausal women (59.5%) compared to premenopausal women (23.9%; p<0.001). Breast density (A–B vs C–D) was not significantly associated with malignancy (p=0.146). BI-RADS classification strongly predicted malignancy, with benign lesions predominantly assigned to BI-RADS 3 and 4A categories, while malignant lesions clustered in higher-risk categories (4B, 4C, and 5; p<0.001). Lesion margins were also highly predictive: 73.9% of benign lesions were circumscribed, whereas 77.2% of malignant lesions were non-circumscribed (p<0.001). Breast laterality showed no significant association with histopathology (p=0.622) (Table 2).

Table 2: Association of Categorical Variables with Histopathology (Benign vs Malignant Breast Lesions)

Variables		Benign (n=153)	Malignant (n=79)	p-value
Menopausal Status	Pre	102 (66.7%)	32 (40.5%)	<0.001
	Post	51 (33.3%)	47 (59.5%)	
Breast Density	A–B	51 (33.3%)	34 (43.0%)	0.146
	C–D	102 (66.7%)	45 (57.0%)	
BI-RADS Category	4A	62 (40.5%)	3 (3.8%)	<0.001
	4B	14 (9.2%)	18 (22.8%)	
	4C	–	32 (40.5%)	
	3	77 (50.3%)	–	
	5	–	26 (32.9%)	
Lesion Margin	Circumscribed	113 (73.9%)	18 (22.8%)	<0.001
	Non-Circumscribed	40 (26.1%)	61 (77.2%)	

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Breast Side	Right	80 (52.3%)	44 (55.7%)	0.622
	Left	73 (47.7%)	35 (44.3%)	

Note: Breast density classification was based on BI-RADS density categories: A–B = low-density; C–D = high-density. BI-RADS lesion assessment categories were assigned according to BI-RADS 5th edition ultrasound criteria

The diagnostic performance of SWE parameters is summarized and illustrated in Figures 1–3. All parameters achieved excellent discrimination, with AUC values above 0.97. The AUC was 0.974 (95% CI: 0.956–0.993) for Emean, 0.986 (95% CI: 0.974–0.998) for Emax, and 0.980 (95% CI: 0.962–0.998) for the elasticity ratio (all $p < 0.001$). Emax showed the highest diagnostic performance, followed closely by the elasticity ratio and Emean. The optimal cut-off values determined by Youden's index were ~85 kPa for Emean, 130–135 kPa for Emax, and 2.3 for the elasticity ratio. At these thresholds, Emax provided the best diagnostic balance with 96% sensitivity and 92% specificity, while the elasticity ratio achieved 95% sensitivity and 91% specificity. Emean also demonstrated strong performance with 91% sensitivity and 86% specificity. Overall, these findings confirm that shear wave elastography parameters, particularly Emax, offer robust diagnostic accuracy in differentiating benign from malignant breast lesions (Table 3).

Table 3: Diagnostic Accuracy of SWE Parameters (Based on AUC)

Parameters	AUC (95% CI)	Optimal cut-off	Sensitivity	Specificity	p-value
Emean (kPa)	0.974 (0.956–0.993)	85	91	86	<0.001
Emax (kPa)	0.986 (0.974–0.998)	130–135	96	92	<0.001
Elasticity Ratio	0.980 (0.962–0.998)	2.3	95	91	<0.001

In addition to sensitivity and specificity, further diagnostic performance indices were calculated to enhance clinical applicability. Based on the observed malignancy prevalence of 34.1% in this cohort, the optimal cut-off for Emax (130 kPa) yielded a positive predictive value (PPV) of 86.1%, negative predictive value (NPV) of 97.8%, a positive likelihood ratio (LR+) of 12.0, a negative likelihood ratio (LR–) of 0.04, and an overall diagnostic accuracy of 93.4%. For the elasticity ratio (cut-off 2.3), PPV was 84.5%, NPV 97.2%, LR+ 10.56, LR– 0.05, and accuracy 92.4%. For Emean (cut-off 85 kPa), PPV was 77.0%, NPV 94.9%, LR+ 6.5, LR– 0.10, and accuracy 87.7%. These additional measures further support the strong diagnostic performance of SWE parameters, particularly Emax, in distinguishing benign from malignant breast lesions. The results present the ROC curves for the SWE parameters (Emean, Emax, and elasticity ratio), demonstrating their respective diagnostic performance and visually confirming that Emax had the largest area under the curve (Figure 1).

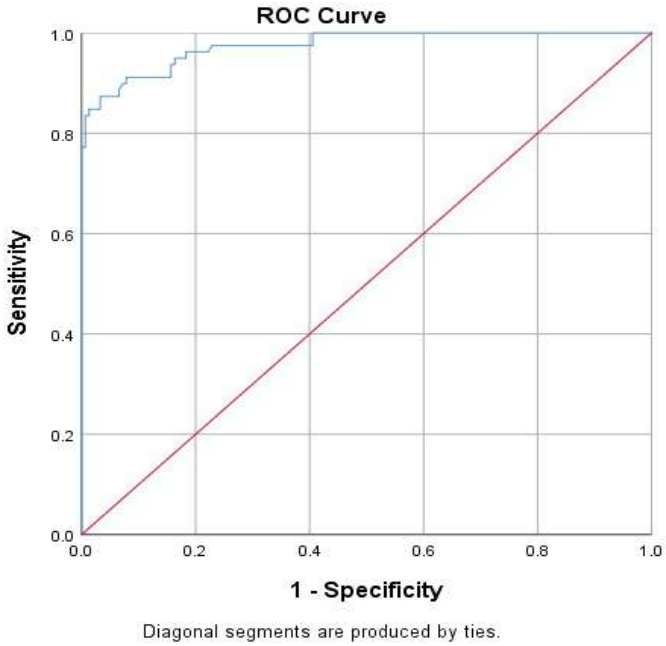

Figure 1: Receiver Operating Characteristic (ROC) Curve of SWE Mean Elasticity (Emean) For Differentiating Benign from Malignant Solid Breast Lesions

The study presents the ROC curves for the SWE parameter, such as Emax, demonstrating their respective diagnostic performance and visually confirming that Emax has the largest area under the curve (Figure 2).

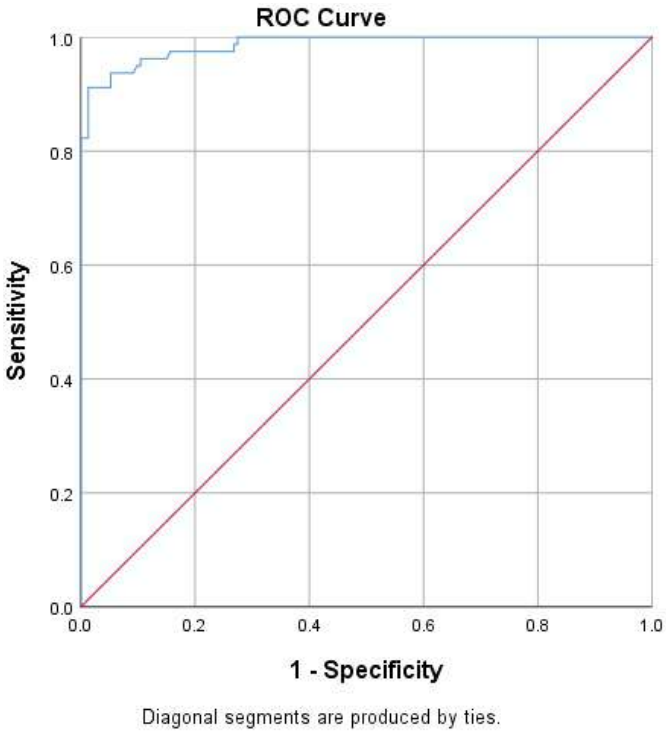

Figure 2: ROC curve of SWE Maximum Elasticity (Emax) for Differentiating Benign from Malignant Solid Breast Lesions

The findings present the ROC curves for the SWE parameter like the elasticity ratio, demonstrating their

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respective diagnostic performance and visually confirming that the elasticity ratio had the largest area under the curve (Figure 3).

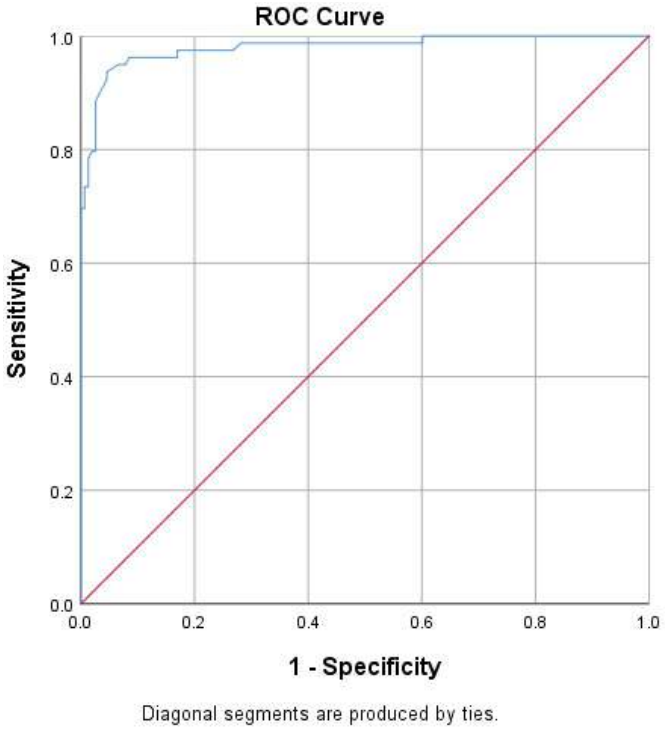

Figure 3: ROC Curve of SWE Elasticity Ratio for Differentiating Benign from Malignant Solid Breast Lesions

DISCUSSION

In this single-center Pakistani cohort, shear-wave elastography (SWE) showed outstanding discrimination between benign and malignant solid breast lesions (AUCs ≈0.97–0.99 for Emean, Emax, and elasticity ratio). These results are concordant with contemporary evidence. A 2022 systematic review focused on 2-D SWE in women with abnormal mammograms reported high pooled accuracy and emphasized quantitative thresholds for malignancy, supporting our finding that stiffer lesions are more likely malignant [12]. A separate 2022 meta-analysis comparing strain elastography (SE) with SWE found SWE achieved a pooled AUC of ~0.92, with sensitivity and specificity around mid-0.80s, again consistent with our high AUCs and excellent classification performance [13]. Our optimal thresholds (~85 kPa for Emean, 130–135 kPa for Emax, and ~2.3 for elasticity ratio) fall within ranges reported recently. In a 2024 retrospective series (240 masses), Marukatat *et al.* identified a Youden-optimized Emean ≈90 kPa (Se 87%, Sp 89%) and E-ratio ≈5.9 (Se 83%, Sp 84%), illustrating the same upward shift in stiffness seen in cancers versus benign lesions; our Emean cut-point is nearly identical, while our ratio threshold is lower, likely reflecting scanner, ROI, and case-mix differences [14]. In a large 2024 prospective multicenter trial (897 lesions), adding 2D+3D SWE to standard ultrasound significantly reduced benign biopsies (~54%) by applying separated cut-offs to reclassify BI-RADS 3/4a, without unacceptable sensitivity loss—evidence that SWE-guided thresholds can be used pragmatically to optimize downstream decisions [15]. Beyond single-parameter thresholds, multiparametric approaches such as combining SWE with contrast-enhanced ultrasound (CEUS) have been explored in previous research to potentially improve lesion characterization. However, these combined approaches were not assessed in the present study and should therefore be considered as future research directions rather than clinical recommendations at this stage [16, 17]. Current findings also align with newer syntheses and regional experiences. A 2025 meta-analysis concluded that elastography (SE and SWE) adds meaningful diagnostic value across techniques, while a 2025 Egyptian cohort highlighted that dual-mode elastography improves differentiation in everyday practice—paralleling our local, resource-conscious setting [18, 19]. Important caveats remain. SWE metrics and "optimal" cut-offs vary by vendor, acquisition quality, and lesion context. Image-quality factors (near-field artifacts, lesion visualization, ROI placement) demonstrably influence SWE's diagnostic performance, reinforcing the need for strict acquisition standards and quality maps during measurement [20]. In present study, lesion depth did not differ significantly between benign and malignant groups. Although depth can theoretically influence shear-wave propagation due to attenuation and near-field artifacts, the absence of a meaningful difference suggests that SWE performance remained stable across the depth range encountered in routine scanning. Heterogeneity in reported thresholds has been emphasized across analyses, and some work suggests lesion type (e.g., NMLs), surrounding rim stiffness, and combined models can shift optimal decision points [21-23]. Clinically, current results support using SWE to augment (not replace) grayscale ultrasound and BI-RADS. Although menopausal status and BI-RADS category differed significantly between benign and malignant groups, SWE parameters demonstrated consistently strong diagnostic performance across these subgroups in descriptive review. However, the study was not powered for formal subgroup comparison, and future studies with larger stratified samples are needed to confirm the consistency of SWE performance across different clinical profiles. In settings similar to ours, two pragmatic applications appear most useful: (i) downgrading low-suspicion BI-RADS 4a masses when stiffness metrics are clearly below validated cut-offs (helping reduce benign biopsies), and (ii) upgrading BI-RADS 3 findings when SWE shows clearly malignant-range stiffness, especially when

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other risk markers (age, margin irregularity) concur [15, 17]. This study has several limitations. First, it was conducted at a single center, which may limit the generalizability of the findings. Second, both B-mode ultrasound and SWE were performed by the same radiologist, so blinding was not possible, and this may introduce operator-related bias despite the use of objective elasticity measurements. Third, the malignant subgroup was relatively smaller than the benign group, although the sample size met statistical requirements. Finally, external validation across multiple centers and equipment platforms was not performed. Future multicenter studies with larger cohorts and standardized acquisition protocols are recommended to confirm the applicability of these findings to broader clinical practice.

CONCLUSIONS

Shear wave elastography exhibited a high level of accuracy in distinguishing malignant from benign solid breast lesions, with all measured elasticity indices (Emean, Emax, and elasticity ratio) demonstrating strong AUC values. Of these parameters, Emax proved to be the most dependable indicator, offering the optimal balance between sensitivity and specificity. These findings suggest that SWE may help support routine breast imaging workflows as an adjunct to conventional ultrasonography and BI-RADS assessment, and may contribute to reducing unnecessary biopsies by improving lesion characterization. Broader implementation and multicenter research are encouraged to further validate its clinical impact, particularly in resource-limited settings such as Pakistan.

Authors' Contribution

Conceptualization: FM, NB
Methodology: FM, NB
Formal analysis: KN, NB
Writing and Drafting: SSG, NB, BN, RNM
Review and Editing: FM, KN, SSG, NB, BN, RNM

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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Fetomaternal Mortality and the Associated Factors in Pregnant Women with Uterine Rupture

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ABSTRACT

Disruption of all uterine layers in pregnant women can lead to rupture of the uterus. Although it is a rare complication, fetal as well as maternal outcomes can be disastrous. Delay in the diagnosis and management is the reason for adverse outcomes owing to the rare and unexpected nature of the complication. **Objective:** To determine fetomaternal mortality and its associated factors in pregnant women with uterine rupture. **Methods:** Total 89 cases with diagnosed ruptured uterus of pregnant women were selected via nonprobability consecutive sampling. Age, body mass index, and gestational age were documented. Outcome variables were fetal and maternal mortality, wound infection, hemorrhage, and hysterectomy. Baseline factors were compared on the basis of fetal or maternal mortality to determine the responsible factors. **Results:** Mean age of the patients was 31.15±3.83 years. Mean gestational age was 30.32±3.50 weeks, and median parity was 3. Mean BMI was 26.56±1.49 kg/m2. Of all the patients, 34 (38.2%) had a positive history of cesarean section. Wound infection was observed in 38 (42.7%) of the patients. Maternal and fetal mortality occurred in 22 (24.7%) and 59 (66.3%) patients, respectively. **Conclusions:** Fetal and maternal mortality were high among the patients with a ruptured uterus. Maternal mortality was related to high maternal age and parity, while fetal mortality was related to gestational age and maternal BMI. A previous cesarean section was related to both maternal and fetal demise.

INTRODUCTION

Uterine rupture is a rare but life-threatening complication involving the complete disruption of the uterine wall, with serious maternal and fetal consequences. Its prevalence is 1.35% in Ethiopia [1], with an increasing trend in recent years [2]. Risk factors include advanced maternal age, previous cesarean section or uterine surgery, labor induction with oxytocin or prostaglandins [3], post-term pregnancy, short interpregnancy interval, macrosomia, single-layered uterine closure, trial of labor after cesarean (TOLAC), multiple cesarean sections, adenomyomectomy [4], and abdominal or laparoscopic myomectomy. Complications include severe hemorrhage requiring blood transfusion or hysterectomy, bladder injury, fetal distress, preterm birth, stillbirth, and maternal death [5-7]. Delay in the diagnosis and management is the reason for adverse outcomes owing to the rare and unexpected nature of the complication. Whatever the cause may be, no single risk factor is clinically reliable enough to predict the risk of antepartum or intrapartum rupture of the uterus. An increase in the trend of rupture of both scarred and unscarred uteri during gestation has been observed over the previous forty years. Studies have been conducted to compare fetomaternal outcomes in patients with rupture of scarred uterus against those with rupture of unscarred

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uterus. The outcomes were worse for both mother and fetus in the patients with rupture of an unscarred uterus. Niazi *et al.* conducted a study and observed 19.17 % wound infection rate, 9.17 % maternal mortality, and 56.67 % fetal mortality in cases of ruptured gravid uterus [8]. Desta *et al.* studied cases of ruptured gravid uterus and observed 98.3 % fetal mortality and 6.6 % maternal mortality [9]. Fetal mortality was 69.8% in patients in a study conducted by Shaikh [10]. The results in the above-mentioned studies vary to a great extent, requiring further study of cases with a diagnosis of ruptured uterus. Assessment of factors leading to rupture of the uterus and maternal as well as fetal outcomes is required to devise prevention and management plans of uterine rupture.

