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EDITORIAL

The Triad of Modern Healthcare: Unifying Accreditation, Technology, and Safety Culture

Abdul Basit Baig

For healthcare institutions in Pakistan, the journey toward world-class patient care often hinges on a critical ambition: achieving international accreditation. Organizations like the Joint Commission International (JCI) or Accreditation Canada offer more than just a symbolic certification; they're a powerful force for a complete overhaul of how patient care is delivered. But to truly unlock this potential, we need to go beyond simply ticking boxes. The real transformation happens when we blend three essential elements: the strict discipline of accreditation, the game-changing power of technology, and the fundamental shift to a proactive safety culture. It's a triad, and each part is crucial.

At its heart, accreditation gives us a solid framework for constant improvement. It forces a deep dive into every corner of our operations, from making sure we've got the right patient to managing medications and keeping infections at bay. But here's the thing: that framework today is totally tied to technology. The digital shift is not an optional extra; it's a critical part of a successful accreditation strategy. Think about it. Manual, paper-based processes aren't just slow, they are a huge source of errors that can put patients at risk. The meticulous record-keeping and streamlined workflows that accreditation demands are a perfect match for what modern technology can do.

Electronic Health Records (EHRs), for instance, create a single source of truth for patient data. Clinical decision support systems, many of them now with some AI-enabled clinical decision support (CDS), act as a safety net. They can flag a bad drug interaction, alert a doctor to a patient's declining condition, and make sure everyone on the care team has the most up-to-date information. In a way, accreditation pushes us to adopt the very tools that make our systems stronger, more reliable, and ultimately safer.

While systems and tech provide the skeleton of quality healthcare, a robust culture of patient safety is the lifeblood. The best tech and the toughest standards will crumble if staff are too scared to report mistakes or near-misses. This is where clinical governance becomes so incredibly vital: in building a just culture. This is a huge shift away from a blame-game model where errors are met with punishment. Instead, it creates an environment where staff feel safe to speak up, learn from what happened, and help fix the system.

This proactive mindset is genuinely transformative. It lets hospitals learn from their mistakes instead of just reacting to them after the fact. Data analytics, for example, can spot subtle patterns in readmission rates, surgical site infections, or other significant events. By using this information, hospital leaders can move from a reactive stance only by dealing with problems after they have caused harm to a predictive model, where risks are identified and handled before they can ever materialize. That's the essence of a mature risk management strategy, and it is all built on a foundation of trust.

For the healthcare community in Pakistan, the path forward is clear. We can't see these three dimensions as separate pillars. They are interconnected parts of one single, unified strategy. The discipline that comes from accreditation, the safety and efficiency enabled by technology, and the human-centered focus of a proactive safety culture must all work together in harmony. However, let's be honest, it's a marathon with a lot of steep hills. While the three pillars are the ideal blueprint, building them isn't easy. The most immediate challenge is simply money; a top-tier EHR system or a complete infrastructure overhaul for international accreditations cost a fortune, and many hospitals, especially public ones, just don't have that kind of cash. Then there's the issue of connectivity. We can't talk about a digital healthcare system if reliable internet isn't provided everywhere, especially in our rural and far-flung areas. And finally, perhaps the

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trickiest part of all is change management. It's one thing to buy new tech; it's a whole different ball game to get a diverse, often overworked staff to actually embrace it. This means a lot of training, a lot of patience, and a delicate touch to build trust instead of resistance. These aren't minor issues, but they're not roadblocks either. They're part of the reality we have to face, demanding a careful, strategic plan and genuine commitment from everyone, from government to private hospital owners.

Accreditation starts the conversation, making us rethink our systems. Technology gives us the tools to make those systems smart and resilient. And a just culture ensures that every person from the top administrator to the frontline nurse is an active participant in this ongoing quest for excellence. Only by embracing this comprehensive, three-dimensional blueprint can we truly raise the bar, protect our patients, and secure a future of world-class healthcare for our nation.

The feedback loop between these three elements is where real magic happens. Technology, for instance, doesn't just support accreditation; it actively fuels the safety culture. Imagine an Electronic Health Record (EHR) system that not only meets JCI's data integrity standards but also automatically flags a high-risk patient to the entire care team. This immediate, system-driven alert reinforces the safety-first mindset and allows for real-time risk mitigation. Similarly, a strong safety culture empowers frontline staff to suggest technological improvements or identify gaps in accreditation standards. When a nurse reports that a particular step in the patient admission process is prone to error, leadership, in a just culture, can then use this insight to redesign the workflow, potentially integrating new technology to make the process more resilient and compliant with accreditation requirements. This isn't a linear process; it is a dynamic and continuous cycle of improvement where each component strengthens the others.

Ultimately, this unified approach is a testament to strong leadership and a commitment to long-term vision. It requires leaders who see the bigger picture who understand that investing in a robust EHR system is not just an IT expense but a foundational investment in patient safety and accreditation readiness. It means fostering an environment where accountability isn't about assigning blame but about learning from mistakes and empowering staff. The journey toward international accreditation is a marathon, not a sprint. The institutions that succeed are those that embed this three-part strategy into their organizational DNA, viewing it as a core business function rather than a temporary project. By doing so, they not only achieve certification but also build a sustainable framework for delivering world-class healthcare for generations to come.

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CONFLICT OF INTEREST

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ORIGINAL ARTICLE

Incidence of Measles with Disease Manifestations in Infants: Do Infants Need Measles Vaccine Earlier than 9 Months?

Sidra Tul Muntaha[1], Afrah Tariq[2], Jawad Ahmad khan[3], Arslan Farooq[4], Farhan Hassan[5]

ABSTRACT

Objective: To find out the incidence of measles with disease manifestations in infants equal to and less than 9 months of age.

Study Design: It was a descriptive cross-sectional study based on secondary data analysis.

Place and Duration of Study: It was carried out at Cantonment General Hospital Department of Paediatrics from 1st January 2023 to 30th September 2023 (9 months).

Materials and Methods: It was a secondary data analysis of all records collected of expanded programme of immunization from Rawalpindi District, Punjab from 1st January 2023 to 30th September 2023. Data included all infants equal to and less than 9 months of age of both genders presenting with signs and symptoms of measles. Infants with positive measles serum IgM antibodies were labelled as confirmed measles cases. Data was analyzed using windows SPSS version 24.0. Results described in both in frequencies and percentages.

Results: In our study total of 470 infants were enrolled. Out of which 294(62.6%) were measles IgM positive. Of the total cases, 182 (61.9%) were male and 112 (38.1%) were female. Among them, 20 (6.8%) were vaccinated, whereas 274 (93.2%) were unvaccinated. Age wise distribution showed that IgM positive cases at 1,2,3,4,5,6,7,8,9 months were 3(1%), 4(1.4%), 16(5.4%), 19(6.%%), 33(11.2%), 52(17.7%), 52(17.7%), 81(27.6%), 34(11.6%) respectively. Common symptoms seen were fever 294(100%), cough 287(97.6%), coryza 95((32.3%), conjunctivitis 41(13.9%), rash 294(100%). Complications were seen in 41(13.9%) with mortality of 5(1.7 %).