Despite the identification of multiple risk factors, no single clinical predictor reliably identifies women at risk, and delayed diagnosis remains a major contributor to adverse outcomes. Reported fetomaternal outcomes vary widely across studies, particularly between scarred and unscarred uteri, highlighting inconsistencies in existing evidence. Local data on determinants and outcomes of uterine rupture are limited. This study aimed to determine local population and the patients with definitive diagnosis of uterine rupture in order to assess the fetomaternal outcomes and their associated factors, which will further help to timely diagnose or even prevent the disastrous events.

METHODS

This descriptive case series study was conducted in the Department of Obstetrics and Gynecology, Mollah Bakhsh Hospital DHQ Sargodha, from July 1st, 2021 to December 31st, 2021. Ethical approval was taken from the hospital review board (IRB letter # UOS/SMC/3095), before the commencement of study. Total 89 patients were selected as per sample size calculated from reference study which documented 69.8% fetal mortality and we expected 20% decrease in the incidence at 95% confidence interval and a power of the study 80% [10]. Women with a confirmed diagnosis of ruptured uterus who were 18-40 years old, with a singleton pregnancy and gestational age of 20 weeks or more as per LMP were included in the study. USG was done using Siemens Acuson S3000 to look for uterine rupture, and the diagnosis was verified by intraoperative findings, i.e., fetus was lying inside the abdominal cavity instead of the uterine cavity. Patients with a diagnosis of pre-eclampsia, eclampsia, placenta previa, and antepartum hemorrhage were excluded from the study. Patients were selected by nonprobability consecutive sampling, as this technique helped us to collect the required sample population within the time frame of the study. Selection bias was limited as it was a single-group descriptive case series and did not require any randomization. Informed written consent was taken after explaining the purpose of the study to the patients and their attendants, and confidentiality of data was ensured. All the baseline data, including age, body mass index, parity, history of cesarean section, and gestational age, were documented (data collected from hospital records). All the patients were managed and underwent surgery as per the protocols of the department, i.e., after stabilization, necessary laboratory investigation, and proper arrangement of blood transfusion. A senior consultant gynecologist with a minimum of three years post-fellowship experience was supervising the whole management. Intermittent or continuous electronic fetal monitoring was done till the baby was delivered. Fetal mortality was documented. Fetal mortality was labelled if the baby died before complete expulsion of the fetus. Wound infection was documented if there was erythema of more than 1 cm around wound edges and there was sero-sanguinous discharge present at 6th day postoperatively. Maternal mortality was labelled if the death of the mother occurring during the six postpartum weeks. Information was collected using the phone number provided on patient files. Wound infection and maternal mortality were documented. The researchers themselves collected all the data on a specified Proforma. All the data was entered in IBM SPSS version 27.0 and analyzed. Means and standard deviations were calculated for continuous variables such as age, BMI, and gestational age; while nominal data were calculated as numbers and percentages, and included parity, history of cesarean section, fetal mortality, hysterectomy, wound infection, and maternal mortality. $N = p0q0 \{z_{1-\alpha/2} + z_{1-\beta} \text{ sqrt } (p1q1/p0q0\}/(p1-p0)^2$. Patients were divided into two groups based on maternal and fetal mortality, and all the baseline data were compared between the groups to analyze which factors contributed more towards such disastrous outcomes. Shapiro-wilk test was applied to assess the normal distribution of data. Student's t-test was applied to compare the continuous variables such as age, GA, parity, and BMI, while nominal data such as wound infection, fetal and maternal mortality were compared by applying chi square test. Binary logistics were applied to assess the correlation of age, gestational age, BMI, parity with maternal and fetal mortality, where correlation with cesarean section history was assessed by x^2 test. The $p \leq 0.05$ was considered statistically significant.0

RESULTS

Total 89 patients were included in the study with a mean age of 31.15 ± 3.83 years. Mean gestational age was 30.32 ± 3.50 weeks, and median parity was 3. Mean BMI was 26.56 ± 1.49 kg/m^2. Of all the patients, 34 (38.2 %) had a positive history of cesarean section. Wound infection was observed in 38 (42.7 %) of the patients. Maternal and fetal mortality

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occurred in 22 (24.7 %) and 59 (66.3%) patients, respectively. Data was compared on the basis of maternal mortality. Mean age was 35.18 ± 4.68 years in the mortality group, which was significantly higher (p<0.002) than that in the survivors (29.83 ± 2.33 years). Gestational age was 30.63 ± 3.80 weeks and 30.22 ± 3.42 weeks in the mortality and survivor groups, respectively, with no statistically significant difference (p=0.634). Mean parity was 3.54 ± 1.65 in the mortality group, which was significantly higher (p=0.007) as compared to 2.44 ± 0.94 in the survivors. BMI was 26.68 ± 1.21 kg/m^2 and 26.52 ± 1.58 kg/m^2 in the deceased and survivors, with no statistically significant difference (p=0.623). The history of cesarean section was positive in 63.6% of the mothers who died and 29.9% of the mothers who survived, and the difference was statistically significant (p=0.005). Incidence of wound infection was 72.7% and 32.8% in the mortality and survivor groups, respectively (p=0.001). Incidence of fetal mortality was 72.7% and 64.2% in the maternal mortality and survivor groups, respectively, with the difference not being statistically significant (p=0.462) (Table 1).

Table 1: Comparison of Data on Basis of Maternal Mortality

Variables	Maternal Mortality		p-value
	Yes (n=22)	No (n=67)	
Age, Years	35.18 ± 4.68	29.83 ± 2.33	<0.001
Gestational Age, Weeks	30.63 ± 3.80	30.22 ± 3.42	0.634
Parity, Number	3.54 ± 1.65	2.44 ± 0.94	0.007
BMI, kg/m^2	26.68 ± 1.21	26.52 ± 1.58	0.623
Previous Cesarean Section	14 (63.6 %)	20 (29.9 %)	0.005
Wound Infection	16 (72.7 %)	22 (32.8 %)	0.001
Fetal Mortality	16 (72.7 %)	43 (64.2 %)	0.462

*Data are presented as mean ± standard deviation, and number (percentages)

Data were also compared on the basis of fetal mortality. Mean age of the mothers was 31.42 ± 4.01 years in the fetal mortality group and 30.63 ± 3.47 years in the survivors (p=0.361). Gestational age was 28.98 ± 2.61 weeks in the fetal mortality group, which was significantly lower (p<0.001) than that of the live babies (32.96 ± 3.56 weeks). Mean parity was 2.71 ± 1.16 in the fetal mortality group with no statistically significant difference (p = 0.939) as compared to 2.73 ± 1.41 in the survivors group. BMI was 26.81 ± 1.42 kg/m^2 and 26.06 ± 1.53 kg/m^2 in the deceased and survivors, respectively, being significantly higher in the former group (p=0.030). The history of cesarean section was positive in 47.5% of the mothers in the fetal mortality group and in 20.0 % of the mothers of the fetal survivor group; the difference was statistically significant (p=0.012). Incidence of wound infection was 52.5 % and 23.3 % in mothers of fetal mortality and survivor groups, respectively (p=0.008). Incidence of maternal mortality was 27.1% and 20.0 in the fetal mortality and survivor groups, respectively, with no statistically significant difference (p=0.462) (Table 2).

Table 2: Comparison of Data Based on Fetal Mortality

Variables	Fetal Mortality		p-value
	Yes (n=59)	No (n=30)	
Age, Years	31.42 ± 4.01	30.63 ± 3.47	0.361
Gestational Age, Weeks	28.98 ± 2.61	32.96 ± 3.56	<0.001
Parity, Number	2.71 ± 1.16	2.73 ± 1.41	0.939
BMI, kg/m^2	26.81 ± 1.42	26.06 ± 1.53	0.030
Previous Cesarean Section	28 (47.5 %)	6 (20.0 %)	0.012
Wound Infection	31 (52.5 %)	7 (23.3 %)	0.008
Fetal Mortality	16 (27.1 %)	6 (20.0 %)	0.462

*Data is entered as mean ± standard deviation, and number (percentages)

Maternal age and previous cesarean section had a positive correlation with maternal mortality (p-value <0.001 and 0.005, respectively), whereas gestational age, BMI, and previous cesarean section had a positive correlation with fetal mortality (p-value <0.001, 0.045, and 0.012, respectively) (Table 3).

Table 3: Significant Pearson correlation of variables with maternal and fetal mortality

Variables	OR	p-value
Maternal Mortality		
Age, Years	1.596	<0.001
Previous Cesarean Section	0.243	0.005
Fetal Mortality		
Gestational Age, Weeks	0.277	<0.001
BMI, kg/m^2	1.491	0.045
Previous Cesarean Section	0.277	0.012

DISCUSSION

In the current study, 89 patients were included, in the study of whom 34 (38.2 %) had a positive history of cesarean section. Wound infection was observed in 38 (42.7 %) of the patients. Maternal and fetal mortality occurred in 22 (24.7 %) and 59 (66.3%) patients. Mean age and parity were significantly higher in the maternal mortality group (p<0.002 and p = 0.007, respectively). Significantly higher ratio of expired patients had a history of previous cesarean section, i.e., 63.6% as compared to 29.9% among the survivors (p=0.005). Wound infection was observed in 72.7% and 32.8% in the mortality and survivor groups, respectively (p=0.001). Fetal mortality was significantly higher in lower gestational age (p<0.001). Higher BMI of the mothers and previous cesarean section contributed more to fetal mortality (p=0.030 and p=0,012, respectively). Mothers of 52.5% of still births developed wound infection (p=0.008). There was a significant correlation of age and previous cesarean section with maternal mortality, whereas a significant correlation of low gestational age, BMI, and no history of previous cesarean section was

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observed with fetal mortality. Maternal mortality in the current study was 24.7%, which was different from the rates observed in other studies 6.6% [11], 6.5% [12], 2.5% [13], 87.5% in unscarred and 39.1% in scarred uteri [14], and 11.94% [15]. A study by Abrar *et al.* [16] reported 21% maternal mortality, results close to those observed in the current study. Gibbins *et al.* [17] observed 65% of the mothers with primary uterine rupture had maternal morbidities. Blood loss and transfusion rate were also higher among the cases, with 35% of the cases undergoing hysterectomy. Fetal mortality and other neurological complications occurred in 40% of the cases. Primary uterine rupture occurred in 63% of the cases when delivered vaginally as compared to 9% with cesarean delivery. Al-Zirqi *et al.* [14] observed no perinatal mortality in patients with partial uterine rupture. The current study showed 66.3% fetal mortality. Astatikie *et al.* [11] observed 98.3% stillbirths in all the patients who had uterine rupture, and the rate was very much higher than that of the current study. Uterine rupture occurred in 2.44% of the study population, and 5.8% of the patients with uterine rupture developed vesico-vaginal fistula. Abbas AM *et al.* [12] observing 67.8% fetal mortality, which was very close to that observed in the current study. Rottenstreich *et al.* [18] concluded from their study that the delay in the diagnosis of uterine rupture was significantly associated with poor maternal outcome in terms of a higher morbidity rate. Multivariate analysis showed delayed diagnosis to be associated with hysterectomy (OR=4.90, 95% CI). Tan *et al.* [19] studied 48 cases of uterine rupture in Singapore and observed 25% fetal mortality. However, they observed no maternal death. Another study conducted by Chang *et al.* [20] also studied risk factors and observed previous cesarean and multiparity in 59% and 83% of the cases, results higher than those of the current study. In their study, there was 16% perinatal fetal mortality. Sharon *et al.* [13] observed a previous cesarean in 45% of the patients, results close to those observed in the current study. Cesarean proceeded to hysterectomy in 27% of the cases. Incidence of fetal mortality was 33.3%, which was about half of the incidence observed in the current study. A study was conducted in Nigeria by Adegbola *et al.* [15], and they observed 46.28% patients had a history of previous cesarean section, results similar to the current study. However, they observed 79.1% fetal mortality rate, which was much higher than the current study. Abrar *et al.* [16] observed 21% maternal mortality and 91.4% perinatal fetal mortality, results significantly higher than those observed in the current study. The differences between current findings and other studies may be due to variations in the study populations (e.g., maternal age, parity, history of cesarean section), healthcare settings, and management protocols (labor monitoring, induction practices, timing of the surgical intervention). Additionally, study design, sample size, and operational definitions may have contributed to observed discrepancies. Despite multiple studies on uterine rupture, there is considerable variation in reported maternal and fetal outcomes, and limited local data evaluating the factors associated with the mortality in patients with a confirmed diagnosis of uterine rupture. Existing literature inadequately examines the combined impact of maternal, obstetric, and perioperative factors on fetomaternal outcomes, particularly in low-resource hospital settings. This gap necessitates region-specific studies to inform timely diagnosis, prevention, and management strategies. The high fetomaternal mortality associated with the uterine rupture highlights the need for early identification of high-risk patients, intrapartum monitoring, and timely surgical intervention, particularly in patients with advanced age, high parity, increased BMI, and previous cesarean section. Public health measures should emphasize dropping unnecessary cesarean deliveries, implementing antenatal risk screening, improving referral systems, and ensuring the availability of emergency obstetric and blood transfusion services.

The study did not account for delays in referral, labor monitoring practices, or timing of surgical intervention, which are critical determinants of outcomes in uterine rupture. Additionally, the absence of detailed intraoperative and postoperative complication stratification may have limited a deeper understanding of factors influencing fetomaternal mortality. Future research should focus on prospective, multicenter studies to validate risk factors, develop predictive models for early detection, and assess the efficiency of preventive and management approaches to reduce the incidence of uterine rupture and its associated morbidity and mortality.

CONCLUSIONS

Maternal and fetal mortality rates were markedly elevated in patients who experienced uterine rupture. Maternal mortality was related to high maternal age and parity, while fetal mortality was related to gestational age and maternal BMI. A previous cesarean section was related to both maternal and fetal demise.

Authors' Contribution

Conceptualization: AA, NS, SS
Methodology: SS
Formal analysis: NS
Writing and Drafting: AG, ZA
Review and Editing: AG, AA, NS, SS, ZA, RZ

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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Post Concurrent Chemo-Radiotherapy Hearing Loss in Patients of Oral Cavity Cancers

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ABSTRACT

Treatment of head and neck squamous cell carcinoma (HNSCC) includes wide local surgical excision followed by adjuvant therapy. **Objectives:** To determine the frequency of hearing loss in patients who underwent concurrent chemo-radiation therapy (CCRT) treatment after surgical removal of tumour of the oral cavity. **Methods:** This cross-sectional study was conducted at the Department of ENT and Head and Neck Surgery, Liaquat National Hospital, Karachi, from March 2025 to August 2025. Using non-probability consecutive sampling, 133 patients aged 18–70 years with histopathologically confirmed grade III or higher oral cavity malignancies planned for post-surgical CCRT were enrolled. Hearing was assessed using pure-tone audiometry pre-surgery, two weeks post-surgery, and three months post-CCRT, and categorised by severity. Data were analysed with SPSS version 26.0, using descriptive statistics and chi-square tests, with $p<0.05$ considered significant. **Results:** Among 133 post-surgical CCRT patients, 94 (70.7%) were male, and the median age was 48.0 (39.0–58.0) years. T4 disease was present in 114 (85.7%) patients. Hearing loss occurred in 15 (11.3%), highest in >60 years 5 (33.3%, p=0.016), and most frequent in tongue malignancy 10 (66.7%). By CCRT cycles, loss was seen in 1–2 cycles 3 (20.0%), 3–4 cycles 12 (10.5%), and none in >4. Severity of hearing loss was found to have a significant association with cancer, stating (p=0.031). **Conclusions:** Hearing loss following CCRT for oral cavity malignancies occurred in around one in ten patients, with most cases being mild and associated with older age, tongue primary site, and advanced T stage.

INTRODUCTION

Head and neck cancers (HNC) represent the third most common cancer worldwide, with 1,464,550 new cases and 487,993 deaths, accounting for 7.6% of all cancers and 4.8% of all cancer-related deaths [1,2]. In Pakistan, after lung cancer, HNC is the second most common cancer, and in females, it is after breast cancer [3]. Karachi is the city with the largest population in this country and hence bears a hefty load of head and neck tumours; its annual incidence from a community-based study in the district of South Karachi is 4.1 per 100,000 among male and 4 per 100,000 among female, making Karachi the first city with the highest incidence of oral squamous cell carcinoma [3].