Conclusion: We conclude that a significant number of infants are being infected with measle virus before reaching the age of first recommended vaccine inoculation against measles. It is affecting children as young as one month old.

Key Words: *Infants, Immunity, Measles, Measles IgM Antibodies, Vaccine.*

Introduction

Measles is highly contagious disease caused by measles virus and carries high morbidity and mortality among children under 5 years of age.[1] It affects around 30 million of people annually with around 0.5 million deaths.[2] Around two third of these mortalities occur in Pakistan. Highest death rate of almost around 10 % seen in areas with high prevalence of malnutrition, poor vaccination practices and non availability of health facilities.[3,4] Maternal antibodies usually persists till 15 months of age but recent research showed that maternal antibodies protect only from 3 to 4 months of age and are not detectable in blood in most of infants at age of 6 months. [4,5] Breastfeeding provides secretory IgA and other immune factors that offer partial protection against measles in early infancy; however, it does not sustain protective antibody titres, making vaccination essential for long-term immunity. Most commonly encountered disease complications are pneumonia, encephalitis, optic neuritis, gastroenteritis and meningitis. [5,6]

Disease control relies on vaccination. WHO recommends vaccination at 9 months of age in high risk areas, however in very high risk areas vaccination as early as 6 months of age has been

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explored in regions like Nitherland, East & West Africa.[6,7,8] Low birth weight infants having diminished maternal antibodies and malnourished infants are highly susceptible to disease related complications & early vaccination can be helpful in such infants.[7,8] In Pakistan vaccine is given according to expanded programme of immunization at 9 months of age and 15 months of age. Introduction of measles vaccine led to decline in cases. Vaccine is free of cost, effective with rare side effects.[9] Studies showed that infants vaccinated at 6 months of age generates a primary immune response & provide protection in high risk environment & is safe with similar adverse events observed in older infants.[10]

Loachlain LM et. al,[11] conducted on measles vaccination effects below 9 months of age and concluded that administering vaccine below 9 months of age resulted in increase vaccine effectiveness and T cell response with high seropositivity.

Detection of measles-specific IgM antibody remains the gold standard for laboratory confirmation of measles. It provides high sensitivity and specificity, particularly when obtained within the first few days after rash onset. The presence of IgM strongly supports acute infection, helping to differentiate measles from other exanthematous illnesses. Its reliability and rapid availability make IgM serology the cornerstone of measles diagnosis in both clinical and epidemiological settings.

Rationale of the study is that with increasing measles outbreak each year, study will help authorities to revise recommended age of vaccination. Due to high morbidity and mortality associated with it and grave complications of disease vaccine is only way to prevent disease. In developing countries like Pakistan, where population density is high, number of unvaccinated children and continuously migrating population is also high. Outbreaks are observed in infants less than 9 months of age. The aim of study was to find incidence of measles in infants below 9 months to decrease recommended age of vaccine.

Materials and Methods

It was a descriptive cross-sectional study based on secondary data analysis of all expanded programme of immunization records collected from Rawalpindi District, Punjab from 1st January 2023 to 30th September 2023. The study was conducted across 21 healthcare centers, including all major public sector hospitals within the Rawalpindi district as well as selected private hospitals and pediatric clinics. Approval was taken from ethical committee reference no admin/321-A/22/15/2022. Data included all children equal to and less than 9 months of age of both genders presenting with signs and symptoms of measles. All infants ≤9 months of age presenting with clinical suspicion of measles were enrolled. Blood samples were taken, and IgM testing was performed. Cases with positive IgM antibodies were labelled as confirmed measles. Any child in whom clinician suspects measles infection or any child with fever and maculopapular rash, severe cough and coryza or conjunctivitis was labelled as suspected case of measles. Infants fulfilling operational definition of measles were enrolled and 3 ml of blood specimen was collected using sterile method during 4th to 28th day of rash onset for IgM test and stored in cold chain of 2 to 8 °C. The sample was properly labeled and accompanied by the surveillance report from the respective health facility. It was submitted to the District Health Authority Office, Rawalpindi, and subsequently forwarded to the National Institute of Health (NIH), Islamabad, where laboratory testing was performed. Infants with positive measles serum IgM antibodies were labelled as confirmed measles cases. Data was analyzed using SPSS version 24.0. Frequency of disease in infants equal to and under the age of 9 months was calculated. Results were described in terms of frequencies as well as percentages.

Results

A total of 470 infants were enrolled in the study, of whom 294 (62.6%) were confirmed measles IgM positive. Among these, 182 (61.9%) were male and 112 (38.1%) were female. The majority of cases, 274 (93.2%), were unvaccinated, while only 20 (6.8%) had received measles vaccination, till 9 months of age single dose of measles vaccine is given as shown in Table I & Figure 1.

Age-stratified analysis revealed that IgM positive cases were observed as early as one month of age. The highest frequency was noted at 8 months (81; 27.6%), followed by 6 and 7 months (52 each; 17.7%). The lowest frequency occurred at 1 month (3; 1.0%) as shown in Figure 2.

The most common symptoms among IgM positive

infants were fever (294; 100%), rash (294; 100%), cough (287; 97.6%), coryza (95; 32.3%), and conjunctivitis (9; 3.1%) as shown in Table II.

Complications were documented in 41 infants (13.9%), predominantly pneumonia and encephalitis. There were 5 deaths (1.7%) recorded among IgM positive cases and cause of death was pneumonia & encephalitis as shown in Table III.

Chi-square test was applied to assess associations between age groups, gender, vaccination status, and measles positivity. The association between vaccination status and measles infection was statistically significant ($p < 0.05$).

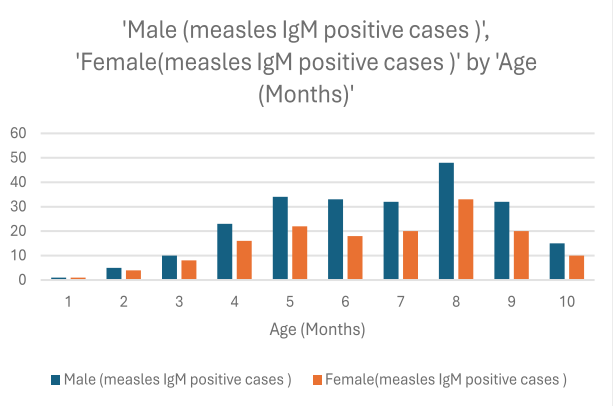

Figure 1: Gender Distribution of Measles IgM Positive Cases N=294

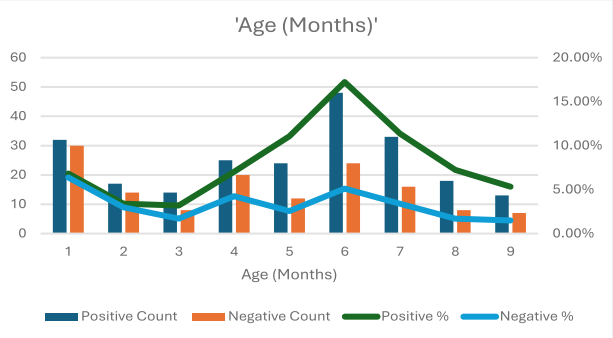

Figure 2: Age Wise Distribution of Measles IgM Positive & Negative cases. N=470

Table I: Measles IgM positive demographics gender, vaccination status, : N=294

Measles IgM Positive		Frequency	Percent(%)
Gender			
	Male	182	61.9%
	Female	112	38.1%
Vaccination Status			
	Not vaccinated	274	93.2%
	Vaccinated(single dose)	20	6.8%

Table II: Clinical Features Among Measles Igm Positive Infants (n=294)

Symptoms	Frequency	Percentage (%)
Fever	294	100.0%
Rash	294	100.0%.
Cough	287	97.6%
Coryza	95	32.3%
Conjunctivitis	9	3.1%

Table III: Complications and Outcomes Among Measles IgM Positive Infants (n=294)

	Frequency	Percentage (%)
Pneumonia/Encephalitis	41	13.9
Mortality	5	1.7

Discussion

In this study, 470 infants with clinical suspicion of measles were enrolled, and IgM testing was performed for all. Of these, 294 (62.6%) were laboratory confirmed as measles IgM positive. The results demonstrated a clear male predominance (61.9%) and higher disease frequency among unvaccinated infants (93.2%). The significant association between vaccination status and measles infection ($p < 0.05$) emphasizes the critical role of immunization in preventing infection. Gianniki et. al.,[12] reported a similar gender distribution with male predominance (55.7%) and highlighted the importance of vaccination coverage and surveillance, findings that align with our observations.

When analyzing age distribution, a rising trend in measles positivity was observed beyond five months of age peaking at eight months (27.6%). Although cases were documented as early as one month of age, the most affected group was between six and eight months. This trend correlates with waning maternal antibody levels after three to four months of age as described by previous studies.[4,5] Jamal et. al.,[13] observed similar age-specific vulnerability and highlighted the need for considering earlier vaccination strategies. The persistence of infections before the first scheduled dose at nine months underscores a potential window of susceptibility requiring programmatic attention.

Gender-based and sociocultural factors likely influenced Healthcare seeking behavior. Jamal etal., suggested that female children are less frequently presented to health facilities, which may partially

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explain the higher representation of males in our cohort.[13] Such disparities emphasize the need for community education and equitable healthcare access.

The post-COVID-19 period may have exacerbated measles transmission dynamics. Asghar etal., reported a 30% incidence among children aged six to nine months, while our study showed a higher positivity rate (63%), potentially due to reduced vaccination coverage during pandemic-related disruptions and increased population movement[14] Strengthened surveillance systems introduced in recent years may also have contributed to improved case detection.

The study also revealed that complications occurred in 13.9% of IgM positive infants, with pneumonia and encephalitis being predominant, and an overall mortality of 1.7%. Sindhu et. al.,[15] similarly reported higher complication rates in infants compared to older children. The findings are consistent with evidence that measles-related morbidity is aggravated by immune suppression and secondary infections, as discussed by Bogler et. al.,[16] and Muhammad et. al.,[17]

The Importance of vaccination is further highlighted by global studies. Fisker et. al.,[18] observed improved antibody responses and reduced mortality with early measles vaccination and Zucker et. al.,[19] noted that undervaccination was associated with outbreaks and hospitalization. These observations reinforce the study's conclusion that timely vaccination remains the cornerstone of measles control.

Finally, the rising incidence observed from five to nine months of age supports the notion of declining maternal immunity and the critical vulnerability window preceding the first vaccine dose.[4,5] Similar findings were reported by Welaga et. al.,[21] Lo Vecchio et. al.,[22] and Patel et. al.,[23] who emphasized strengthening immunization programs and possibly revisiting vaccination schedules in high-risk settings.

This district-level analysis, encompassing public and private healthcare facilities, is among the first in Punjab to quantify measles burden in infants below nine months. Although limited by its geographic scope, it provides valuable insights to policymakers for optimizing vaccination timing and strategies.

Conclusion

We conclude that a significant number of infants are being infected with measles before reaching the age of first recommended vaccine inoculation against measles. It is affecting children as young as one month old.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Diagnostic Utility of P57 Immunomarker in Differentiating Complete and Partial Hydatidiform Mole

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ABSTRACT

Objective: To assess diagnostic utility of p57 in differentiating complete and partial hydatidiform mole.

Study Design: Cross-sectional descriptive study.

Place and Duration of Study: Histopathology department at Chugtai's Institute of Pathology, Lahore, Pakistan for a period of six months starting from 1st January 2022 to 30th June 2022.

Materials and Methods: A total of 50 cases of molar pregnancies were included in this study. Age, gross findings, and histomorphological features were noted. p57KIP2 immunostain was applied on diagnostic histology slide for definitive subtyping into complete and partial mole. The Chi-squared test and Fisher Exact test were used to assess associations between different variables, with statistical analysis conducted using SPSS version 26.

Results: The preliminary diagnosis based on morphology alone revealed 29 (58%) cases of complete mole while 21 (42%) cases of partial mole. However, when p57 antibody was interpreted in conjugation with histology the final diagnosis revealed 37 (74%) cases turned out to be complete mole and 13 (26%) cases were categorized as partial mole.

Conclusion: p57KIP2 immunostain is a useful and reliable ancillary test to reach final diagnosis which helps in accurate diagnosis in the best interest of patients.