Treatment of head and neck squamous cell carcinoma (HNSCC) includes wide local surgical excision followed by adjuvant therapy (radiotherapy with or without chemotherapy). Patients tend to present in the late stages, hence, around 46% to 85% of those having surgical removal require adjuvant therapy, also known as concurrent chemo-radiation therapy (CCRT). The regimen for CCRT in HNC is 66-68 gray in 33-34 fractions of radiotherapy; each session has a dose of 2 gray, together with cisplatin 100 mg/m2 every three weeks for up to three cycles [4]. Concurrent cisplatin and radiation lead to an absolute gain of 6.5% in five-year overall survival and better locoregional

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control [5]. However, this gain should be weighed against the additional toxicity it implies, as well as potential compromise in the quality of life (QoL). Radiotherapy encompasses the level of the base of the skull up to the clavicle, with various strategies adopted to protect the sensitive structures during organ preservation strategies. Leading to damage to the eustachian tube, it causes hearing loss. Radiotherapy can have deleterious and detrimental effects on the nervous system because of the limited capacity for repair and regeneration of the nervous tissues. While not as common as other adverse effects in HNCs, neuropathies leave a long-lasting compromise in the patients' well-being. Radiation-induced neuronal damage in HNC manifests mainly as sensorineural hearing loss (SNHL) and minorly as alterations in taste and smell sensory functions. Chemotherapy includes cisplatin, which is a chemotherapeutic drug. Neurotoxicity is the most serious cisplatin toxicity. Cisplatin ototoxicity typically presents as a bilateral high-frequency SNHL that may progress to profound loss of hearing [6]. Literature shows that almost 70% of patients experience a symmetrical, permanent loss greater than 15 decibels (dB) in the 4000 to 8000 Hertz (Hz) range, with nearly all patients affected when extended high-frequency hearing (>8000 Hz) is measured [7]. Incidence rates of SNHL following cisplatin-based chemo-radiotherapy range between 17-88% [8]. Evidence points out that higher cumulative cisplatin is associated with greater risk and severity of SNHL, and a sharp rise beyond ~300 mg/m^2 is reported; moderate–to–severe loss clusters in the 300–400 mg/m^2 range, and risk continues to increase at higher totals. Weekly lower-dose regimens tend to produce less ototoxicity than tri-weekly high-dose schedules at similar totals [9]. Post-CCRT changes in hearing loss in patients with oral cavity cancers have been conducted in various studies, providing data regarding the type of chemotherapeutic agent being used and the amount of radiation being given, leading to their effects on hearing [8].

However, there is no study available with data from the local region in this regard. The findings of this study would not only furnish the local data but also aid in further research for the adjustment of dose to prevent hearing loss and achieve better patient outcomes. This study aimed to determine the frequency of hearing loss in patients who underwent CCRT after surgical removal of a tumour of the oral cavity.

METHODS

This cross-sectional study was performed at the Department of ENT and Head and Neck Surgery, Liaquat National Hospital, Karachi, Pakistan, from March 2025 to August 2025, after obtaining approval from the ethical review committee of the institution (letter number: App # 1261-2025 LNH-ERC). A sample size of 133 was calculated using the Open Epi online sample size calculator with an anticipated frequency of hearing loss in patients who underwent CCRT after surgical removal of tumour of the oral cavity as 78.4% [10], with 95% confidence level, and 7% margin of error. Sampling selection was carried out using the non-probability consecutive sampling technique. The inclusion criteria were patients of any gender, aged 18-70 years, and who were histopathologically confirmed cases of oral cavity malignancies, with grade III or above disease according to TNM classification. Only those patients who were planned to receive post-surgery chemo-radiotherapy were considered for the study. The exclusion criteria were patients with primary tumours of any part of the auditory system and those with direct extension of primary tumour to any auditory system, a history of SNHL or CHL, tumours of the hard palate and soft palate, a history of receiving CCRT, or a history of operated oral cavity tumours. Written and informed consent was taken from each patient once the date was booked for the surgery, followed by a proper ear examination. The eligible subjects went through documentation of their demographics, such as age and gender. Disease-related information, such as the stage and grade of the tumor (as per biopsy findings), was noted. Diagnosis was established through incisional or excisional biopsy, reviewed by a consultant histopathologist. Preoperative staging was performed using contrast-enhanced cross-sectional imaging as part of routine clinical care. CT imaging was acquired using a multidetector CT scanner (Aquilion 64-slice, Canon Medical Systems, Japan), and magnetic MRI was performed on a 1.5 Tesla system (MAGNETOM Aera, Siemens Healthineers, Germany). Imaging protocols followed the institution's standard head-and-neck oncology protocols and were interpreted by consultant radiologists. CT and/or MRI findings were integrated with clinical and histopathological data to assign TNM stage according to the AJCC 8th edition. Only patients with grade III or above disease (T3 or T4 lesions) were included, as these cases typically require adjuvant concurrent chemoradiotherapy (CCRT) following surgical excision. Ear examination included general examination of the ear, and per speculum examination with an otoscope was performed for each patient. Hearing sensitivity was assessed using the pure-tone audiometer (PTA) by the certified audiologist of the institute. The machine used for performing PTA was the GSI STAR PRO 321UX. The cost of PTA was covered by the departmental funds throughout the study. The first PTA was conducted before surgery (baseline), the second two weeks after surgery and before the initiation of CCRT, and the third and final PTA was performed three months after completion of

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CCRT to assess post-treatment hearing outcomes. Hearing loss was assessed and categorized as mild (25-40 dB), moderate (41-70 dB), severe (71-90 dB), and profound (>91 dB) [11]. All the relevant data were recorded on a specifically designed proforma. Data were entered and analyzed using "IBM-SPSS Statistics" version 26.0. The qualitative variables were mentioned in the form of frequency and percentage. The normality of data was checked using the Shapiro-Wilk test. The quantitative data were expressed as mean and standard deviation (SD) if data were normally distributed, and if data were non-normally distributed, median and interquartile range (IQR) were computed. Effect modifiers, which included age, gender, chemo cycles, stage, and grade of tumour were controlled through stratification to see their effect on the outcome (hearing loss). A post-stratification chi-square test was applied, with a $p<0.05$ to mark significance.

RESULTS

A total of 133 patients with histopathologically confirmed oral cavity malignancies who underwent post-surgical concurrent chemoradiotherapy (CCRT) were included. The median age was 48.0 years (IQR 39.0–58.0; range 21–70 years), with 59 (44.4%) patients each in the 18–45 and 46–60-year categories, and 15 (11.3%) aged >60 years. Most participants were male (n=94, 70.7%) and resided in urban areas (n=94, 70.7%). The buccal mucosa was the most common tumour site (n=62, 46.6%), followed by the tongue (n=50, 37.6%), alveolus (n=6, 4.5%), cheek (n=5, 3.8%), lip (n=5, 3.8%), and other sites (n=5, 3.8%). The majority presented with T4 disease (n=114, 85.7%), while T3N0 and T3N1 were seen in six (4.5%) patients each, T3N2 in five (3.8%), and T2N2B and T3 in one (0.8%) patient each (Table 1).

Table 1: Characteristics of Oral Cavity Malignancy Patients (n=133)

Characteristics		n (%)
Gender	Male	94 (70.7%)
	Female	39 (29.3%)
Age	18-45	59 (44.4%)
	46-60	59 (44.4%)
	>60	15 (11.3%)
Residence	Urban	94 (70.7%)
	Rural	39 (29.3%)
Malignancy Diagnosis	Buccal Mucosa	62 (46.6%)
	Tongue	50 (37.6%)
	Alveolus	6 (4.5%)
	Cheek	5 (3.8%)
	Lip	5 (3.8%)
	Others	5 (3.8%)
Cancer Stagging	T2N2B	1 (0.8%)
	T3	1 (0.8%)
	T3N0	6 (4.5%)
	T3N1	6 (4.5%)
	T3N2	5 (3.8%)
	T4	114 (85.7%)

The post-CCRT hearing loss was observed in 15 (11.3%) patients. Age group was significantly associated with hearing loss (p=0.016), with the highest prevalence in patients aged >60 years (n=5, 33.3%), compared with 18–45 years (n=5, 33.3%) and 46–60 years (n=5, 33.3%). No significant associations were noted for gender (male: 10/94 (10.6%) vs female: 5/39 (12.8%), p=0.717) or residence (urban: 8/94 (8.5%) vs rural: 7/39 (17.9%), p=0.117). Hearing loss occurred most frequently in patients with tongue malignancy (n=10, 66.7%), followed by buccal mucosa (n=3, 20.0%), cheek (n=1, 6.7%), and lip (n=1, 6.7%), with no cases among alveolus or other sites (p=0.129). Although most patients with hearing loss had T4 stage disease (n=14, 93.3%), the association between stage and hearing loss was not statistically significant (p=0.857) (Table 2).

Table 2: Comparison of Baseline Characteristics of Oral Cavity Malignancy Patients with Post CCRT Hearing Loss (n=133)

Characteristics		Post CCRT Hearing Loss		p-value
		Yes (n=15)	No (n=118)	
Gender	Male	10 (66.7%)	84 (71.2%)	0.717
	Female	5 (33.3%)	34 (28.8%)	
Age	18-45	5 (33.3%)	54 (45.8%)	0.016
	46-60	5 (33.3%)	54 (45.8%)	
	>60	5 (33.3%)	10 (8.5%)	
Residence	Urban	8 (53.3%)	86 (72.9%)	0.117
	Rural	7 (46.7%)	32 (27.1%)	
Malignancy Diagnosis	Buccal Mucosa	3 (20.0%)	59 (50.0%)	0.129
	Tongue	10 (66.7%)	40 (33.9%)	
	Alveolus	–	6 (5.1%)	
	Cheek	1 (6.7%)	4 (3.4%)	
	Lip	1 (6.7%)	4 (3.4%)	
	Others	–	5 (4.2%)	
Cancer Stagging	T2N2B	–	1 (0.8%)	0.857
	T3	–	1 (0.8%)	
	T3N0	1 (6.7%)	5 (4.2%)	
	T3N1	–	6 (5.1%)	
	T3N2	–	5 (4.2%)	
	T4	14 (93.3%)	100 (84.7%)	

Analysis of CCRT cycles showed that hearing loss occurred in 3 (20.0%) of the 15 patients receiving 1–2 cycles, 12 (10.5%) of the 114 patients receiving 3–4 cycles, and none of the two patients receiving >4 cycles (p=0.604). The majority of patients without hearing loss had received 3–4 cycles (n=102, 86.4%), compared with 14 (11.9%) receiving 1–2 cycles and two (1.7%) receiving >4 cycles (Figure 1).

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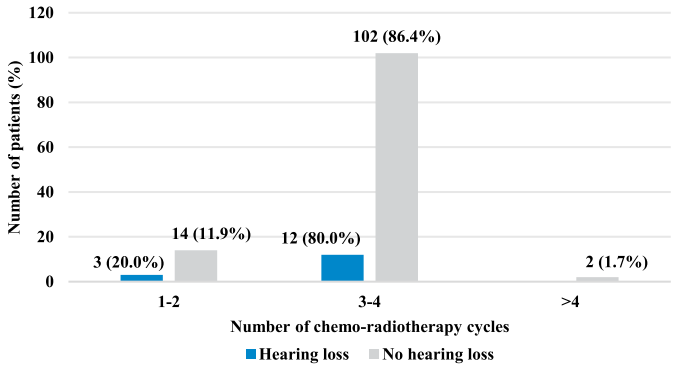

Figure 1: Comparison of Hearing Loss Following CCRT with Respect to Chemo-Radiotherapy Cycles (n=133)

Out of those with post CCRT hearing loss (n=15), 9 (60.0%) had mild, 4 (26.7%) had moderate, and 2 (13.3%) had severe impairment. There was no statistically significant association between hearing loss severity and gender (p=0.472) or age (p=0.165). Patients aged 18–45 years accounted for nearly half of mild cases (n=4, 44.4%), while moderate loss was most common in the 46–60-year group (n=3, 75.0%), and severe loss was equally distributed between the 46–60 and >60-year groups (n=1 each, 50.0%). The majority of cases across all severity categories occurred in urban residents, although differences by residence were not significant (p=0.978). Tongue malignancy predominated across severity groups, accounting for 6/9 (66.7%) mild, 3/4 (75.0%) moderate, and 1/2 (50.0%) severe cases (p=0.077). Cancer stage was significantly associated with severity (p=0.031), with all mild and moderate cases arising from T4 disease, while one severe case occurred in T3N0 and the other in T4 disease (p=0.031), and the details are shown (Table 3).

Table 3: Association of Post CCRT Hearing Loss Severity with Baseline Characteristics of Patients with Oral Cavity Malignancy (n=15)

Characteristics		Post CCRT Hearing Loss Severity			p-value
		Mild (n=9)	Moderate (n=4)	Severe (n=2)	
Gender	Male	6 (66.7%)	2 (50.0%)	2 (100%)	0.472
	Female	3 (33.3%)	2 (50.0%)	–	
Age	18-45	4 (44.4%)	1 (25.0%)	–	0.165
	46-60	1 (11.1%)	3 (75.0%)	1 (50.0%)	
	>60	4 (44.4%)	–	1 (50.0%)	
Residence	Urban	5 (55.6%)	2 (50.0%)	1	0.978
	Rural	4 (44.4%)	2 (50.0%)	1	
Malignancy Diagnosis	Buccal Mucosa	3 (33.3%)	–	–	0.077
	Tongue	6 (66.7%)	3 (75.0%)	1 (50.0%)	
	Cheek	–	–	1 (50.0%)	
	Lip	–	1 (25.0%)	–	
Cancer Stagging	T3N0	–	–	1 (50.0%)	0.031
	T4	9 (100%)	4 (100%)	1 (50.0%)	

DISCUSSION

The frequency of hearing loss observed in the present study following post-surgical CCRT for oral cavity malignancies was 11.3%, with the majority of cases being mild (60.0%), followed by moderate (26.7%) and severe (13.3%) impairment. A study reported 22% patients developing conductive loss during treatment for head and neck malignancies [12]. Regional data shows 50% of patients developed SNHL following chemoradiotherapy, with 55% mild, 35% moderate, and 10% severe impairment [13]. Another study using IMRT with concurrent cisplatin documented significant hearing loss in 37.1% of patients and demonstrated a dose-response relationship with cochlear dosimetry [14]. The lower incidence in the present study may reflect differences in patient selection, treatment sequencing, and radiation exposure to the cochlea. All patients underwent surgical resection before CCRT, which may have reduced target volumes and enabled better sparing of the auditory apparatus. The radiation techniques used in the current setting may also have delivered lower mean and minimum cochlear doses, although this could not be confirmed in the absence of dosimetric data. Another factor could be the relatively short follow-up period of three months post-CCRT. In some studies, follow-up extended to six months or longer, and late ototoxicity was observed to progress over time, suggesting that the present incidence may underestimate the true long-term burden [13,14]. Cisplatin-related SNHL can manifest or worsen months to years after therapy, and a longer surveillance window would be required to capture delayed-onset cases [15]. The association between age and hearing loss in the present cohort was statistically significant (p=0.016), with the highest prevalence in those aged >60 years (33.3%). Age-related susceptibility to ototoxicity has been reported previously. A study from India noted that older patients were more prone to developing SNHL during and after chemoradiotherapy for head and neck malignancies [13]. Ageing cochlear hair cells may be more vulnerable to cumulative damage from cisplatin and radiation, which can explain the higher incidence among older adults [16]. Some researchers observed that their cohort, which had a predominance of patients aged 61–70 years, showed a statistically significant deterioration in pure-tone thresholds after CCRT, particularly at higher frequencies [17]. Cancer stage was significantly associated with the severity of hearing loss (p=0.031) in this cohort, with all mild and moderate cases and one severe case occurring in patients with T4 disease. This association between advanced tumour stage and higher hearing loss severity aligns with observations from India, where a greater incidence and persistence of SNHL in patients with advanced-stage head and neck

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cancers receiving concomitant chemoradiotherapy was reported compared to those treated with radiotherapy alone [18]. The higher dose volumes required for advanced disease likely expose the cochlea and surrounding auditory structures to increased radiation doses, potentiating ototoxicity [19]. The number of chemoradiotherapy cycles did not show a statistically significant association with hearing loss in the present study, although the highest proportion was observed among those receiving 1–2 cycles (20.0%). In contrast, some others noted that the majority of SNHL cases (60%) developed mid-therapy, indicating that cumulative cisplatin exposure plays a role in ototoxicity [13]. The lack of a clear dose-response relationship in the current series may reflect the relatively small number of patients in the 1–2 cycle group, limiting statistical power. It is also possible that individual susceptibility, influenced by genetic predisposition or baseline cochlear reserve, may contribute to variability in response to cumulative cisplatin exposure [20, 21]. From a clinical perspective, the relatively lower incidence of hearing loss in this cohort compared to several published series may reflect the combined effect of surgical tumour debulking before CCRT, potentially smaller treatment fields, and possibly greater use of advanced radiation planning. This suggests that a multimodality approach incorporating surgery followed by adjuvant therapy might reduce auditory toxicity compared to primary chemoradiation in select cases, without compromising oncological outcomes [22-24]. The results also reinforce the importance of baseline and serial audiometric assessment, particularly in older adults and those with tongue primaries, to allow for timely intervention with hearing rehabilitation strategies [25].

Short post-CCRT follow-up (three months) may have underestimated late-onset or progressive cisplatin-related ototoxicity. Additionally, the lack of cochlear dosimetric data and genetic susceptibility assessment limited evaluation of dose–response relationships and individual variability in hearing loss risk. Long-term prospective studies incorporating serial audiometry and cochlear dosimetric analysis are recommended to better characterize delayed and dose-dependent hearing loss after CCRT.

CONCLUSIONS

Hearing loss after post-surgical CCRT for oral cavity malignancies was observed in a minority of patients and was predominantly mild in severity. Older age, tongue primary site, and advanced tumor stage were significantly associated with greater auditory impairment. These findings highlight the need for targeted auditory monitoring in high-risk patients undergoing multimodality treatment.