Key Words*: Complete hydatidiform mole, Gestational trophoblastic disease, grape like vesicles, partial hydatidiform mole, p57 protein.*

Introduction

A kind of gestational trophoblastic disease (GTD) known as hydatidiform mole has been identified as a noteworthy pathological entity with a special capacity for both local invasion and distant metastasis. There are three types of this condition: invasive mole (IM), partial hydatidiform mole (PHM), and complete hydatidiform mole (CHM).[1] Since hydatidiform moles were first described as a disorder characterized by aberrant growth of trophoblastic tissue and distinctive hydropic degeneration of chorionic villi, our understanding of these entities, both clinically and pathologically, has changed significantly.[2] Only histomorphological evaluation could distinguish between complete and partial moles. Overlapping morphological traits, however, frequently present difficulties for this method, particularly when specimen preservation is inadequate or diagnostic expertise is lacking.[3] The genetic etiology of these entities has been clarified by recent developments in molecular genetics. CHM is usually the result of a single sperm fertilizing an enucleated ovum, giving rise to a diploid androgenetic origin. On the other hand, PHM, is the outcome of two sperm fertilizing an ovum producing diandric triploidy. Despite these developments, precise and dependable subtyping is still essential since it has a big impact on patient care and follow-up.[4]

The clinical significance of subtyping molar pregnancies for risk assessment and follow-up monitoring to stop the development of gestational trophoblastic neoplasia (GTN) is established by the literature now in publication. It is commonly

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recognized that CHM is more likely to progress into gestational trophoblastic neoplasia (GTN) than PHM.[5] To guarantee correct subtyping, there are still gaps in the standardization of diagnostic procedures, especially in areas with restricted access to sophisticated genetic testing. In this regard, immunohistochemical markers such as p57, a protein that is expressed by the mother and has a paternal imprint, have become useful adjuncts.[6] Although p57 antibody usefulness has been investigated, little information is available from South Asian communities, where the prevalence of molar pregnancies and the ensuing GTN is far greater than in Western cultures.

Our work sought to fill these gaps by assessing the diagnostic value of the p57 immunomarker in distinguishing between partial and complete hydatidiform moles in a Pakistani sample. We aimed to improve diagnostic precision and offer data to support clinical judgment by integrating histomorphological evaluation with p57 immunostaining. This study is also noteworthy since it offers insights specific to a certain location and emphasizes the need of integrating p57 staining into regular diagnostic procedures, which may standardize care and enhance results.

In this study, we studied molar pregnancies to improve patient care by guaranteeing proper management and follow-up plans, we postulated that combining p57 immunostaining with histological examination would greatly increase the accuracy of subtyping molar pregnancies.

The rationale for this study was its ability to bridge the gap in region-specific evidence on the usefulness of the p57 immunomarker and to solve the diagnostic difficulties presented by histology alone. This work adds to our understanding of GTD and highlights its importance in high-incidence communities by clarifying the role of p57 immunostaining in the subtyping of molar pregnancies.

The objective of this research was to evaluate the diagnostic potential of p57 immunostaining in distinguishing between complete and partial hydatidiform moles, thereby offering a dependable supplementary instrument for precise diagnosis and enhanced clinical handling of molar pregnancies.

Materials and Methods

This cross-sectional descriptive study was conducted over six months, from January 1, 2022, to June 30, 2022, at Chughtai's Institute of Pathology, Lahore, Pakistan. The permission to carry out this research was obtained from institutional review board at Chughtai's Institute of pathology under letter number (*CIP/IRB/1095A*). After approval data was actively collected for a period of six months. Approval for the waiver of informed consent was obtained from the Institutional Review Board prior to the commencement of this study. The waiver was granted because most of the data were sourced from electronic medical records, and there was no direct involvement of the study subjects. We receive specimens from different hospitals from all over country. Cases reported as molar pregnancy (complete or partial mole) were actively collected on daily basis and their processed formalin fixed paraffin embedded blocks were recut for subsequent immunostaining. Total 50 cases were included in this study. While non-molar products of conception, products of conception with hydropic change and invasive mole were excluded. One diagnostic Hematoxylin & Eosin (H&E) slide was kept from the archives. The type of antibody applied was Polyclonal rabbit anti-p57 KIP2 oncoprotein using Dako Link 48 auto stainer. External control was applied to each batch of cases for quality assurance. The IHC staining was carried out using the heat-induced epitope retrieval method followed by a standard streptavidin–biotin peroxidase complex technique (MRH534 L obtained from Biocare Medical, USA). Positive reactivity was interpreted only when distinct nuclear staining was identified. In at least 10% of villi nuclear positivity of p57 antibody in the cytotrophoblasts and stromal cells were considered positive. However internal control was considered positive when it stained maternal decidua and syncytiotrophoblasts.[1]

Two pathologists, both belonging to a different stratum of pathology with reporting experience of up to 5 years independently interpreted all the fifty slides of H&E and p57 antibody and gave their final diagnosis. Data was then analysed, quantitative variable like age was calculated as mean while qualitative variables like vesicle and cistern formation, fetal parts, p57 expression were calculated as frequency and percentage. The Chi-squared test and Fischer Exact test was used to

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assess associations between different variables, with statistical analysis conducted using SPSS version 26 (IBM, Armonk, NY, USA), and a p-value of < 0.05 was considered statistically significant.

Results

Total 50 cases of molar pregnancies were included in this study. Minimum age of patient was 17 and maximum age was 46. Mean age was 26 ± 5.74 standard deviation (SD). We did not find any significant correlation of age with the final diagnosis. The interpretation of histomorphological features has been shown in Table I.

The preliminary diagnosis based on morphology alone revealed 29 (58%) cases of complete mole while 21 (42%) cases of partial mole. However, when p57 antibody was interpreted in conjugation with histology the final diagnosis revealed 37 (74%) cases turned out to be complete mole and 13 (26%) cases were categorized as partial mole. (Figure 1)

When the gross feature of grape like vesicle was correlated with final diagnosis. We found that out of 37 (74%) cases diagnosed as complete mole in 15 (40.54%) cases grape like vesicle were absent and in 22 (59.46%) cases grape like vesicle were present grossly. While in case of partial mole out of 13 (26%) cases in 4(30.77%) cases grapes like vesicles were absent and in 9 (69.23%) cases grapes like vesicles were present grossly. According to Fisher Exact test, P value is 0.390 (statically insignificant).

When the histomorphological features were correlated with final diagnosis. We found that out of 37 (74%) cases diagnosed as complete mole 20 (54.05%) cases of complete mole showed circumferential trophoblastic proliferation on histology (Figure 2) and 17 (45.95%) cases showed polar proliferation on histology (Figure 3). While in case of partial mole out of 13 (26%) cases 3(23.08%) showed circumferential trophoblastic proliferation on histology and 10 (76.92%) cases showed polar proliferation on histology. According to Fisher Exact test, P value is 0.053 (statically insignificant).

When the presence of fetal parts was correlated with final diagnosis. We found that out of 37 (74%) cases diagnosed as complete mole in all 37 (100%) cases fetal parts were absent grossly. While in case of partial mole out of 13 (26%) cases in 8 (61.54%) cases fetal parts were absent and in 5 (38.46%) cases fetal parts were present. According to Fisher Exact test, P value was 0.001 (statically significant).