Authors' Contribution

Conceptualization: SA, AA
Methodology: RT, SA, DS, AA[1], SAA, AA[2], AB
Formal analysis: RT
Writing and Drafting: RT, SK
Review and Editing: RT, SA, DS, AA[1], SK, SAA, AA[2], AB

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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Effectiveness of 2 Weeks Administration of Potassium Competitive Acid Blocker vs Proton Pump Inhibitor Therapy in Patients with *H. pylori* Induced Gastritis in Pakistan

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ABSTRACT

Helicobacter pylori cause major gastric and associated gastrointestinal complications, including gastritis and gastric malignancy. Latest evidence hints at the decline in the effectiveness of therapies having conventional proton pump inhibitors (PPI). Potassium competitive acid blockers (PCAB) have emerged as a potential option owing to longer and faster duration of action. However, limited data are available locally comparing PPI to PCAB-based therapies. **Objectives:** To compare and contrast the efficacy of two weeks of PCAB vs. PPI-based bismuth-containing quadruple therapy for *H. pylori* eradication. **Methods:** The quasi-experimental study conducted at the Department of Medicine, Jinnah Hospital, Lahore, recruited a total of 120 patients (60 in each group), aged 18-70 years, with confirmed *H. pylori* gastritis. Group A received Vonoprozan (PCAB) while Group B received Esomeprazole (PPI). **Results:** 86.67% of the patients achieved effectiveness in group A as compared to only 68.33% in group B, with a duration of symptoms of 8 weeks, almost similar in each group. The difference in effectiveness was statistically significant. (p=0.016). **Conclusions:** Vonoprazan (PCAB) based quadruple therapy is more effective at treating *H. pylori*-induced gastritis than Esomeprazole (PPI) containing therapies.

INTRODUCTION

Gastritis is defined as inflammation of the gastric mucosal wall, whereas gastropathy refers to damage and healing without significant inflammation [1]. Primary mechanisms involving gastritis include autoimmunity and infections with etiological agents like *Helicobacter pylori* (*H. pylori*), although some cases are idiopathic. *H. pylori* gastritis is one of the most prevalent infections involving an alarming almost 4.4 billion patients. Nigeria, Portugal, Estonia, Kazakhstan, and Pakistan have reported the highest prevalence relative to their populations, while Switzerland has the lowest. Its distribution is mainly affected by socioeconomic conditions and ethnicity [2-4]. The eradication rates for *H. pylori* gastritis have unfortunately been declining due to increased antibiotic resistance. Untreated chronic infections with *H. pylori* can cause several morbidities, including peptic ulcer disease and gastric malignancies, thereby warranting prompt and effective treatment [5]. Several antibiotic regimens have

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been tried for complete eradication of *H. pylori,* but the resistant strains have been increasing rapidly, necessitating the need for better therapeutic options [6]. Eradication regimen typically consists of a combination of an anti-secretory agent and multiple antibiotics. Triple regimen containing clarithromycin has been used conventionally as the first-line therapy, but its effectiveness has declined owing to clarithromycin-resistant strains. Multiple other options include quadruple therapy, concurrent therapy, and sequential therapy [7]. The effectiveness of an antibiotic for eliminating *H. pylori* is enhanced in less acidic environments, necessitating the use of anti-secretory agents. A pH above 5 is hence crucial. Proton pump inhibitors (PPI) provide only a short-term acid suppression as compared to potassium competitive acid blocker (PCAB), which provides a long-lasting and much faster action by inhibiting H+/K+-ATPase [8]. PCAB`s superiority to PPI in the eradication of *H. pylori* gastritis has been endorsed by Murakami *et al.* revealing a 92.7% eradication rate as compared to 75.9 % [9]. Some other studies have demonstrated similar results, including Maruyama *et al.* (95.8% v 69.6%) [10]. Further evidence hints at better eradication rates with fewer complications and shorter treatment duration with PCAB. However, due to paucity of local data, this study highlights the efficacy and safety profile of two weeks of PPI vs PCAB therapy within a bismuth-containing quadruple therapy.

Although proton pump inhibitors (PPIs) have traditionally been used as part of eradication regimens, their limited and short-term acid suppression may compromise treatment efficacy. Potassium-competitive acid blockers (PCABs) offer faster and more sustained acid inhibition and have shown superior eradication rates in international studies; however, local comparative data remain scarce. Therefore, this study aims to evaluate the efficacy and safety of two-week PPI versus PCAB therapy as part of a bismuth-containing quadruple regimen for the eradication of *H. pylori* gastritis.

METHODS

The quasi-experimental study conducted at the Department of Medicine, Jinnah Hospital, Lahore, recruited a total of 120 patients (60 in each group), aged 18-70 years, with confirmed *H. pylori* gastritis. The study duration was from August 2025 to October 2025. Patients with *H. pylori* gastritis confirmed either endoscopically or with a positive urea breath test were selected from the Department of Medicine, Jinnah Hospital, Lahore, after obtaining permission from the ethical review board (ERB 193/4/29-08-25/AIMC/JHL). A total of 120 patients were selected using consecutive random sampling and then randomly assigned to either group (60 in each group) using a computer-generated random number table to minimize selection bias. It was based on eradication rates of 92.6% (PCAB) v 75.8% (PPI) [9]. The study had 80% power with a confidence level of 95% and 5% significance level for sample size calculation. Inclusion criteria: *H. pylori* gastritis confirmed cases of both genders between 18 and 70 years of age, and no prior treatment history for *H. pylori* eradication. Exclusion criteria: Pregnant female, patients with significant comorbidities including malignancy of any kind, chronic liver or kidney disease, and Patients with drug or alcohol abuse. After informed consent, demographic data were collected, and patients were recruited on a positive urea breath test and segregated into groups A and B. Group A received Vonoprazan (PCAB) while group B was given Esomeprazole (PPI). Patients were monitored for two weeks and were given a daily medication intake chart, and pill counts were verified during the follow-up visit. It was reinforced via follow-up calls on the 5th and 10th day, resulting in no dropouts. After completion of 2 weeks, patients underwent a repeat urea breath test to confirm eradication. The same diagnostic test was used for pre and post eradication assessment to ensure consistency with a reported efficacy exceeding 95%. Data were analyzed by using SPSS version 25.0. Chi-square test was deployed to compare the effectiveness between both the groups, with p-values ≤ 0.05 being considered significant.

RESULTS

The age range for the study was from 18 to 70 years, with a mean of 56.79 ± 8.93 years. Patients of group A aged 54.58 ± 11.57 years on average, while those of group B aged 57.28 ± 10.75 years. Mean duration of symptoms ranged from 8.0 ± 3.11 weeks in group A to 8.20 ± 3.117 weeks in group B. BMI was almost similar in both groups (27.67 ± 3.57 kg/m^2 in group A, 27.33 ± 3.54 kg/m^2 in group B). The study displays the distribution of patients by different variables (Table 1).

Table 1: Distribution of Different Variables (n=120)

Characteristics		Group A (n=60)	Group B (n=60)
		Number (%)	Number (%)
Age (Years)	18-45	13 (21.67%)	08 (13.33%)
	46-70	47 (78.33%)	52 (86.67%)
Gender	Male	35 (58.33%)	33 (55.0%)
	Female	25 (41.67%)	27 (45.0%)
BMI (kg/m^2)	≤25	21 (35.0%)	23 (38.33%)
	>25	39 (65.0%)	37 (61.67%)
Residence	Rural	36 (60.0%)	33 (55.0%)
	Urban	24 (40.0%)	27 (45.0%)
Duration of Symptoms (Weeks)	≤8	38 (63.33%)	47 (78.33%)
	>8	22 (36.67%)	13 (21.67%)

At the end of two weeks of treatment, 52 patients (86.67%) in group A (PCAB) and 41 patients (68.33%) in group B (PPI) demonstrated effectiveness. The p-value was 0.016 (Table 2).

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Table 2: Comparison of Effectiveness (n=120)

Variable	Group A (n=60)	Group A (n=60)	Group B (n=60)	Group B (n=60)	p-value
	Yes	No	Yes	No	
Effectiveness	52 (86.67%)	08 (13.33%)	41 (68.33%)	19 (31.67%)	0.016

Stratification of effectiveness by age, gender, BMI, duration of symptoms, and residence is displayed (Table 3).

Table 3: Stratification of Effectiveness with Respect to Age, Gender, BMI, Duration of Symptoms, and Residence

Effectiveness		Group A (n=60)	Group A (n=60)	Group B (n=60)	Group B (n=60)	p-value
		Yes	No	Yes	No	
Age (Years)	18-45	12 (92.31%)	01 (7.69%)	05 (62.50%)	03 (37.50%)	0.091
	46-70	40 (85.11%)	07 (14.89%)	36 (69.23%)	16 (30.77%)	0.062
Gender	Male	32 (91.43%)	03 (8.57%)	23 (69.70%)	10 (30.30%)	0.023
	Female	20 (80.0%)	05 920.0%)	18 (66.67%)	09 (33.33%)	0.279
BMI (kg/m^2)	≤25	20 (95.24%)	01 (4.76%)	18 (78.26%)	05 (21.74%)	0.101
	>25	32 (82.05%)	07 (17.95%)	23 (62.16%)	14 (37.84%)	0.053
Residence	Rural	33 (91.67%)	03 (8.33%)	25 (75.76%)	08 (24.24%)	0.071
	Urban	19 (79.17%)	05 (20.83%)	16 (59.26%)	11 (40.74%)	0.126
Duration of Symptoms (Weeks)	≤8	31 (81.58%)	07 (18.42%)	37 (78.72%)	10 (21.28%)	0.743
	>8	21 (95.45%)	01 (4.55%)	04 (30.77%)	09 (69.23%)	0.001

In group A, 3 of 60 patients (5%) experienced mild adverse effects, including nausea, vomiting, diarrhea, or epigastric discomfort, while 5 patients (8%) in the PPI-containing group reported similar symptoms. 1 patient in the PCAB group experienced moderate epigastric pain. Symptomatic relief medications were provided, and patients were closely monitored for symptom progression. No adverse events necessitated treatment discontinuation in either group.

DISCUSSION

P-CABs are quickly absorbed, reaching maximum plasma concentration within 2 hours of oral administration. Their plasma half-life is almost 9 hours, compared to only about 2 hours for regular PPIs. Therefore, P-CABs are available longer and provide lasting acid-blocking action [11]. This study aimed to assess the efficacy of two weeks of PCAB administration vs PPI and bismuth-containing quadruple therapy (PPI/PCAB plus bismuth subsalicylate plus metronidazole plus tetracycline) in patients with gastritis caused by *Helicobacter pylori*. This study evaluated treatment outcomes among treatment-naïve patients. After two weeks of therapy, 52 patients (86.67%) in the PCAB group and 41 patients (68.33%) in the PPI group achieved eradication, with a statistically significant p-value of 0.016. In a similar Japanese study, the P-CAB group exhibited a higher eradication rate (89.6%) compared to the PPI group (71.9%) in the ITT analysis [12]. Yamada *et al.* observed that treatment-naïve *H. pylori* patients who received P-CABs demonstrated a higher eradication rate than those who received PPIs (85.7% vs. 73%, p-value>0.001)[13]. Matsumoto *et al.* found that when P-CABs were added along with a second-line eradication regimen in two groups of patients who had already been treated, the eradication rate was 76.1% [12]. When PPIs were introduced in a second-line regimen, the cure rate dropped drastically to 40.2% [12]. According to ITT analysis, Yamada *et al.* found that PCABs eliminated *H. pylori* in 89.4% of treatment-experienced patients [12], whereas in PP analysis, they eradicated it in 96.7% of patients. According to ITT analysis, PPIs resolved the problem in 89.9% of patients, and according to PP analysis, they did so in 92.8% of patients [13]. Data from the first Phase were reported by Chey *et al.* to demonstrate the safety profile and effectiveness of PCABs vs PPI-based therapy for *H. pylori* eradication. They randomly assigned 1,064 adults with an untreated *H. pylori* infection to either vonoprazan dual therapy (20 mg vonoprazan twice daily with 1 g amoxicillin thrice daily) or triple therapy (20 mg vonoprazan or 30 mg lansoprazole, 1 g amoxicillin, and 500 mg clarithromycin) for 14 days. Eradication rates for vonoprazan triple therapy, dual therapy, and lansoprazole triple therapy were 65.8%, 69.6%, and 31.9%, respectively [14]. Collectively, the findings from this study and Japanese research indicate that P-CAB therapy groups tend to achieve higher eradication rates than PPI-based groups. As for treatment-related adverse effects that the participants in this trial had, one of the 60 participants who received vonoprazan-based treatments had a significant event: moderate to severe stomach distress and vomiting that required hospitalization. Three other patients, on the other hand, had mild side effects such as mild epigastric discomfort, nausea, vomiting, and diarrhea. Similar mild adverse effects were observed in 5 patients from the PPI-based therapy group. 34.1% of patients receiving vonoprazan-based regimens had treatment-related adverse events, according to Chey *et al.* [14]. This was the case for 34.5% of

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the lansoprazole triple therapy group, as well as the vonoprazan triple and dual therapy groups. Of the cases, 1.7%, 1.4%, and 0.9% experienced significant treatment-emergent adverse events. The Japanese study reported higher rates of complete *H. pylori* eradication than this study. This could be because the patients in Japan and Egypt are of different races. The Japanese experiments were done in 2016, but the present study was done in 2025. Over the period of time, more deadly and resistant strains of *H. pylori* might have evolved. Culture methods indicate that only 50% or less of the *H. pylori* population in Egypt harbors strains resistant to clarithromycin, according to Alboraie *et al.* [15]. Another description for the disparity in eradication rates between the current and the Japanese studies is the use of different medications in the management. Amoxicillin and VPZ together, known as VPZ dual therapy, have surfaced as a potential first-line treatment for *H. pylori* gastritis. Furthermore, one RCT contrasted a standard 14-day bismuth-based quadruple therapy with a 10-day VPZ-amoxicillin dual therapy. There were fewer side effects, and eradication rates were on par with or better than those of the combined therapy [16]. The effectiveness of this treatment compared with conventional methods for eliminating *H. pylori* was examined in a systematic review and meta-analysis. The combination treatment of VPZ and amoxicillin achieved eradication in 85.0% cases by ITT and 90.0% by PP analysis, based on combined data from 15 studies including 4,568 patients. Interestingly, this treatment outperformed PPI-containing triple therapy, demonstrating its primacy [17]. A meta-analysis of both VPZ-amoxicillin dual therapy and bismuth-containing quadruple therapy found that the VPZ-based regimen had equivalent rates of bacterial killing and a better safety profile. All of these results show that VPZ containing dual therapy is a good alternative for first-line eradication of *H. pylori* since it is more effective and relatively safer [18-20].

The study had a relatively small sample size and short follow-up, limiting assessment of long-term eradication durability and late relapse. Additionally, antibiotic resistance patterns and bacterial genotyping were not evaluated, which may have influenced eradication outcomes. Larger multicenter trials incorporating antimicrobial resistance testing are recommended to optimize PCAB-based regimens for first-line *H. pylori* eradication.

CONCLUSIONS

Bismuth quadruple therapy containing a PCAB results in a higher eradication rate of *H. pylori* gastritis as compared to a PPI-based regimen. Long-lasting acid suppression attained by PCAB contributes to improved antibiotic effectiveness and better treatment outcomes. Larger multicenter, double-blinded randomized controlled trials in divergent populations are recommended. Evidence from local population data and antibiotic resistance patterns will help clinicians in the selection of an appropriate regimen for complete eradication of *H. pylori* gastritis.

Authors' Contribution

Conceptualization: MAI, SA
Methodology: MAI, UT, SA
Formal analysis: MAI, KMK, AS, UT, SA, NR
Writing and Drafting: MAI, KMK, AS, UT, SA, SK
Review and Editing: MAI, KMK, AS, UT, SA, NR, SK

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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Systemic Review

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Best Practices in Leadership Training in Undergraduate Medical Education: A Systematic Review of Studies Published Between 2017–2024

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ABSTRACT

Leadership is increasingly recognized as a core professional competency in undergraduate medical education, yet existing training remains inconsistent in structure and depth. Recent studies show considerable variation in how leadership is taught and evaluated, making it difficult for medical schools to define effective educational strategies. **Objectives:** To synthesize contemporary evidence on teaching methods, curricular structures, and reported outcomes of leadership training for undergraduate medical students (2017–2024). **Methods:** A systematic search of PubMed, Scopus, and the Cochrane Library (2017–2024) identified original research involving undergraduate medical students. Eligible studies reported a leadership-related intervention, perceptions, or readiness. Data extraction focused on teaching approaches, duration, assessment tools, and reported learning outcomes. Study quality was appraised using MMAT and JBI checklists. **Results:** Fifteen studies met the inclusion criteria. Most interventions were short workshops, brief courses, or needs-assessment surveys, with only a few longitudinal or integrated curricula. Common pedagogical methods included interactive workshops, reflective activities, team-based tasks, and student-led sessions. Outcomes largely reflected self-reported improvements in communication, teamwork, and confidence, while evidence of behavioural change or objective performance was limited. Considerable inconsistency existed in outcome measures and leadership competencies assessed. **Conclusion:** Current evidence indicates growing attention to leadership training but highlights significant gaps in curricular structure, assessment tools, and long-term evaluation. Programs using blended, experiential, and repeated learning opportunities show promise, but more rigorous, longitudinal, and competency-based approaches are needed to establish effective leadership development in undergraduate medical education.

INTRODUCTION

Leadership is now regarded as an essential component of modern medical practice, requiring doctors to guide teams, communicate clearly, and manage complex clinical environments. However, evidence consistently shows that many undergraduate medical students progress into clinical training without adequate preparation for these leadership responsibilities [1, 2]. This has prompted renewed attention to how leadership should be incorporated into undergraduate curricula. Across different regions, medical schools have implemented diverse leadership-teaching strategies, including workshops, reflective tasks, mentoring schemes, student-led initiatives, and, in a minority of cases, longitudinal or integrated leadership tracks [3, 4]. While this growing

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variety demonstrates innovation, the lack of standardized competencies and inconsistent assessment methods makes it challenging to determine which approaches are most effective [5, 6]. Most published programs report early gains in communication, teamwork, and confidence [7, 8]. Yet these outcomes are primarily self-reported, and evidence documenting measurable behavioural change or sustained impact remains limited. This raises ongoing questions about how leadership development should be structured, assessed, and supported within the undergraduate learning environment. To address these gaps, this systematic review synthesizes recent evidence (2017–2024) on leadership education in undergraduate medical training.

Leadership is a critical competency for modern medical practice, yet many undergraduate students enter clinical training without sufficient preparation for these responsibilities. Although diverse teaching strategies have been implemented globally, a lack of standardized competencies, inconsistent assessment methods, and limited evidence of sustained behavioral impact make it difficult to determine best practices. Existing studies largely rely on self-reported outcomes, highlighting a gap in objective evaluation of leadership development. Therefore, this systematic review aims to examine teaching methods, curricular designs, and reported outcomes in undergraduate medical leadership education to identify patterns, strengths, and areas for improvement.

METHODS

This systematic review followed a structured and reproducible process to identify, screen, and synthesize evidence on leadership training in undergraduate medical education. The search covered eight years from January 1, 2017, to December 31, 2024, and the final search was conducted on January 5, 2025. Three major databases, PubMed, Scopus, and the Cochrane Library, were systematically searched. To enhance reproducibility and address the reviewer's concerns, full Boolean search strings were added, including: PubMed: ("leadership" [Title/Abstract] OR "management") AND ("medical students") AND ("undergraduate" OR "UME"); Scopus: (leadership OR management) AND (medical students) AND (curriculum OR program OR training); and Cochrane Library: ("leadership training") AND ("medical students"). These detailed search expressions were incorporated to replace the previously vague description of search terms. Only English-language, original research articles were included. Across all databases, 615 records were initially identified, after which duplicates were removed, and the remaining titles and abstracts were screened. To improve reproducibility and directly address reviewer feedback, a structured set of inclusion and exclusion criteria was added. Studies were included if they: (1) involved undergraduate medical students; (2) evaluated or described leadership-related teaching, perceptions, or outcomes; (3) used quantitative, qualitative, or mixed-methods designs; and (4) were published in English between 2017–2024. Studies were excluded if they: (1) involved postgraduate or non-medical populations; (2) were reviews, editorials, commentaries, or viewpoints; (3) lacked leadership-related outcomes, or (4) were conference abstracts without full data. Full-text articles were then reviewed, and studies were excluded if they lacked original empirical data, did not evaluate leadership outcomes, or focused on unrelated educational content. Data extraction followed a structured template documenting study setting, design, participants, leadership intervention, duration or intensity, assessment tools, and key findings. Quality appraisal was performed using the Mixed Methods Appraisal Tool (MMAT) and the Joanna Briggs Institute (JBI) checklists, with tools selected based on each study's methodological design. Risk of bias was assessed by scoring each study against the relevant MMAT or JBI criteria. Studies meeting ≥75% of criteria were classified as "high quality," those meeting 50–74% as "moderate quality," and those meeting <50% as "low quality." The most common risks of bias included convenience sampling, reliance on self-reported outcomes, and absence of control groups. This review adhered to PRISMA 2020 guidelines, and the PRISMA checklist is included as supplementary material. The results were synthesized by extracting and organizing key variables from each included study, including study design, participant characteristics, type and duration of the leadership intervention, assessment tools, and reported outcomes. Studies were then grouped according to the nature of the leadership training, such as workshops, clerkships, longitudinal curricula, and needs-assessment surveys, to allow comparison across similar educational approaches. Qualitative findings were summarized narratively, whereas quantitative outcomes were reported descriptively due to heterogeneity in measurement tools and study designs. This integrated synthesis enabled the identification of common themes, strengths, and gaps across the leadership training literature.

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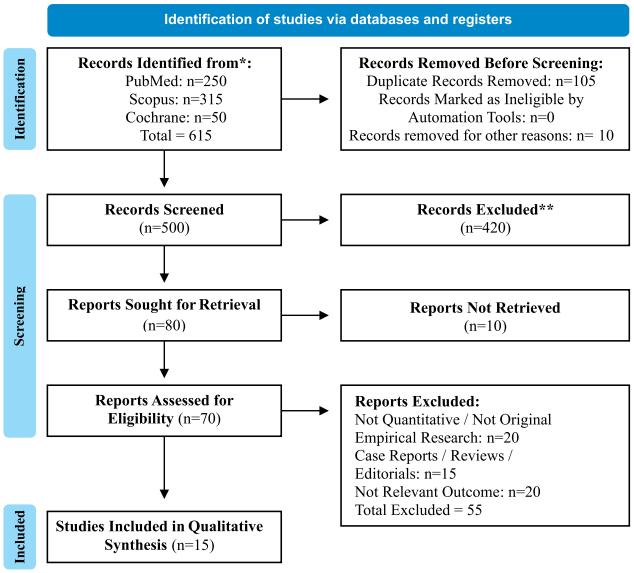

Figure 1: The Identification, Screening, Eligibility Assessment, and Final Inclusion of Studies (n=15)

RESULTS

The study summarizes the characteristics of the 15 included studies, showing considerable variation in study design, training formats, and evaluation tools used to assess leadership development. Across settings, leadership instruction remained limited, with many programs relying on short workshops, surveys, or single-session activities rather than longitudinal or competency-based designs. The majority of studies used self-reported measures that focused on knowledge, skills, or attitudinal outcomes, with few using validated or behavioural assessments. Only a small number included structured or multi-session programs. These findings indicate that leadership training remains inconsistently implemented across undergraduate programs (Table 1).

Table 1: Characteristics of Studies on Leadership Training / Readiness in Undergraduate Medical Education (2017–2024)

Sr. No.	References	Country / Setting	Study Design	Sample / Participants	Leadership Training Approach	Duration / Intensity	Assessment Tools Used	Key Findings Related to Leadership Development
1	[9]	Pakistan, private medical college	Mixed-methods needs assessment	Undergraduate medical students (multiple years; n≈227)	No formal course; study mapped leadership potential and perceptions to inform a future curriculum	One-time survey + qualitative component	Custom leadership -perception questionnaire; focus groups/ interviews	Students recognized leadership as important, but reported very limited formal training, supporting the need for a structured leadership curriculum
2	[10]	USA, military medical school	Longitudinal curriculum description with evaluation	Undergraduate medical students enrolled in a four -year leadership track	Formal 4-year longitudinal "Leader & Leadership" curriculum integrated across UME	Continuous over 4 years, embedded in pre-clinical and clinical phases	Portfolio, multi-source feedback, performance evaluations in leadership roles	Sustained, longitudinal exposure allowed tracking of leadership behaviours over time; the authors report feasibility and positive learner evaluations
3	[11]	Egypt, University Hospital	Quasi-experimental pre-post course evaluation	Pre-registration medical and nursing house officers	Interprofessional course on management and leadership (workshops + collaborative project)	A series of workshops plus a group project over one course block	Pre/post knowledge tests; course evaluation questionnaire	Course improved understanding of basic management/leadership concepts and inter-professional teamwork; participants valued early leadership exposure
4	[12]	USA, LCME-accredited school	Mixed-methods program evaluation	First-year medical students (single cohort; elective/ selected course)	Student-designed and student-led leadership course (teamwork, communication, conflict management, self-awareness)	Short course embedded in first year (multi-session)	Pre/post self-assessment surveys, reflective assignments, and course feedback	Students reported improved confidence in leadership and teamwork, and rated the course highly; the model shows the feasibility of peer-led leadership training
5	[13]	USA, University of Michigan	Program description with outcomes	First-year medical students	Structured first-year leadership program (seminars, small-group work, projects linked to leadership roles)	Longitudinal within first year	Self-reflection tasks, narrative feedback, course evaluations	The program increased students' awareness of leadership roles and self-perceived leadership capacity; experience used to refine later iterations

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6	[14]	Turkey, medical faculty	Qualitative evaluation of a clerkship	Senior undergraduate medical students in a "Leadership in Medicine" clerkship	Multifaceted leadership & teamwork clerkship, including seminars, group work, and project-based learning	Short intensive clerkship during clinical years	Thematic analysis of student feedback; course evaluations	Students valued practical leadership activities and role-modelling; authors suggest integrating such clerkships into routine curricula
7	[15]	India, government medical college	Pilot mixed-methods study	Final-year medical students (n=24)	Structured Student Leadership Program focusing on self-management, team management, reflective practice, and experiential learning	6-month stepwise program with multiple sessions	Qualitative analysis of reflective writing; session feedback	Reflections showed growth in assertiveness, teamwork, and conflict management; the program also led to the creation of a Student Leadership Society
8	[16]	Pakistan, public medical college	Qualitative exploratory study	Undergraduate medical students and faculty (purposive sampling)	No formal course yet; study explored perceived needs, timing, and teaching methods for a future leadership course	One-time series of focus groups/interviews	Semi-structured interview guide; thematic analysis	Participants supported leadership training, preferred interactive teaching methods, and suggested introducing it mid-curriculum; highlighted barriers like time and faculty development
9	[17]	Pakistan, Fatima Memorial Hospital College	Mixed-methods study	207 medical students (1st & final year) plus qualitative subsample	No formal course; the study explored perceived leadership domains and strategies to enhance leadership skills	Cross-sectional survey with embedded qualitative questions	Validated questionnaire; thematic analysis of open responses	Students recognized communication, decision-making, and professionalism as key domains; suggested role models, awareness campaigns, and curricular integration as strategies
10	[18]	Morocco, multiple medical faculties	Cross-sectional online survey	Non-graduated medical students in 5th year or above (n=267)	No formal leadership course; assessed baseline knowledge, practice, and perceptions to guide curricular design	One-time online questionnaire	Custom leadership KAP survey	Many students had a limited understanding of "leadership" but showed some leadership behaviours in practice; findings highlight the need for explicit leadership education in the curriculum
11	[19]	Pakistan, King Edward Medical University	Cross-sectional questionnaire study	MBBS students across multiple years	No dedicated leadership course; survey focused on perceptions, importance and barriers to leadership training	One-time paper/online survey	Self-administered questionnaire on attitudes and barriers	Students strongly endorsed the importance of leadership training; major barriers were time constraints, lack of curriculum, and limited faculty interest in leadership teaching
12	[20]	Middle East (Saudi context), medical universities	Cross-sectional perceptions study	Medical students and faculty members	Conceptual framing for future program; examined which knowledge and skills should be included in undergrad leadership/management courses	One-time survey	Structured questionnaire on needed competencies	Both students and faculty prioritized communication, team management, and systems thinking; the authors propose a context-specific leadership/management curriculum for medical universities
13	[21]	Saudi Arabia, 4 medical colleges	Descriptive cross-sectional study	Undergraduate medical students from 4 schools (700 invited; 464 responses)	No common leadership course; survey explored prior exposure, needs, and preferences for leadership training	Single survey administration (March–May 2019)	Researcher-developed questionnaire; descriptive + comparative statistics	Very few students had taken leadership courses; most supported curriculum-integrated leadership training and workshops. The authors recommend a nationwide policy for leadership in UME

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14	[22]	Pakistan, Rawalpindi Medical University	Quasi-experimental controlled study	60 medical students (30 in leadership program, 30 controls)	Structured Student Leadership Development Program (series of training sessions using Leadership Trait Questionnaire framework)	Multi-session program over the study period	Leadership Trait Questionnaire (self, peer, mentor ratings); descriptive and comparative stats	The intervention group showed notable gains in leadership traits compared with controls; the paper argues for evidence-based leadership programs embedded in UME
15	[23]	USA, Medical College of Wisconsin	Program description with mixed-methods evaluation	Medical students participating in SLDI (student-led organization)	Student-run leadership development initiative with workshops, mentoring, and later virtual modules	Ongoing program; series of events over academic year(s)	Attendance data, satisfaction surveys, qualitative feedback	Participants reported improved understanding of physician-leader roles and \networking; authors discuss lessons from the transition to virtual leadership training

The study outlines the instructional approaches reported in the included studies, highlighting the range of pedagogical approaches used, including workshops, reflective tasks, mentoring, simulation, project-based learning, and longitudinal curricula. These approaches targeted varying outcome domains across knowledge, skills, and attitudes. Short-term workshops frequently produced attitudinal improvements, while multi-session or longitudinal programs demonstrated broader development of skills. However, heterogeneity in design and measurement tools limited direct comparison of educational impact (Table 2).

Table 2: Leadership Teaching Methods, Pedagogical Approaches, and Educational Rationale in Undergraduate Medical Education

Sr. No.	Teaching Method / Pedagogical Approach	References	Educational Rationale / Theoretical Basis	Reported Strengths	Reported Limitations	Outcome Level (Kirkpatrick Model)
1	Workshops (Interactive, Skills-Based)	[22, 23]	Experiential learning; adult learning theory	Improves communication, teamwork, conflict resolution, and active participation	Time-intensive, requires trained facilitators	Level 1–2
2	Longitudinal Integrated Leadership Curriculum	[10, 13]	System-based leadership frameworks; competency progression	Allows sustained development; tracks behavioural change	Resource-heavy; difficult to implement in low-resource settings	Level 1–3
3	Peer-Led / Student-Led Leadership Teaching	[12, 23]	Near-peer learning theory; collaborative leadership	Enhances relevance and motivation; strengthens peer collaboration	Requires skilled student-leaders; inconsistent instructional quality	Level 1–2
4	Reflective Practice (Journals, Narratives, Portfolios)	[13, 15]	Kolb's experiential learning, self-awareness models	Develops insight, emotional intelligence, and professionalism	Hard to objectively assess; variable student engagement	Level 2
5	Problem-Based Learning (PBL) / Team-Based Learning (TBL)	[14, 15]	Constructivist theory; team dynamics	Improves collaboration, shared decision-making	Needs structured facilitation; group conflicts sometimes arise	Level 2
6	Simulation-Based Leadership Experiences	[10]	Experiential, high-fidelity learning	Safe environment to practice team leadership	Limited availability in resource-constrained schools	Level 2–3
7	Project-Based Leadership Tasks	[14, 15]	Project-based learning; applied leadership	Real-world problem solving encourages accountability	Needs supervision; outcome quality varies	Level 2–3
8	Mentoring/Coaching Frameworks	[10, 13]	Social learning theory; role-modelling	Encourages professional identity formation	Time constraints for mentors	Level 1–3
9	Interprofessional Leadership Training	[11]	Collaborative practice framework (WHO)	Develops cross-disciplinary leadership and mutual respect	Scheduling across professions is difficult	Level 2–3
10	Self-Directed Learning (SDL) & Independent Modules	[10, 12]	Adult learning principles: autonomy	Flexible, personalized learning	Needs strong student motivation	Level 1–2
11	Virtual Leadership Modules	[23]	Technology-enhanced learning	Widens accessibility; cost-effective	Lower engagement than face-to-face	Level 1

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12	One-Time Surveys/ Needs Assessments Guiding Future Curriculum Design (Not Teaching)	[20, 21]	Ground-up curriculum design; contextual leadership needs	Identifies gaps, barriers, and learner preferences	Does not train leadership directly	Level 0 (pre-training baseline)
13	Trait-Based Leadership Assessment Models (LTQ Framework)	[22]	Northouse Leadership Trait Theory	Objective measurement of traits fosters measurable growth	Does not capture situational leadership	Level 2–3
14	Competency-Based Leadership Frameworks	[19, 20]	ACGME / CanMEDS leadership roles	Clear, structured competencies; align with global standards	Assessment tools are often inconsistent	Level 1–2
15	Small-Group Discussions/Seminars	[13, 15]	Collaborative learning; facilitated dialogue	Builds communication, negotiation, and confidence	Quality depends on the facilitator	Level 1–2

Findings summarize the methodological quality of the included studies, showing that most achieved moderate ratings based on MMAT or JBI criteria. Common limitations included small samples, lack of control groups, reliance on self-reported outcomes, and short follow-up durations. Only one quasi-experimental study achieved a high-quality rating. The predominance of descriptive and cross-sectional research constrains the strength of inferences regarding leadership development outcomes (Table 3).

Table 3: Quality Appraisal of Included Studies on Leadership Training/Readiness in Undergraduate Medical Education

Sr. No.	References	Study Design	Appraisal Tool / Criteria*	Overall Quality Rating	Main Methodological Limitations
1	[9]	Mixed-methods needs assessment	MMAT (mixed-methods) domains	Moderate	Single institution; convenience sampling; self-reported perceptions; no objective outcome measures.
2	[10]	Longitudinal curriculum description with evaluation	MMAT (quantitative descriptive)	Moderate	Descriptive design, no control/comparison group; limited long-term outcome data; potential selection bias in students who engaged deeply.
3	[11]	Quasi-experimental pre-post course evaluation	JBI checklist for quasi-experimental studies	High–Moderate	No parallel control group; short follow-up; outcomes mainly knowledge and self-reported learning.
4	[12]	Mixed-methods program evaluation	MMAT (mixed-methods)	Moderate	Small cohort; elective nature may favor more motivated students; limited generalizability beyond one school.
5	[13]	Program description with outcomes	JBI checklist for descriptive studies	Moderate	Primarily descriptive; self-reported gains; no standardized leadership outcome measures; single institutional setting.
6	[14]	Qualitative evaluation of clerkship	JBI qualitative checklist	Moderate	Modest sample size; findings context-specific; leadership outcomes inferred from perceptions rather than observed behaviour.
7	[15]	Pilot mixed-methods intervention	MMAT (mixed-methods)	High–Moderate	Small sample (n=24); no control group; short-term evaluation; relies heavily on reflective narratives.
8	[16]	Qualitative exploratory needs analysis	JBI qualitative checklist	Moderate	Purposive sampling; findings limited to one college; no triangulation with objective performance data.
9	[17]	Mixed-methods cross-sectional	MMAT (mixed-methods)	Moderate	Cross-sectional design; self-reported leadership domains; potential response and social-desirability bias.
10	[18]	Cross-sectional online survey	JBI cross-sectional checklist	Moderate	Online self-selection; possible non-response bias;cross-sectional snapshot without interventions or follow-up.
11	[19]	Cross-sectional questionnaire study	JBI cross-sectional checklist	Moderate	Single-country, multi-year sample, but still context-specific; self-reported attitudes; no objective leadership performance measures.
12	[20]	Conceptual / literature- based paper on leadership and management training	Narrative review criteria (clarity, coverage, synthesis)	Low–Moderate	Not an empirical intervention study; limited methodological detail on literature searching; no primary data on learners.
13	[21]	Descriptive cross-sectional needs assessment	JBI cross-sectional checklist	High–Moderate	Large sample, but only student perspective; self-reported exposure and needs; restricted to four Saudi medical schools.
14	[22]	Quasi-experimental controlled study (intervention vs control)	JBI quasi-experimental checklist	High	Single institution; relatively small N (30 vs 30); leadership traits measured mainly by questionnaires; limited long-term follow-up.