When the presence of nucleated RBC's was correlated with final diagnosis. We found that out of 37 (74%) cases diagnosed as complete mole in 33 (89.19%) cases nucleated RBCs were absent on histology and 4 (10.81%) cases showed nucleated RBCs on histology. While in case of partial mole out of 13 (26%) cases in 11 (84.62%) cases nucleated RBCs were absent and 2 (15.38%) cases showed presence of nucleated RBCs. According to Fisher, Exact test, P value was 0.049 (statically insignificant).

When the presence of cistern formation (Figure 4) was correlated with final diagnosis. We found that out of 37 (74%) cases diagnosed as complete mole in 12 (32.43%) cases cistern formation were absent on histology and 25 (67.57%) cases showed cistern formation on histology. While in case of partial mole out of 13 (26%) cases in 8 (61.54%) cases cistern formation were absent and 5 (38.46%) cases showed presence of cistern formation. According to Fisher Exact test, P value was 0.066 (statically insignificant).

Table I: The interpretation of Histomorphological features (n=50)

Histomorphological features	Interpretation	Cases (n)	Percentage (%)
Grape like vesicle	Absent	19	38.0
	Present	31	62.0
Cistern formation	Absent	20	40.0
	Present	30	60.0
Nucleated RBC's	Absent	44	88.0
	Present	6	12.0
Fetal parts	Absent	45	90.0
	Present	5	10.0

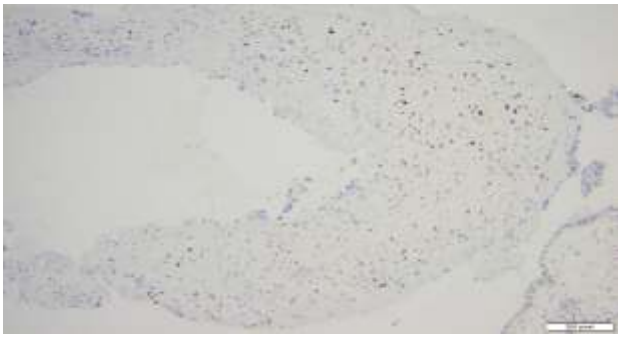

Figure 1: Positive Staining of p57 in Partial Mole at 400x Magnification

Discussion

The diagnostic value of the p57 immunomarker in distinction between partial and complete hydatidiform moles was assessed in this study. 74%

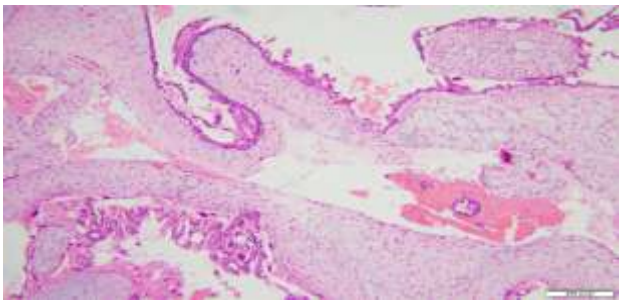

Figure 2: Circumferential Trophoblastic Proliferation at 400X Magnification

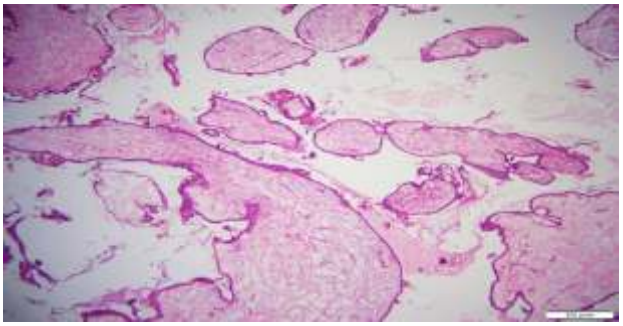

Figure 3: Polar Trophoblastic Proliferation and Admixture Of Variable Sized Villi At 200X Magnification

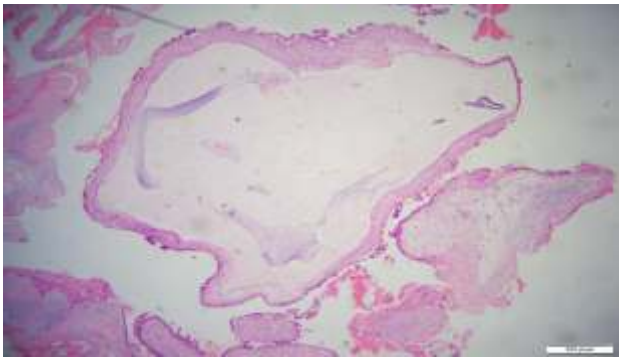

Figure 4: Cistern Formation is Seen in a Dilated Villi Seen in a Diagnosed Case of CHM at 200X Magnification

of cases were found to be complete moles and 26% to be partial moles when p57 immunostaining and histological examination were combined, highlighting the crucial role that p57 plays in enhancing diagnostic precision.

Although grape-like vesicles were found in 62% of cases, 40.54% of complete moles did not have them, which emphasizes the necessity of further diagnostic methods. Histologically, polar trophoblastic proliferation dominated partial moles (76.92%), whereas circumferential trophoblastic proliferation was seen in 54.05% of complete moles. Despite their use, these histological characteristics were not statistically significant (p = 0.053), which emphasizes the relevance of p57 immunostaining.

Complete moles had no fetal components at all, while 38.46% of partial moles had them, which is a statistically significant difference (p = 0.001). Despite being more prevalent in complete moles, nucleated RBCs and cistern development did not significantly differ across the groups, indicating their poor diagnostic accuracy on the basis of histology alone.

There is significant interobserver variability in diagnosing molar pregnancies based on histomorphological features alone as per previous studies as well as in current study.[5,6,7] This variation in morphological features is well established which is related to several factors such as flawed histologic criteria as well as its subjective application for diagnosis and variation in histological features dependent on gestational age of the sample. Since the features are less developed on histological examination, the early diagnosis of molar pregnancies in first trimester scans emphasizes the necessity of a well-established diagnostic criteria.[8]

Like our study research carried out in Iran, CHM was diagnosed on the presence of variable size of chorionic villi from miniscule to very large with central cistern formation and circumferential proliferation of both cytotrophoblasts and syncytiotrophoblasts on histology. PHM was diagnosed based on two types of chorionic villi, focal trophoblastic proliferation, and presence of pseudo-inclusions. However, our study showed significant variable histological features in both entities.[9]

In addition, diagnostic criteria of early CHM can overlap with PHM showing minimal cistern formation, mild hydropic change, fetal blood vessels, irregular villous hyperplasia and pseudo-inclusions in the villi further adding to variable histologic picture.[10]

Classic morphologic features that are diagnostic of molar and non-molar pregnancies on histology are well defined in literature. Although in early gestation the typical morphology is vague making it even difficult to differentiate between hydropic and molar pregnancies, however whenever molecular methods are applied there is considerable discordance between initial and final diagnosis.[11]

We only found presence of fetal parts to be statically significant as presence of abnormal fetal parts in partial mole is due to Di spermic fertilization

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eventually producing a triploid set of chromosomes.[12]

The use of p57KIP2 immunostain to distinguish between partial and full hydatidiform moles is recommended by several national, regional, and worldwide studies in order to prevent interobserver variability and provide a definitive diagnosis.[13, 14, 15] By confirming the use of p57 immunostaining in regional contexts with disparate diagnostic resources and proficiency, our study adds even more value by emphasizing how it might enhance diagnostic precision and lessen interobserver variability in these kinds of situations. A study carried out by Erol O et. al.,[16] used four immunomarkers that are p57, c-erbB-2, CD117 and Bcl-2 in differential diagnosis of hydatidiform mole and hydropic abortion. All four immunostains proved to be efficient, cost effective and simple methods for differentiation among them.