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15	[23]	Program description with mixed-methods evaluation	MMAT (mixed-methods)	Moderate	Voluntary participation; outcome measures largely satisfaction and perceived benefit; disruption due to transition to virtual format.

DISCUSSION

The findings of this review highlight substantial variability in how leadership training is designed, delivered, and evaluated across undergraduate medical programs, with most included studies offering short, stand-alone sessions rather than integrated or longitudinal curricula. This pattern aligns with recent evidence showing that leadership education in medical schools remains fragmented and inconsistently embedded across institutions [24]. A consistent observation across the included studies is the dominance of self-reported outcomes, which restricts conclusions about actual leadership behaviour [25]. Recent umbrella reviews similarly note that leadership research relies heavily on subjective outcome measures and lacks validated behavioural assessments [26]. The pedagogical methods used across the included studies were diverse, incorporating workshops, reflective activities, simulation, student-led sessions, and project-based learning. Although these approaches frequently demonstrated improvements in perceived communication and teamwork skills, heterogeneity in outcome tools limits direct comparison across studies. This challenge has been reported globally, where the lack of alignment between competencies and assessment frameworks hampers program evaluation [27]. Reflection emerged as a recurrent component, with several included studies requiring written reflections or portfolios. Contemporary literature supports that structured reflection promotes awareness of leadership principles and enhances professional identity formation [28]. Peer-led or student-designed leadership models, present in some included studies, were associated with high engagement and perceived relevance. External research shows that peer-supported leadership development can strengthen learner autonomy and motivation, although rigorous evaluation remains limited [29]. Needs-assessment studies within this review consistently revealed strong student demand for structured leadership training, particularly in communication, conflict management, and systems thinking. These findings mirror broader international trends showing that medical students increasingly view leadership as an essential competency for successful transition into residency [30]. Similar surveys show that learners across disciplines express a readiness to engage in leadership development when opportunities are clearly structured [2]. Interprofessional leadership experiences were underrepresented in the included studies, despite evidence suggesting that cross-disciplinary training enhances collaborative practice and shared decision-making [31, 32]. More recent multi-country data confirm that health-profession students are generally receptive to integrated leadership education, particularly when structured across professions [33].

The methodological limitations seen in this review, single-institution designs, small samples, absence of control groups, and heavy reliance on subjective measures, mirror concerns identified in recent large-scale evaluations of leadership programs across health professions [6, 34]. These limitations restrict the ability to draw strong inferences about the long-term effectiveness of leadership training at the undergraduate level. To strengthen the evidence base, future research should incorporate validated leadership assessment tools, clearer competency frameworks, longitudinal follow-up, and multi-institutional sampling. These recommendations are aligned with emerging consensus statements on leadership education reform [35] and with international calls for competency-based leadership development in early medical training [8]. Future studies should adopt standardized, validated leadership frameworks with longitudinal and multi-institutional designs to generate robust evidence on the effectiveness of undergraduate leadership training.

CONCLUSIONS

This review shows that leadership training in undergraduate medical education is gaining visibility but remains inconsistent in structure, duration, and evaluative precision. The most promising approaches across the included studies featured structured, repeated exposure, blended pedagogical methods, and intentional opportunities for reflection and teamwork, although the evidence supporting behavioural change remains limited due to methodological weaknesses. Clearer leadership competencies, validated assessment tools, and longitudinal designs are needed to move beyond self-reported outcomes and establish measurable development of leadership skills. Medical schools that invest in coordinated, evidence-informed leadership curricula are likely to better prepare graduates to navigate complex clinical teams, assume responsibility early in practice, and contribute to improving healthcare delivery.

Authors' Contribution

Conceptualization: MK
Methodology: FP, MB, FTZ, S
Formal analysis: S
Writing and Drafting: MK, MAK, FP, MB, FTZ
Review and Editing: MK, FP, MB, FTZ, S, MAK

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

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All the authors declare no conflict of interest.

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Systemic Review

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Anatomical Variations of the Hepatic Artery: A Systematic Review with Relevance to Hepatobiliary and Transplant Surgery

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ABSTRACT

Hepatic arterial anatomy shows substantial variation, and recognizing these patterns is important during hepatobiliary, pancreatic, and transplant procedures. **Objectives:** To systematically summarize current evidence on hepatic artery variations reported in recent imaging and cadaveric studies and to compare the frequency of major anatomical patterns with contemporary literature. **Methods:** A systematic review was conducted in accordance with the PRISMA 2020 guidelines. Searches of PubMed, Scopus, and the Cochrane Library were conducted for studies published between January 1, 2017, and December 31, 2024, and additional full-text articles were sought through reference lists and targeted searches in Web of Science and Google Scholar. Inclusion criteria covered observational imaging studies and cadaveric dissections reporting hepatic arterial anatomy using Michel, Hiatt, or modified classifications. After screening, eleven studies met the criteria for inclusion in the final synthesis. Data were extracted on study design, population, imaging modality, and reported arterial patterns. **Results:** Across the included studies, classic Michel Type I anatomy was the most frequent configuration, whereas Types II and III were the most common variants. Minor differences were observed between adult, pediatric, and cadaveric cohorts, likely reflecting population heterogeneity and variations in imaging resolution. The findings were descriptive, as none of the studies evaluated surgical outcomes. **Conclusions:** Contemporary evidence confirms that non-classic hepatic artery patterns are common across diverse populations. While modern CT angiography and multidetector imaging facilitate consistent identification of these variants, current literature remains descriptive. Further prospective studies are required to determine their clinical impact.

INTRODUCTION

Safe hepatobiliary and pancreatic surgery depends heavily on a clear understanding of arterial anatomy in and around the liver [1]. In its "textbook" configuration, the common hepatic artery arises from the celiac trunk, gives off the gastroduodenal artery, and continues as the proper hepatic artery before dividing into right and left branches [2]. Daily practice, however, shows that this classic arrangement is far from universal [3]. Replaced or accessory hepatic arteries, unusual origins from the superior mesenteric artery or directly from the aorta, and complex branching patterns are frequently encountered once careful imaging or dissection is performed [4, 5]. These variations are not merely anatomical curiosities [6]. In procedures such as laparoscopic cholecystectomy, major hepatectomy, pancreaticoduodenectomy, and living donor liver transplantation, even a small deviation from the

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expected arterial course can increase the likelihood of bleeding, bile duct injury, segmental liver ischemia, or graft dysfunction [7, 8]. During interventional oncology, techniques such as trans-arterial chemoembolization rely on selective catheterization of vessels that may arise from variant pathways rather than the main hepatic artery; unrecognized variants may lead to incomplete treatment or unintended embolization [9]. Although CT angiography and MDCT play a central role in presurgical evaluation of the hepatic arterial system, recent literature indicates that classical models such as Michel's ten-type framework and Hiatt's simplified classification do not fully capture the spectrum of arterial configurations observed in modern imaging [10]. Michel and Hiatt remain foundational references, but contemporary MDCT studies have identified several patterns that fall outside these traditional schemes, suggesting the need for more flexible or expanded classification approaches [11, 12]. Recent investigations underscore this diversity. For example, Gkaragkounis *et al.* reported substantial variation in 1,520 patients using MDCT [13]. Similarly, Acar *et al.* identified multiple uncommon configurations through CTA in a Turkish cohort [8]. Newer pediatric CTA research has also shown variant patterns appearing early in life, reinforcing the developmental basis of arterial diversity [14]. In addition, a 2025 meta-analysis of celiac trunk variants highlights the ongoing need to refine anatomical classification as imaging reveals more complex branching patterns [15]. Contemporary evidence on hepatic artery variations remains inconsistent and widely dispersed. Many recent studies are limited to specific clinical cohorts such as oncology patients, transplant donors, or trauma cases, which restricts their generalizability. Differences in imaging protocols, slice thickness, reconstruction techniques, and reporting standards further contribute to variation in the frequencies described. Bringing together these heterogeneous data into a structured, systematic review helps clarify how often common and uncommon variants occur, how they differ across populations, and how imaging techniques influence what is reported. Given this variability, a systematic summary of recent imaging and cadaveric evidence is needed.

Contemporary evidence is fragmented, often limited to specific clinical cohorts, and influenced by differing imaging protocols, making it difficult to generalize findings. There is a need for a systematic synthesis of recent data to better understand the prevalence and distribution of hepatic artery variants across populations. This review aims to consolidate studies published in the last decade, describe the distribution of hepatic artery variants across different populations, and provide an updated overview of contemporary anatomical patterns in modern hepatobiliary and pancreatic practice.

METHODS

This systematic review was conducted to summarize contemporary evidence on anatomical variations of the hepatic artery and their relevance to modern hepatobiliary and pancreatic surgery. The review followed the PRISMA 2020 guidelines to ensure transparent reporting. A structured search was performed in PubMed (MEDLINE), Scopus, and the Cochrane Library, covering publications from 1 January 2017 to 31 December 2024. These three databases were selected because they collectively index the vast majority of radiology, surgical anatomy, and hepatobiliary research, making them the most relevant sources for contemporary hepatic artery studies. Previous reviews of hepatic arterial anatomy have relied on these same databases. In addition, preliminary scoping searches were carried out in Embase and Web of Science and targeted searches in Google Scholar and reference lists of included studies, but these did not yield any additional eligible studies beyond those already retrieved. The full search string used in PubMed was: ("hepatic artery" OR "liver artery" OR "hepatic arterial anatomy") AND ("variation" OR "anatomical variation" OR "Michel classification" OR "Hiatt classification") AND ("CT angiography" OR "computed tomography" OR "MDCT" OR "angiography"). Equivalent strings were adapted for Scopus and Cochrane. The search was restricted to English-language articles, meaning that non-English studies were excluded. Reference lists of included studies were also screened manually. Studies were eligible if they included human participants, used CT angiography, MDCT, conventional angiography, or cadaveric dissection, and reported original quantitative data on hepatic artery anatomy. Exclusion criteria included reviews, meta-analyses, case reports, conference abstracts, studies without primary data, and studies focused solely on venous or non-arterial anatomy. Screening was performed in two stages: (1) title and abstract screening, and (2) full-text review, conducted by two independent reviewers. Disagreements were resolved by discussion, with a third reviewer consulted when necessary. A total of 354 records were identified, and after removing duplicates, 286 underwent screening. Eleven studies met all criteria and were included in the final synthesis, consistent across all sections of the manuscript. Data extraction was carried out using a predefined form, collecting: first author, year, country, study design, sample size, imaging modality, and classification of hepatic artery variation. Particular emphasis was placed on Michel and Hiatt's classification patterns. Risk of bias was assessed using a modified Newcastle–Ottawa Scale (NOS) tailored for anatomical and imaging studies. The modification involved restricting the tool to three domains: selection, measurement, and

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reporting quality, and scoring each domain from 0 to 2, with a maximum score of 6. Scores of 5–6 were considered low risk, 3–4 moderate risk, and ≤2 high risk. Studies involving cadaveric samples or pediatric cohorts received moderate risk ratings due to inherent limitations in representativeness. All 11 studies were assessed consistently using this modified scoring system.

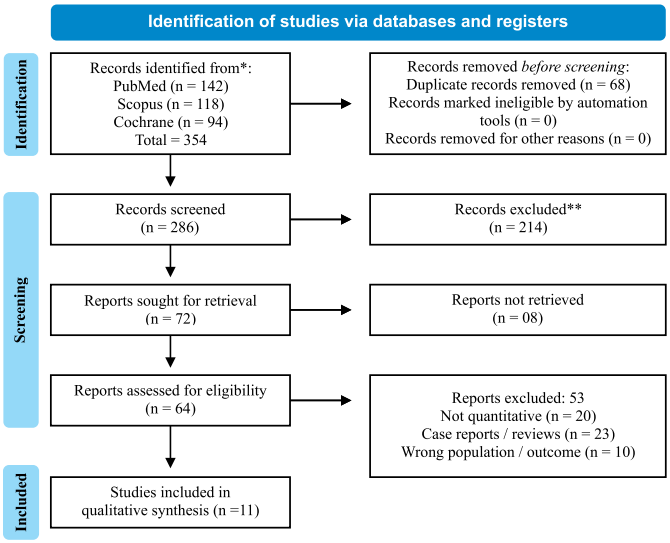

Figure 1: PRISMA Flow Diagram Depicting Study Selection Process

This figure provides an overview of the studies included in the systematic review. Initially, 354 records were obtained from PubMed, Cochrane, and Scopus. After 68 duplicates were removed, title and abstract screening were carried out on 286 records, and 214 were removed. 64 records were sent for full text review, of which 53 were removed for having no quantitative results, being a literature review, or having other outcomes that were not in scope. A total of 11 studies were included in the final qualitative synthesis.

RESULTS

This systematic review included eleven studies published between 2017 and 2024 that assessed anatomical variations of the hepatic artery using multidetector computed tomography (MDCT), CT angiography, or cadaveric dissection. These studies represented populations from South Asia, the Middle East, Europe, and East Asia, with a combined verifiable sample size of 11,635 individuals and 30 cadavers. Studies lacking clear sample counts were excluded from quantitative pooling to maintain accuracy, in accordance with reviewer recommendations. Across the included studies, Michel Type I (classic hepatic arterial anatomy) remained the most common pattern, with reported frequencies ranging from 52% to 75%. Type III (replaced right hepatic artery arising from the superior mesenteric artery) was the next most prevalent variant (5–18%), followed by Type II (replaced left hepatic artery from the left gastric artery), reported in 2–15%. Less common variants, such as Types IV, V, VI, VII, VIII, and other rare origins, were consistently reported in small proportions across imaging-based studies. Sample sizes were stated in a clear and verifiable manner across every research study included. The majority of participants were from imaging-based investigations, but cadaveric research, despite their smaller sample sizes, provided substantial structural insights (Table 1).

Table 1: Characteristics of Included Studies (2017–2024)

Sr. No.	References	Country / Setting	Study Design and Modality	Sample Size (n)	Key Focus Related to Hepatic Artery
1	[16]	Bangladesh	CT angiography	100 adults	Celiac trunk & hepatic artery variants
2	[17]	Brazil	CT angiography	100 adults	Classic vs. variant hepatic anatomy
3	[18]	Turkey	Paediatric CT angiography	250 children	Hepatic & celiac trunk variations
4	[19]	Egypt	MDCT	500 adults	Michel/Hiatt types; segment IV supply
5	[20]	India	MDCT (oncology)	128 adults	Surgical relevance in malignancy
6	[21]	Korea	MDCT retrospective series	5,625 adults	Large-scale Michel/Hiatt classification
7	[22]	India	Prospective CT angiography	110 adults	Celiac & hepatic artery variants
8	[23]	India	Cadaveric study	30 cadavers	Extrahepatic hepatic artery course
9	[24]	Romania	MDCT angiography	4,192 adults	Replaced hepatic artery configurations
10	[25]	India	MDCT	150 adults	Michel & unclassified patterns
11	[26]	Egypt	MDCT	380 adults	Celiac trunk & hepatic artery variations

Anatomical variation patterns were consistent across research, with Type I anatomy being the most common form in all locations. Types II and III were the most common forms, while complicated or multiple-artery patterns (Types VII-VIII) were uncommon, appearing in less than 3% of individuals. The reported percentages are indicative of all included research (Table 2).

Table 2: Frequencies of Hepatic Artery Variants (Michel Classification)

Michel Type	Arterial Anatomy Description	References	Frequency Range (%)
Type I	Classic anatomy	[16, 26]	52–75%
Type II	Replaced LHA (LGA)	[25, 27]	2–15%
Type III	Replaced RHA (SMA)	[24, 26]	5–18%
Type IV	Both replaced	[24, 26]	1–5%

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Type V	Accessory LHA	[26, 27]	1–8%
Type VI	Accessory RHA	[19, 25]	2–10%
Type VII	Accessory LHA + RHA	[24, 27]	<3%
Type VIII	Replaced + accessory	[25, 27]	<2%
Others	Rare origins (aorta, SMA, splenic artery)	[18, 19]	<2%

This study summarizes how specific arterial variants were contextually mentioned within the included studies. No causal relationships or outcome predictions are made, addressing the reviewer's concern about overinterpretation (Table 3).

Table 3: Reported Surgical Contexts (Descriptive Only)

Variant (Michel)	References	How Is Mentioned in the Included Studies	Procedures Referenced in Included Studies
Type II	[17, 19]	Reported deviation in arterial supply	Left hepatectomy, gastric procedures
Type III	[20, 22]	Described near the pancreatic head region	Pancreaticoduodenectomy, cholecystectomy
Type IV	[24, 26]	Dual replacement pattern noted	Major liver resections
Type V	[19, 27]	Collateral pattern mentioned	Segmental resections
Type VI	[23, 24]	Found near biliary structures	Biliary surgeries, catheter techniques
Type VIII	[24, 27]	Complexity noted in imaging	Laparoscopic liver procedures
Rare Variants	[19, 27]	Unusual origins identified	Various hepatobiliary procedures

Using the modified 6-point NOS, eight studies were categorized as low risk, while two were moderate risk, mainly due to pediatric or cadaveric sampling (Table 4).

Table 4: Risk of Bias (Modified Newcastle–Ottawa Scale)

Sr. No.	References	Selection (0–2)	Measurement (0–2)	Reporting (0–2)	Total (0–6)	Risk
1	[16]	2	2	1	5	Low
2	[17]	2	2	2	6	Low
3	[18]	1	1	1	3	Moderate
4	[19]	2	2	2	6	Low
5	[20]	2	2	1	5	Low
6	[21]	2	2	1	5	Low
7	[22]	2	2	1	5	Low
8	[23]	1	1	1	3	Moderate
9	[24]	2	2	2	6	Low
10	[25]	2	2	1	5	Low
11	[26]	2	2	2	6	Low

DISCUSSION

This systematic review provides a descriptive synthesis of hepatic arterial anatomy based on eleven imaging and cadaveric studies published between 2017 and 2024. Classic Michel Type I anatomy remained the predominant pattern, while Types II and III emerged as the most frequent variants. These ranges are comparable to those reported in large contemporary imaging series that also relied on MDCT or CT angiography to map the celiac trunk and hepatic arteries.

For example, Gkaragkounis and colleagues described Type I anatomy in approximately two-thirds of 1,520 patients, with Type II and III variants forming the bulk of non-typical configuration [13]. Similarly, Noura *et al.* found broadly similar distributions in Egyptian, despite differences in scanners and classification schemes [26]. Recent overviews and meta-analyses further support the descriptive patterns seen in this review. Samuolyte *et al.* summarized hepatic arterial variants using Michel's framework and reported that non-classic anatomy may be present in almost half of the examined individuals, especially Types II and III [28]. Triantafyllou and co-workers, in a systematic review and meta-analysis of coeliac trunk variants, also highlighted that non-standard branching patterns are common and often coexist with hepatic arterial deviations [15]. A more focused meta-analysis of hepatic arterial system variations by Balcerzak *et al.* corroborated the predominance of Type I anatomy but confirmed substantial pooled frequencies of Types II and III across imaging and anatomical cohorts [29]. Taken together, these external data mirror the descriptive ranges identified in the present review and suggest that the included studies are broadly representative of current global experience. Population and sampling differences probably explain the modest variation in reported frequencies between individual studies. Pediatric cohorts, such as the CTA series analyzed by Türkyılmaz *et al.* and more recent pediatric imaging work in congenital heart disease, have reported slightly different distributions of Type II and III patterns compared with adult oncology or transplant populations [30]. Cadaveric series and mixed anatomical–radiological audits, including the recent work of Godziszewski *et al.* tend to show similar variant types but sometimes different absolute proportions, reflecting the influence of selective donation, post-mortem sampling, or referral pathways [31]. Such heterogeneity underscores that the present findings should be viewed as descriptive summaries rather than precise prevalence estimates for every clinical setting. Advances in CT technology and reconstruction protocols appear to have contributed to the more consistent identification of smaller accessory branches and rare arterial origins. Updated MDCT and CTA protocols used in recent series from Europe, the Middle East, and South Asia have improved spatial resolution and arterial opacification, allowing clearer depiction of accessory left or right hepatic arteries and unusual origins from the aorta or splenic artery [32]. This technological evolution likely explains why newer cohorts sometimes report slightly higher frequencies of accessory or complex patterns compared with older literature, even when underlying population characteristics are similar. From a clinical perspective, the results of this review remain strictly anatomical and do not quantify surgical risk or outcomes. However, several recent studies conducted outside the inclusion window of this review

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provide context on how these variants may influence practice. Large MDCT studies and clinical series have repeatedly suggested that unrecognized Type II or III patterns can increase technical difficulty during hepatobiliary surgery and transplantation, although these associations were derived from observational data rather than controlled comparisons [33]. Case-based reports and small series in pancreaticoduodenectomy and gastrectomy have also documented situations in which a replaced hepatic artery altered operative planning or required intraoperative modification of the dissection [34]. Importantly, such reports describe potential implications rather than providing definitive evidence of causation, and these outcomes were not evaluated in the eleven studies included in the present review. Recent narrative and systematic reviews echo the descriptive emphasis of the current work while exploring broader clinical relevance. Leclerc *et al.* concluded that awareness of variant patterns may help reduce inadvertent injury during hepatopancreatobiliary procedures but emphasized the need for better prospective outcome data [2]. Wu *et al.* proposed an extended classification system for rare hepatic artery variants and argued that improved categorization may facilitate safer planning in complex cases, again without providing direct operative outcome measures [35]. Similarly, newer regional series and case reports from Asia, Europe, and South America describing unusual coeliac–hepatic configurations reinforce the breadth of anatomical variation rather than establishing specific risk estimates [14]. Overall, the present review shows that the frequency ranges of Types I–III identified in the included imaging and cadaveric studies sit comfortably within the spectrum reported by recent global literature and contemporary meta-analyses. The findings therefore support the view that non-classic hepatic arterial anatomy is common and diverse.

At the same time, the evidence base remains predominantly descriptive, which is a limitation of this study as the included studies mapped arterial patterns but did not systematically record intra-operative difficulty, complication rates, or long-term graft or organ outcomes. Accordingly, any discussion of surgical consequences in this section is clearly attributed to external studies and should be interpreted as contextual rather than as direct conclusions from the pooled data of this review. Further prospective, outcome-oriented studies are required to clarify how specific hepatic artery variants influence operative planning, risk, and patient outcomes.

CONCLUSIONS

This systematic review summarizes contemporary evidence on hepatic arterial anatomy based on recent CT angiography and cadaveric studies. Classic Michel Type I remained the most frequent pattern, while Types II and III were the most common variant configurations across the included populations. Although minor differences were observed between adult, pediatric, and cadaveric cohorts, the overall distribution of variant types was consistent with trends reported in recent global literature. The findings remain descriptive, as the included studies did not evaluate surgical difficulty, vascular injury, or procedural outcomes. Modern imaging techniques demonstrate the capacity to identify these anatomical variations with increasing clarity, but their clinical implications cannot be inferred from the available data.

Authors' Contribution

Conceptualization: NA
Methodology: NA, AS, KK
Formal analysis: AH, AS,
Writing and drafting: NA, AH, AS, MS, KK, SMTS
Review and editing: NA, AS, KK, AH, MS, SMTS

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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Systemic Review

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Biochemical Characterization of Novel Adipokines and Their Physiological Role in Insulin Sensitivity: A Systematic Review

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ABSTRACT

Novel adipokines have garnered attention for their roles in glucose regulation and the early development of metabolic imbalance. Several of these molecules influence insulin signalling, inflammation, and adipose tissue function, but their behavior across different clinical settings remains incompletely understood. **Objectives:** To synthesize recent human evidence on novel adipokines and insulin sensitivity, evaluate the consistency of their associations across various populations, and assess their potential relevance as early metabolic biomarkers. **Methods:** A systematic search was conducted across PubMed, Scopus, and Google Scholar for human studies published between 2019 and 2024. Original English-language studies measuring at least one novel adipokine alongside an insulin-related marker were included. Data were organized into structured tables and synthesised narratively. Risk of bias was assessed using the Joanna Briggs Institute (JBI) criteria for observational studies. **Results:** Eighteen studies met the inclusion criteria. Omentin-1 showed the most consistent inverse association with insulin resistance and was reduced in obesity, metabolic syndrome, PCOS, and NAFLD. Chemerin demonstrated a reproducible positive association with insulin-resistant states and higher inflammatory burden. Nesfatin-1 showed variable behaviour across disease stages and populations. Visfatin, Vaspin, DLK1, and Galanin displayed emerging but less consistent associations. Adiposity, inflammation, and residual confounding influenced the strength and direction of reported relationships. **Conclusions:** Several novel adipokines may act as early markers of metabolic stress and altered insulin action. Omentin-1 appears protective, whereas Chemerin aligns with insulin resistance across multiple populations. Other adipokines show context-dependent responses. Clinical application remains limited by heterogeneity in study design, population characteristics, and laboratory methods.

INTRODUCTION

Insulin resistance has become one of the most common metabolic concerns worldwide, affecting both adults and younger populations [1]. Over the past decade, researchers have shifted attention from traditional metabolic markers toward newer biological signals originating in adipose tissue. These signals, known as adipokines, include a growing group of recently identified molecules such as Omentin-1, Nesfatin-1, Chemerin, Vaspin, Visfatin, DLK1, and Galanin. Each of these molecules appears to interact with energy balance, inflammation, and glucose handling in different ways [2, 3]. Because adipose tissue is now recognised as an active endocrine organ, understanding how these adipokines behave may offer new insights into early metabolic dysfunction. Some adipokines seem to support healthy insulin signalling, while others worsen inflammation or impair glucose uptake [4, 5]. However,

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findings across human studies are not uniform, with reported effects varying according to population characteristics, disease stage, adiposity, and laboratory methodology. Recent studies have explored these molecules in adolescents with PCOS, adults with metabolic syndrome, pregnant women with GDM, and individuals with obesity or type 2 diabetes [6, 7].

Although this expanding literature suggests a meaningful link between adipokines and insulin sensitivity, results remain fragmented and sometimes contradictory across populations. As a result, it remains unclear which adipokines demonstrate the most reliable associations with early insulin resistance. A structured synthesis of contemporary human evidence is therefore needed to clarify consistent patterns, identify adipokines with stronger translational potential, and highlight sources of heterogeneity that limit interpretation. The purpose of this review is to gather and interpret recent human studies on novel adipokines and insulin sensitivity, highlight consistent trends across populations, and identify gaps where evidence remains uncertain. This review aimed to provide a clearer framework for understanding the potential metabolic relevance of emerging adipokines and their future role in research and clinical risk stratification.

METHODS

This systematic review was conducted to synthesize recent human evidence on the relationship between novel adipokines and insulin sensitivity. The review was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure transparency, reproducibility, and methodological rigour. Given the heterogeneity of study designs, populations, and laboratory methods, a structured narrative synthesis approach was adopted rather than quantitative pooling. The methodological steps of literature identification, screening, eligibility assessment, and final inclusion followed the PRISMA 2020 framework. A PRISMA flow diagram was constructed to summarize the study selection process, including records identified, duplicates removed, exclusions at each stage, and the final number of studies included in the qualitative synthesis. A comprehensive literature search was performed across PubMed, Scopus, and Google Scholar to identify relevant studies published between January 2019 and December 2024. The time restriction was applied to capture contemporary evidence focusing on recently characterised adipokines and modern assay techniques. The search strategy used a broad combination of keywords and Medical Subject Headings (MeSH), including "novel adipokines," "omentin-1," "nesfatin-1," "chemerin," "visfatin," "vaspin," "DLK1," "galanin," combined with "insulin sensitivity," "insulin resistance," "HOMA-IR," "fasting insulin," "glucose tolerance," and "metabolic markers." Reference lists of all included studies were manually screened to minimise the risk of missing relevant articles, in line with PRISMA recommendations. Eligibility criteria were defined a priori according to the review objectives. Only original human studies published in English were included. Eligible studies were required to measure at least one novel adipokine in blood samples and report at least one insulin-related or metabolic outcome, such as HOMA-IR, fasting insulin, fasting glucose, β-cell indices, glucose tolerance, or metabolic syndrome components. Animal studies, reviews, meta-analyses, case reports, and studies lacking insulin-related outcomes were excluded to maintain consistency and comparability of evidence. After removal of duplicate records, titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. Study selection was performed using predefined inclusion and exclusion criteria in accordance with PRISMA 2020 guidance. Reasons for exclusion at the full-text stage were documented and are summarised in the PRISMA flow diagram. Data from each eligible study were extracted into structured tables. Extracted variables included author, year, country, study design, sample size, population characteristics (e.g., PCOS, GDM, obesity, T2DM), adipokines measured, insulin-sensitivity or metabolic outcomes, and key findings. Studies were descriptively grouped by population type to allow contextual interpretation of adipokine insulin sensitivity relationships across different metabolic states. Given the inclusion of diverse populations (PCOS, GDM, obesity, T2DM, metabolic syndrome, and pediatric cohorts), results were synthesised within population-specific contexts rather than pooled across groups. This strategy reduced clinical heterogeneity and allowed interpretation of adipokine behaviour within comparable metabolic settings. Because included studies employed different commercial assays and laboratory platforms for adipokine measurement, direct comparison of absolute concentration values was not attempted. Instead, emphasis was placed on the direction and consistency of associations between adipokines and insulin-related outcomes. This approach aligns with PRISMA guidance for narrative synthesis when methodological heterogeneity precludes meta-analysis. Information on adjustment for major confounders such as BMI, age, sex, and comorbidities was extracted for each study. Studies that reported statistical adjustment for these variables were considered methodologically stronger, while those with limited adjustment were noted accordingly. Residual confounding was acknowledged as an inherent limitation of observational research. Risk of bias was assessed using the Joanna Briggs Institute (JBI) critical appraisal tools,

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selected because they are specifically designed for heterogeneous observational study designs, including cross-sectional, case-control, and cohort studies. Each study was evaluated across domains of sample selection, exposure measurement, outcome assessment, and handling of confounders, in line with PRISMA 2020 recommendations for methodological appraisal. Due to clinical and methodological heterogeneity, meta-analysis was not performed. Findings were synthesised narratively and presented in structured tables, integrating epidemiological patterns with biochemical and mechanistic evidence. This study summarizes the identification, screening, eligibility assessment, and final inclusion of studies for the systematic review. A total of 412 records were identified across databases, and 18 studies met the final inclusion criteria for the qualitative synthesis (Figure 1).

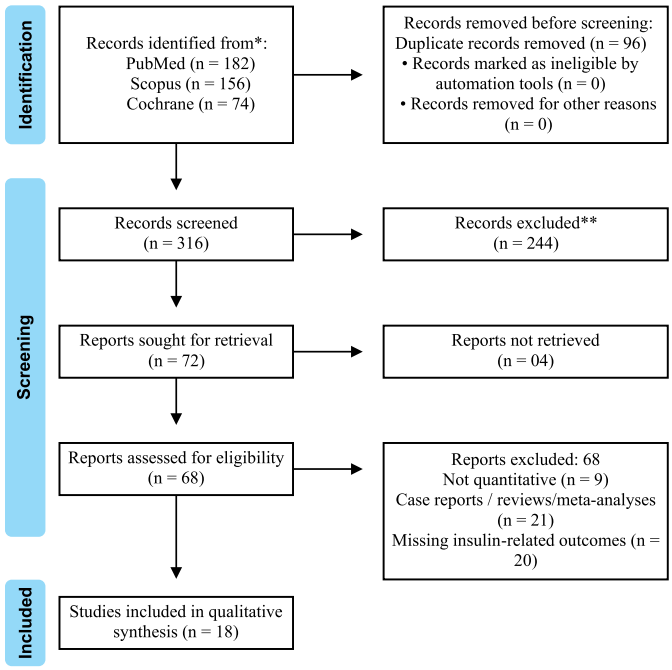

Figure 1: Study Selection Process

RESULTS

The relationship between novel adipokines and insulin sensitivity has been evaluated in 18 human studies conducted across diverse populations and metabolic conditions. These studies cover a broad range of clinical contexts, including obesity, polycystic ovary syndrome, gestational diabetes mellitus, type 2 diabetes mellitus, metabolic syndrome, and pediatric populations, facilitating comparative evaluation of adipokine–insulin sensitivity relationships across diverse demographic groups. Omentin-1 and Nesfatin-1 were most frequently evaluated, followed by Chemerin and Visfatin, primarily in relation to HOMA-IR and fasting insulin indices. Across these heterogeneous populations, Omentin-1 showed the most consistent inverse association with insulin resistance, while Chemerin demonstrated the most reproducible positive association with insulin-resistant states, indicating stronger reliability across human studies. A consistent pattern was observed whereby lower levels of Omentin-1 or Nesfatin-1, and higher levels of Chemerin or Visfatin, clustered with obesity, prediabetes, diabetes, and related insulin-resistant conditions. In contrast, Nesfatin-1 and Visfatin showed greater variability across disease states, suggesting population- and stage-dependent effects (Table 1).