Triratanachat S et. al., concluded in their study that histomorphology has clear cut limitations in accurately diagnosing partial and complete mole with sensitivity of 89.7% and 95.0% respectively. While its specificity turned out to be 95% and 89.7% respectively. They also showed that P57KIP2 immunostain is a helpful cost-effective method to subtype PHM and CHM for their definitive diagnosis.[7] In 2018 Madi JM et. al.,[17] carried out a systemic review & bivariate meta-analysis to determine accuracy of p57kip2 antibody by comparing it with genotyping. Results showed sensitivity of 0.984 (95% confidence interval [CI]: 0.916–1.000) and specificity of 0.625 (95% CI: 0.503–0.736) with significant heterogeneity for specificity (I2 = 71.8, Chi-square P = 0.029) proving high diagnostic accuracy with an area under the curve of 0980.

A recent large study carried out in 2021 of 2017 potentially molar products of conception specimens at john Hopkins further supports that utility of p57 immunohistochemistry and DNA genotyping should be encouraged in routine practice to accurately diagnose and assess the risk of persistent gestational trophoblastic disease. Precise diagnosis of molar conceptus guides the clinician in specific and well-aimed management.[18,19]

Currently molecular genotyping is considered gold standard for subtyping molar pregnancies as it determines ploidy and the paternal origin of molar tissue. Furthermore, it helps in differentiating complete and partial moles from mimics of gestational trophoblastic disease. To establish accurate diagnosis in all cases morphology, p57 immunostain and genotyping must be correlated. Use of genotyping has significantly improved the diagnostic accuracy of GTD which is of clinical significance.[20]

Uterine evacuation and histopathology of the products of conception followed by HCG monitoring are part of obstetric care of molar pregnancy. HCG is an ideal biochemical marker as it precisely reflects the disease burden. Follow up of patients with human chorionic gonadotrophin (HCG) is essential following a diagnosis of molar pregnancy to rule in/out gestational trophoblastic neoplasia. Two normal HCG levels with a one-month gap are recommended for PHM. Follow-up with monthly HCG level for six months is recommended for CHM. The risk of gestational trophoblastic neoplasia following beta HCG normalization was 0.25% for CHM and 0.03% for PHM, according to a large retrospective study of 20,000 women carried out in women who had HCG monitoring following a molar pregnancy. However, even after normalization of HCG levels in complete hydatidiform mole, there was critically increased risk of GTN (0.35%), according to systemic analysis of 19 independent trials. Given the rarity of GTN, another study concluded that extended HCG surveillance, especially following PHM, is not cost-effective. Treatment of GTD entirely depends on FIGO staging system and guidelines.[21] Gestational trophoblastic neoplasia is treated by chemotherapy.[22]

Conclusion

Based on results of this study we concluded that morphological features alone are not reliable in subcategorization of complete and partial molar pregnancies. The only reliable histological parameter is presence of fetal parts that can distinguish between CHM and PHM, yet those might not be present in very early gestations leading to incorrect diagnosis. We recommend application of p57 immunomarker in every case of molar pregnancy for accurate diagnosis and further management of patient. In future reflex genetic testing should be encouraged as it is considered gold standard for establishing ploidy and to differentiate between

CHM and PHM and all the mimics of gestational trophoblastic disease.

Limitation and Future Suggestions

Molecular genotyping unavailability limited our study for a valuable correlation with ploidy. Another study on a larger sample for a longer duration with corresponding Fluorescence in situ hybridization (FISH) studies can provide improved results. Our study's capacity to correlate with ploidy was hindered by the lack of molecular genotyping. Larger sample size, longer study periods, and the use of molecular genotyping methods like (FISH) should improve diagnostic precision and offer a better understanding of hydatidiform moles in the future. Clinical therapy of (GTD) may be enhanced due to accurate diagnosis refined by combining p57 immunostaining with molecular diagnostics.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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Authors have declared no specific grant for this research from any funding agency in public, commercial or nonprofit sector.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Serum Uric Acid as A Biomarker in Bipolar Disorder Type I, Current Episode Manic-Hospital Based Cross-Sectional Study

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ABSTRACT

Objective: To compare serum uric acid in bipolar disorder (BD) type I patients, current episode manic with healthy matched controls.

Study Design: Our study had a cross-sectional, case-control design.

Place and Duration of Study: This research was done at Rawal General & Dental Hospital which is the tertiary care teaching hospital of Rawal Medical & Dental College, Islamabad. The period of study was from 1/10/2023 to 31/03/2024 for a period of 6 months.

Materials and Methods: Thirty patients with BD suffering from manic episode according to DSM-5 criteria, along with 30 matched healthy controls were enlisted in the study. Young Mania Rating Scale (YMRS) was administered to the patients to determine the severity of mania and serum uric acid was determined for both cases and healthy controls (HC). The data was analyzed with Statistical Package for Social Sciences version 22 (SPSS).

Results: Compared to HC (4.4 ± 0.9mg/dl) bipolar patients had elevated plasma uric acid levels (6.06 ± 1.48 ml/dl) [$p = 0.018$]. Age and gender were the two factors that could introduce bias, but after controlling for these, the results were still significant. In the cases YMRS was used to measure the severity of the manic episode, and serum uric acid levels did not have a correlation with this variable ($P > 0.683$).

Conclusion: The level of serum uric acid was significantly higher in cases versus controls in the local population. These results were in line with international studies and pointed to aberrant purine nucleotide turnover in BD.

Key Words: *Bipolar Disorder, Inflammation, Mania, Purine Metabolism, Uric Acid.*

Introduction

Bipolar disorder (BD) is a severe psychiatric condition whose pathophysiological underpinnings are largely unknown.[1] Different pathways involved in the development of BD include abnormalities in neurotransmission, neuroinflammation and neurodegenerative mechanisms.[2] One line of research incriminates purinergic system dysfunction in the neurobiology of BD.[3,4] Adenosine triphosphate (ATP) stored in the cells, serves as the essential energy substrate for vital cellular functions. Diverse mechanisms are involved through which ATP reaches the extracellular space; in turn, neurons express purinergic receptors and binding of the extracellular ATP stimulates many intracellular signaling cascades.[5] The majority of purinergic receptors are located in the hippocampus where they may be involved in such vital processes as the formation of new neurons.[6] Ectoenzymes expressed on the cell surface hydrolyze ATP into adenosine and precisely control extracellular purine concentration.[7] Adenosine wields several functions in the brain via its own receptors, and crucially these include neuroprotection. ATP and adenosine have regulatory immune functions; the former triggers proinflammatory pathways, whereas adenosine acts to dampen inflammation.[8] Increased levels of ATP in the extracellular compartment promote excitotoxicity and neurodegeneration, processes incriminated in the pathophysiology of major neuropsychiatric disorders like BD.[9]

Adenosine is broken down into uric acid (UA), the main nitrogenous end product of purine metabolism and in BD, may serve as a possible indicator of treatment response. Further, during manic episode high serum levels of uric acid may have value as a state marker.[10] It is surmised that raised serum uric

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acid levels specify enhanced purine turnover and diminished adenosine signaling in the CNS. Recent evidence shows that the purinergic system is incriminated in several key brain functions such as mood, sleep, cognitive function, motor activity and behavior.[11] Lesch Nyhan syndrome, regarded as a dysfunction in the purinergic system is exemplified by the production of large amounts of uric acid and raised uric acid levels are linked to impulsivity and irritability in these individuals.[12]

A systematic review and meta-analysis of randomized controlled studies indicated that allopurinol, a modulator of purine metabolism and a xanthine oxidase inhibitor, was helpful in the treatment of acute mania when used in conjunction with lithium.[13] It showed that decrease in YMRS scores from the start to the endpoint was related to a decline in plasma uric acid levels; also, patients who remitted were significantly more likely to have a lower serum uric acid levels as compared to non-remitters.[13] Ostensibly, this implied that uric acid levels were the representative marker of clinical efficacy besides acting as a biomarker during the manic phase of BD.[14] While there is an increasing body of research investigating serum uric acid levels in BD internationally, we could not find any study on this topic in the local context signifying an important gap in the knowledge from our perspective. The objective of the present study was to examine serum uric acid levels in BD subjects in the manic phase and compare those to healthy controls.

Materials and Methods

This was a cross-sectional case-control study and not an observational study. The control group was selected from patients' attendants and hospital visitors provided they gave informed consent. The criteria for selection were that the control subjects must not be suffering from any medical illness and had no past psychiatric history. Thirty bipolar disorder patients in the manic phase according to DSM-V criteria presenting to the Psychiatry Department of Rawal General Hospital were included and these were compared to 30 healthy controls. The sample size was calculated with the help of the formula given below:

$$\text{Unlimited population: } n = \frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2}$$

$$\text{Finite population: } n' = \frac{n}{1+\frac{z^2 \times \hat{p}(1-\hat{p})}{\varepsilon^2 N}}$$

where
z is the z score
ε is the margin of error
N is the population size
p̂ is the population proportion

The population size was 60, the population proportion was 50%; confidence interval was 95% and margin error was 5%. Also guidance was sought from a recently published article in the PubMed database.[15] The sampling technique was convenience, non-purposive and consecutive. The duration of study was from 1/10/2023 to 31/03/2024 for a period of 6 months. Permission to conduct the study was given vide ethical review board approval letter reference number RIHS/DME/07/2023 of Rawal Medical & Dental College, Islamabad.

The study was done in strict compliance with the code of conduct enshrined in the Helsinki Declaration of 2013. It was made certain that no harm would come to any of the participants and confidentiality was maintained at all times. Furthermore, informed consent from all the study subjects was ensured.

The subjects included were aged between 18 and 60 years and suffering from bipolar disorder type I, current episode manic. Excluded from the study were patients who were medically unstable, or suffering from chronic inflammatory conditions. Similarly, patients with gout or any other disease causing hyperuricemia were also left out. Lastly, subjects with a history of heavy smoking or substance abuse were barred from the study.

Psychometric assessment of the bipolar patients was done by administering the Young Mania Rating Scale (YMRS). This is the preferred instrument in research and has good validity and reliability. It comprises of 11 items which are centered on patients' own report of their clinical state during the last 48 hours. The test items are based on the main symptoms of mania, administered by the clinician and rated from 0 to 60 with a cut-off score of 20 in manic subjects. Strong points of the YMRS are its conciseness, simplicity and general acceptability. YMRS was done only once since this was a cross-sectional study to examine

whether severity of mania correlated with serum uric acid levels. In addition, both cases and controls were administered a demographic proforma.

Laboratory assessment was done by taking venous blood samples from both patients and controls using vacutainer tubes. These were centrifuged at 3000×g for 15 min and stored at −80 °C until chemical analysis to determine the value of serum uric acid.

Statistical analysis was done by using SPSS version 22. With respect to demographic variables, Chi-square test was used for categorical variables and Mann-Whitney U test for continuous variables. In order to compare uric acid levels between patients and controls analysis of variance was used. We followed the null hypothesis which stated that there was no difference in the mean serum uric acid levels of cases and controls. The F test in one-way ANOVA compared the primary outcome i.e. variability within groups to variability between groups. For correlation analysis Pearson's correlation coefficient was used. All of the tests were two ended, and a p value of <.05 was considered as significant.

Results

Table I showed the relationship between patients and controls with respect to demographic variables. It could be seen that the two groups were comparable as regards age, gender, marital status, etc. and no statistically significant difference was found between them. Bipolar subjects suffering from manic episode demonstrated greater plasma uric acid levels (6.06 ± 1.48 ml/dl) as compared to healthy controls (4.4 ± 0.9mg/dL) (p = 0.018) (Table II). Analysis of variance was utilized in the SPSS, also referred to as one way ANOVA and plasma uric acid was controlled for age and gender. However, the results remained significant such that these factors did not introduce bias in the study. No correlation was found between serum uric acid levels and the severity of manic episode as assessed by using the YMRS (P >0.683), (Table III).