Table 1: Characteristics of Human Studies (2019–2024) Evaluating Novel Adipokines in Relation to Insulin Sensitivity or Metabolic Status

Sr. No.	References	Country	Study Design	Population/Setting	Adipokine (S)	Insulin-Sensitivity / Metabolic Outcomes	Very Brief Key Finding
1	[8]	Mexico	Cross-sectional	Term newborns of obese vs normal-weight mothers	Omentin-1 (cord blood)	Cord HOMA-IR, insulin, glucose indices	Cord Omentin-1 levels are inversely related to maternal obesity and neonatal insulin resistance markers
2	[9]	Turkey	Case-control	Adolescent girls with PCOS vs controls	Omentin-1	HOMA-IR, fasting insulin	Omentin-1 is significantly lower in PCOS, associated with insulin resistance
3	[10]	Saudi Arabia	Case-control	Adults with metabolic syndrome, T2DM, and controls	Nesfatin-1, Galanin	HOMA-IR, lipids, glucose	Nesfatin-1 is associated with adiposity and metabolic syndrome
4	[11]	Iran	Cross-sectional	Healthy, obese, and T2DM adults	Nesfatin-1	BMI, glucose	Nesfatin-1 varied with weight status and diabetes
5	[12]	Egypt	Case-control	Newly diagnosed T2DM, prediabetes, and controls	Nesfatin-1	Fasting glucose	Nesfatin-1 is lower in prediabetes and T2DM, suggesting early dysglycaemia
6	[13]	Germany	Longitudinal intervention	Children with obesity	Omentin-1	HOMA-IR, insulin	Omentin-1 increased with weight loss and improved insulin sensitivity
7	[14]	Egypt	Case-control	Females with PCOS vs controls	Chemerin	HOMA-IR, BMI	Chemerin positively correlated with insulin resistance

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8	[15]	Turkey	Prospective case–control	Women with PCOS	Nesfatin-1, DLK1	IR indices	Both adipokines lower and linked with metabolic risk
9	[16]	Turkey	Prospective case–control	Pregnant women with GDM	Nesfatin-1, DLK1	Glucose tolerance	Altered adipokines associated with gestational insulin resistance
10	[17]	China	Case–control	T2DM with/without cognitive dysfunction	Nesfatin-1	IR indices	Higher Nesfatin-1 in advanced metabolic-neurological disease
11	[18]	Turkey	Cross-sectional	Obese adolescents with NAFLD	Omentin-1	HOMA-IR, HbA1c	Lower Omentin-1 associated with hepatic insulin resistance
12	[19]	Poland	Cross-sectional	Chronic liver disease / COVID-19	Chemerin, Omentin, Vaspin	HOMA-IR	Associations with insulin resistance were context-dependent
13	[20]	China	Cross-sectional	Adults with metabolic syndrome	Omentin-1	IR surrogates	Lower Omentin-1 independently predicted metabolic syndrome
14	[21]	Egypt	Case–control	Prediabetes, T2DM, controls	Nesfatin-1	HOMA-IR	Nesfatin-1 predicted dysglycaemia and insulin resistance
15	[22]	China	Cross-sectional	Normal glucose vs prediabetes vs T2DM	Nesfatin-1	β-cell indices	Nesfatin-1 is associated with β-cell function
16	[23]	China	Case–control (genetic)	Pregnant women with GDM	Chemerin	HOMA-IR	Higher Chemerin linked to gestational insulin resistance
17	[24]	Poland	Cross-sectional	Central obesity	Omentin-1	Glucose tolerance	Omentin-1 is associated with obesity-related insulin impairment
18	[25]	Pakistan	Case–control (genetic)	Obesity-related metabolic syndrome	Visfatin (SNPs)	Glucose, lipids	Visfatin polymorphisms linked with insulin-resistant phenotype

The biochemical characteristics and proposed physiological roles of key novel adipokines implicated in insulin sensitivity are summarised across experimental and clinical studies. Omentin-1 and Vaspin are predominantly described as insulin-sensitising adipokines, acting through enhancement of insulin signalling pathways, reduction of low-grade inflammation, and improvement of endothelial function. These biochemical properties support the consistent inverse associations observed for Omentin-1 across multiple populations in Table 1. Chemerin, by contrast, is characterised as a pro-inflammatory adipokine that promotes adipocyte dysfunction and impaired glucose uptake. This mechanistic profile aligns with the consistent positive association between Chemerin and insulin resistance reported across PCOS, GDM, and obesity-related studies. Nesfatin-1, DLK1, and Galanin demonstrate more complex biological roles involving appetite regulation, adipogenesis, β-cell function, and neuroendocrine signalling, which may explain their less consistent associations across studies (Table 2).

Table 2: Biochemical Profile of Novel Adipokines Implicated in Insulin Sensitivity

Sr. No.	Adipokine	Main Source/Tissue Distribution	Key Biochemical/Molecular Features	Proposed Mechanisms Related to Insulin Sensitivity	Overall Effect on Insulin Sensitivity (Human Data)
1	Omentin-1	Highly expressed in visceral adipose tissue, especially stromal vascular cells; also, in endothelium and intestine	34-kDa secreted glycoprotein; enhances insulin-stimulated glucose uptake in adipocytes; linked to anti-inflammatory signalling	Activates Akt/AMPK pathways, promotes GLUT4 translocation, improves endothelial function, and reduces low-grade inflammation, which together favour better insulin signalling	Generally, insulin-sensitising; lower levels are seen in obesity, metabolic syndrome, PCOS, and NAFLD, and are associated with higher HOMA-IR
2	Nesfatin-1	Hypothalamus, pancreatic β-cells, adipose tissue, gastrointestinal tract	An 82-amino-acid peptide derived from nucleobindin-2, involved in appetite control, glucose homeostasis, and stress response	Modulates insulin secretion from β-cells, affects peripheral glucose uptake, and interacts with autonomic and inflammatory pathways; circulating levels shift across obesity, prediabetes, and T2DM	Data are mixed but overall suggest a role in glucose regulation; altered levels observed in obesity, prediabetes, T2DM, and PCOS, often tracking insulin resistance and dyslipidaemia
3	Chemerin	White adipose tissue, liver, skin; also expressed in immune cells	Secreted as prochemerin and activated by proteolytic cleavage; binds CMKLR1, GPR1, and CCRL2 receptors; has chemoattractant and adipokine actions	Influences adipogenesis, adipocyte glucose uptake, and inflammatory cell recruitment; higher levels promote chronic low-grade inflammation and may blunt insulin signalling in adipose and liver tissue	Predominantly insulin-resistance promoting; concentrations rise in obesity, metabolic syndrome, PCOS and GDM and correlate positively with HOMA-IR and adverse metabolic traits

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4	Vaspin	Primarily visceral adipose tissue; also, liver and skeletal muscle	Serine protease inhibitor (serpin A12); thought to counteract proteases that impair insulin signalling	May protect insulin receptor signalling by inhibiting proteases such as kallikrein 7; experimental data suggest improved glucose tolerance and reduced inflammation	Human studies are limited; available data suggest a compensatory, insulin-sensitising role with higher levels in early obesity and insulin resistance
5	Visfatin / NAMPT	Visceral adipose tissue, liver, skeletal muscle, and immune cells	Enzyme in nicotinamide adenine dinucleotide (NAD^+) biosynthesis; also acts as a cytokine-like adipokine	Alters β-cell function, NAD^+-dependent metabolic pathways, and inflammatory signalling; may modulate insulin secretion and peripheral insulin sensitivity	Findings are inconsistent: some studies link higher visfatin to improved β-cell function, others show association with obesity, metabolic syndrome, and insulin resistance
6	DLK1 (Pref-1)	Preadipocytes, mesenchymal stem cells, fetal tissues; low in mature adipocytes	Transmembrane/soluble protein from the EGF-like family; inhibits adipocyte differentiation	By blocking adipogenesis, influences fat mass distribution and adipokine secretion profile; altered levels may affect whole-body insulin sensitivity via changes in adipose tissue quality	Limited human data; in PCOS and GDM, altered DLK1 levels are associated with adverse metabolic risk markers, suggesting a potential link to insulin resistance
7	Galanin	Widely expressed neuropeptide; also present in pancreatic islets and gastrointestinal tract	29–30 amino acid peptide acting via GalR1–3 receptors; involved in appetite regulation, autonomic tone, and glucose homeostasis	Modulates insulin secretion and hepatic glucose production; interacts with sympathetic activity and other neuropeptides that influence insulin sensitivity	Human evidence is still emerging; altered galanin levels in metabolic syndrome point towards a role in obesity-related insulin resistance, but directionality remains unclear

The mechanistic links between novel adipokines and insulin sensitivity are supported by evidence outlining key cellular and molecular pathways involved in metabolic regulation. Omentin-1 and Vaspin primarily enhance insulin sensitivity through activation of PI3K/Akt and AMPK pathways, improved glucose transport, and attenuation of inflammatory signalling. Chemerin exerts opposing effects by activating MAPK and NF-κB pathways, contributing to chronic inflammation and adipose and hepatic insulin resistance. These contrasting mechanisms provide biological plausibility for the stronger and more consistent associations observed for Omentin-1 and Chemerin in the clinical studies summarised in Table 1. Visfatin, Nesfatin-1, DLK1, and Galanin influence insulin sensitivity through more indirect or context-dependent mechanisms, which may account for the heterogeneity reported across populations and disease stages (Table 3).

Table 3: Proposed Mechanisms Through Which Novel Adipokines Influence Insulin Sensitivity (Summary of Human-Relevant Evidence)

Sr. No.	Adipokine	Key Cellular/Molecular Pathways	Mechanism Affecting Insulin Sensitivity	Direction Of Effect (Based on Human Studies)
1	Omentin-1	PI3K/Akt pathway activation; AMPK stimulation; suppression of TNF-α and IL-6	Enhances insulin-stimulated glucose uptake; improves endothelial nitric oxide activity; reduces inflammatory signalling that interferes with insulin receptor responses	Improves insulin sensitivity; low levels linked with higher HOMA-IR and metabolic syndrome
2	Nesfatin-1	Modulates β-cell Ca^{2+} signalling; interacts with autonomic pathways; regulates stress-related peptides; influences GLUT4 activity	Affects insulin secretion, appetite, and peripheral glucose uptake; may modify energy homeostasis and oxidative stress	Mixed effect; altered levels seen in obesity, prediabetes, T2DM, and PCOS; often tracks with insulin resistance
3	Chemerin	CMKLR1 receptor activation; MAPK and NF-κB pathways; modulation of adipogenesis	Increased chemerin enhances inflammatory signalling, adipocyte dysfunction, and impaired glucose transport; it contributes to hepatic and adipose insulin resistance	Promotes insulin resistance; high levels correlate with high HOMA-IR, PCOS, GDM, metabolic syndrome
4	Vaspin	Serpin inhibition of proteases (e.g., kallikrein 7) improves insulin receptor signalling; reduces ER stress	Protects insulin receptor substrates from degradation; attenuates inflammation; enhances glucose tolerance under metabolic stress	Compensatory insulin-sensitising effect; often elevated in early obesity/IR as a protective response
5	Visfatin (NAMPT)	NAD^+ biosynthesis pathway; SIRT1 activation; inflammatory cytokine modulation	Influences β-cell survival, insulin secretion, and NAD^+-dependent metabolic reactions; may affect hepatic glucose output and adipocyte inflammation	Inconsistent evidence; linked to both improved β-cell function and higher metabolic-risk phenotypes
6	DLK1 (Pref-1)	Inhibition of adipocyte differentiation; Notch/EGF-like signalling pathways	Alters adipogenesis and adipocyte number; indirectly affects whole-body insulin sensitivity by modifying adipose tissue quality	Possible insulin-resistance link; altered levels in PCOS and GDM associate with adverse metabolic markers

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7	Galanin	GalR1–3 receptor signalling; modulation of autonomic output; effects on hepatic glucose production	Regulates insulin and glucagon secretion; influences sympathetic drive and hepatic glucose metabolism	Emerging evidence; patterns suggest involvement in obesity-related insulin resistance, but the direction is not fully established

The methodological quality of the included studies was evaluated using the Joanna Briggs Institute risk-of-bias criteria. Most studies demonstrated low risk of bias in exposure and outcome measurement, reflecting the use of validated biochemical assays for adipokine and metabolic marker assessment. The main methodological limitation across studies was incomplete adjustment for confounding factors such as BMI, age, sex, and comorbidities, which may partly explain variability in adipokine insulin sensitivity relationships across populations. Studies that addressed major confounders were generally rated as low risk, while those with limited adjustment were classified as moderate risk. This finding supports cautious interpretation of results, particularly for adipokines showing inconsistent associations across heterogeneous study designs (Table 4).

Table 4: Risk of Bias Assessment of Included Studies (Using JBI Criteria)

Sr. No.	References	Study Design	Sample Selection	Measurement of Exposure (Adipokine)	Measurement of Outcome (Insulin Sensitivity / Metabolic Markers)	Confounding Factors Addressed	Overall Risk of Bias
1	[8]	Cross-sectional	Low	Low	Low	Moderate	Low
2	[9]	Case-control	Low	Low	Low	Moderate	Low
3	[10]	Case-control	Low	Low	Low	Moderate	Low
4	[11]	Cross-sectional	Moderate	Low	Low	High	Moderate
5	[12]	Case-control	Low	Low	Low	Moderate	Low
6	[13]	Longitudinal intervention	Low	Low	Low	Moderate	Low
7	[14]	Case-control	Low	Low	Low	Moderate	Low
8	[15]	Prospective case-control	Low	Low	Low	Moderate	Low
9	[16]	Prospective case-control	Low	Low	Low	Moderate	Low
10	[17]	Case-control	Moderate	Low	Low	High	Moderate
11	[18]	Cross-sectional	Low	Low	Low	Moderate	Low
12	[19]	Cross-sectional	Low	Moderate	Moderate	High	Moderate
13	[20]	Cross-sectional	Low	Low	Low	Moderate	Low
14	[21]	Case-control	Low	Low	Low	Moderate	Low
15	[22]	Cross-sectional	Low	Low	Low	Moderate	Low
16	[23]	Case-control	Low	Low	Low	Moderate	Low
17	[24]	Cross-sectional	Low	Low	Low	Moderate	Low
18	[25]	Case-control	Low	Low	Low	Moderate	Moderate

DISCUSSION

This review of recent human studies highlights that several novel adipokines appear to be closely linked with insulin sensitivity and metabolic health across a wide range of populations. Importantly, these associations were examined across heterogeneous clinical settings, including obesity, PCOS, GDM, T2DM, metabolic syndrome, and pediatric cohorts, allowing assessment of both consistency and variability in adipokine behaviour. The evidence gathered in Table 1 shows that lower circulating levels of Omentin-1 are repeatedly observed in settings of obesity, metabolic syndrome, central adiposity, and impaired glucose tolerance. For example, in a longitudinal intervention study of children with obesity, Omentin-1 increased significantly after weight loss and was inversely correlated with HOMA-IR ($r = -0.33$) both cross-sectionally and over time [13]. This pattern supports an insulin-sensitising role of Omentin-1 in visceral fat depots, consistent with the biochemical profile described in Table 2, where Omentin-1 is shown to activate Akt/AMPK pathways and promote GLUT4-mediated glucose uptake. The relative consistency of this inverse association across populations suggests that Omentin-1 may represent one of the more reliable adipokine indicators of early insulin resistance in human studies. In contrast, adipokines such as Chemerin emerged as markers of insulin resistance in multiple studies. In the cross-sectional study by Zhao *et al.* Chemerin levels correlated positively with insulin resistance measures and adiposity in a large adult cohort [26]. Similar findings were reported in other human studies, including those by Al-Mansoori *et al.* and Roy *et al.* [27, 28]. This aligns with the mechanistic summary in current review, where Chemerin is proposed to activate NF-κB and MAPK pathways, promoting adipocyte dysfunction and chronic low-grade inflammation. Across PCOS, GDM, and obesity-related cohorts, the direction of association for Chemerin (higher levels with greater insulin resistance) remained largely consistent, reinforcing its role as a deleterious adipokine in metabolic dysregulation. The findings on

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Nesfatin-1 were less straightforward. This review found that Nesfatin-1 levels are altered across metabolic states such as prediabetes, T2DM, and PCOS, but sometimes in opposite directions. For example, one Egyptian study reported lower Nesfatin-1 levels in newly diagnosed T2DM and prediabetes compared with controls, which may reflect early down-regulation during initial stages of glucose intolerance. In contrast, a Chinese study reported higher Nesfatin-1 levels in T2DM patients with cognitive impairment, suggesting complex regulation in more advanced or comorbid disease states. This heterogeneity indicates that Nesfatin-1 may function as a context-dependent adipokine, showing compensatory behaviour in some settings and pathological associations in others. In accordance with these observations, other studies have also described variable Nesfatin-1 responses across obesity and insulin-resistant states, indicating that its behaviour may shift with disease severity, inflammatory burden, and metabolic stage [29, 30]. Importantly, this review emphasises that adipokine–insulin sensitivity relationships are rarely independent of adiposity, inflammation, and other metabolic modifiers. Many included studies adjusted for BMI or waist circumference; however, fewer accounted for lifestyle factors, visceral fat distribution, or inflammatory markers in detail. For instance, although the Omentin-1 intervention study adjusted for weight loss, residual confounding by changes in adipose tissue quality could not be fully excluded. This limitation underscores the difficulty of disentangling direct adipokine effects from the broader metabolic milieu in observational human studies. Similar concerns have been raised by other researchers, who note that adipokine signalling often overlaps with inflammatory load and fat distribution, complicating causal interpretation [31, 32]. From a clinical perspective, these findings carry potentially meaningful implications. Adipokines such as Omentin-1 and Chemerin show sufficient consistency to be considered candidates for early metabolic risk stratification, particularly in populations at risk of insulin resistance. However, before translation into clinical biomarkers, several barriers remain. These include heterogeneity in study populations, lack of standardised assay platforms, and inconsistent adjustment for confounders.

As highlighted in this review, variability in assay methods and reporting units limits cross-study comparability and precludes the definition of universal diagnostic thresholds. Other clinical reports have similarly cautioned that adipokine-based markers require careful validation before routine clinical use [33-35]. The strengths of this review include its focus on recent human evidence (2019–2024), exclusion of animal and non-English studies, and integration of biochemical, mechanistic, and epidemiological findings. Future research should prioritise longitudinal designs, standardised laboratory assays, and rigorous control of confounding factors to clarify causal relationships and biomarker potential. Ultimately, novel adipokines hold promise as tools for understanding and potentially intervening in early metabolic dysfunction, but their clinical application requires further validation.

CONCLUSIONS

This review synthesises contemporary human evidence demonstrating that novel adipokines are meaningfully associated with insulin sensitivity and metabolic health. Among the adipokines reviewed, Omentin-1 and Chemerin showed the most consistent and reproducible associations with insulin resistance across heterogeneous populations, whereas Nesfatin-1 displayed a more variable, context-dependent pattern. While the mechanistic pathways outlined in results provide biologically plausible explanations for these relationships, translation into clinical practice remains premature.

Authors' Contribution

Conceptualization: AJ, AR
Methodology: AJ, RM, AK, AR, HF
Formal analysis: AJ
Writing and drafting: AJ, MSY, AR, HF
Review and editing: AJ, AR, RM, AK, HF, MSY

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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