Table I:Comparison of Sociodemographic Variables of Healthy Controls and Bipolar Disorder Patients

Variables	BD group N=30	HC N=30	*P*
Age	37 (CI: 30-45)	34 (CI: 29-44)	0.135[a]
Age range 18-25	10 (CI: 20-30)	8 (CI: 18-32)	0.231[a]
Age range 26-45	12 (CI: 22-48)	14 (CI: 24-50)	0.174[a]
Age range 46-60	18 (CI: 38-68)	8 (CI: 41-66)	0.428[a]
Male	21 (70%)	15 (50%)	0.537[b]
Female	9 (30%)	15 (50%)	0.512[b]
Single	10 (33%)	12 (40%)	0.339[b]
Married	20 (66%)	18 (60%)	0.278[b]
Years married < 10	10 (50%)	8 (44%)	0.174[a]
Years married > 10	10 (50%)	10 (56%)	0.295[a]
Married with children	18 (90%)	16 (88%)	0.362[b]
Education (years)	12 (CI: 8-16)	10 (CI: 7-14)	0.174[a]
Not working	6 (20%)	8 (26%)	0.475[b]
Working	24 (80%)	22 (74%)	0.483[b]

BD – bipolar disorder; CI – confidence interval; HC – healthy control; [a]Mann-Whitney U test; [b]Chi-square test

Table II: Comparison of Serum Uric Acid Levels of BD Subjects and Healthy Controls

	BD Manic Episode	Healthy Control	Variability within Groups	Variability between Groups	*P* value
Uric acid level (mg/dl)	6.06 ± 1.48	4.4 ± 0.9	6.122 (95% CI 5.837 – 6.847)	6.361 (95% CI 5.915 – 6.914)	0.018*

BD Bipolar Disorder; * One Way ANOVA (Analysis of Variance); CI Confidence Interval

Table III: Relationship Between YMRS Scores and Serum Uric Acid

Serum uric acid (mean)	YMRS scores (mean)	Pearson's correlation coefficient
6.06 ± 1.48	26 ± 8	>0.683

YMRS Young Mania Rating Scale

Discussion

Our study showed that serum uric acid levels were significantly higher in bipolar disorder patients versus controls. This finding points toward an abnormality in purinergic system in bipolar disorder, at least in the manic phase. A well-cited European study compared bipolar disorder patients with subjects who were suffering from other main psychiatric illnesses like major depressive disorder, obsessive compulsive disorder and schizophrenia. It reported that uric acid levels were raised in BD subjects in comparison with patients in other diagnostic groups and that these remained elevated in all phases of BD, even in euthymic subjects. The study concluded that higher serum uric acid levels might be trait makers in bipolar illness with further rises in the manic phase, such that elevated uric acid

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levels may be a state marker of the manic state.[16] Another study examined bipolar subjects in mania, depression and remission and compared them to healthy controls. In comparison to healthy controls, uric acid levels were found higher in all three phases of BD, i.e. mania, depression and euthymia. A modest relationship was shown in the manic episode between 1st and 2nd week YMRS scores and uric acid levels, and a robust correlation was discovered in the depressive episode between 1st and 2nd week Hamilton Rating Scale for depression scores and uric acid levels. In the manic episode a reduction in serum uric acid level was found to be related to decrease in YMRS scores, whereas a similar relationship was not shown in the depressive episode. These results indicate the possible occurrence of purinergic dysfunction in bipolar subjects, which appear to be associated with all phase of the disorder.[17]

A study investigated serum uric acid levels in drug free, index episode mania cases and compared them to healthy subjects who acted as controls. It was discovered that patients in acute mania had significantly greater levels of serum uric acid compared to HC. No association was seen between the levels of serum uric acid and the severity of mania. These findings suggest that serum uric acid levels represent state marker of bipolar disorder in the manic phase. Moreover, the presence of disturbance in purine nucleotide metabolism in these patients has implications for disordered adenosinergic neurotransmission.[18] This study is important because it demonstrates purinergic dysfunction in first-episode, drug-naïve manic patients. Elevated uric acid in these patients suggests that abnormality in purine nucleotide metabolism is inherent to BD and not a result of chronicity or secondary to the administration of psychotropic medications. Our study seems to replicate some of these findings, particularly the non-significant relationship between YMRS scores and serum uric acid levels. It can be concluded that serum uric acid levels while elevated in the manic phase of BD, do not have a significant relationship with the severity of mania.

Raised serum uric acid levels points towards enhanced purinergic transformation and diminished adenosinergic signaling in the CNS. The latter serves to decrease the excitability of neurons by reducing the release of neurotransmitters.[19] Uric acid specifically acts on adenosine A1 receptors in the limbic areas of the brain and increased level of this final metabolite of purine turnover is supposedly liable for the kindling, excitoxic action. Extending from animal models, this is considered to be the primary association between adenosinergic activity and manic symptoms.[20] Hence, lithium which is the gold standard mood stabilizer purportedly decreases uric acid levels and a comparable mechanism has been described for carbamazepine, while conversely sodium valproate has been found to raise serum uric acid levels.[21]

An interesting study tested the relationship between bipolar disorder and serum uric acid levels, seeking to clarify whether this association was caused by metabolic syndrome and related indices. One hundred and seventy six patients suffering from a variety of psychiatric disorders and 89 healthy controls were included in the study.[22] Among the patients, bipolar disorder was the single diagnostic subclass significantly linked to higher uric acid levels. Furthermore, variables including male sex, metabolic syndrome, increased abdominal circumference and raised serum triglycerides levels had a significant effect on uric acid. Statistical analysis disclosed that the probable effect between bipolar disorder and uric acid levels was only partly the result of metabolic abnormalities. These finding suggest a direct linkage between bipolar disorder and uric acid levels, which is not the result of any associated metabolic abnormalities.[22]

Finally, an innovation in medicine is the application of uric acid linked ratios in different diseases such as diabetes mellitus. The use of these in bipolar disorder was recently reported in a study from the Peoples Republic of China. Noteworthy ratios included uric acid-to-albumin ratio (UAR), uric acid-to-creatinine ratio (UCR), uric acid-to-high-density lipoprotein ratio (UHR), and uric acid-to-lymphocyte ratio (ULR). It was shown that in comparison to healthy controls and subjects with bipolar depression, manic patients had higher ULR, UHR, UCR and UAR. Moreover, in cases with psychotic mania these ratios were even higher when compared to patients with non-psychotic mania. The study concluded that the inflammatory response was more intense in bipolar mania than depression and that

UAR was a risk factor for mania.[23]

We conducted a search of the literature to investigate whether any studies were done locally on the topic of serum uric acid levels and BD. To our dismay we could not find any study on this subject specifically. As such ours is a pioneering study in the local population and because of the importance of uric acid as a marker in bipolar disorder we hope that other researchers from our country will investigate this area further.

Limitations

1) The present study is cross-sectional in nature and in order to validate the results a study with longitudinal, prospective design is needed.
2) The sample size is small and a study with larger sample is needed to corroborate the findings of this study.
3) A multi-centered study, preferably with a multi-national design is required to further examine the utility of serum uric and uric acid related ratios as biomarkers in bipolar disorder.
4) We employed convenience sampling which could have introduced selection bias.
5) We did not control for metabolic syndrome which was a possible source of bias in the study.

Conclusion

Our study shows that serum uric acid may serve as a biomarker in the manic phase of bipolar disorder. This is an inexpensive and readily available test which may be a state marker of mania. Furthermore uric acid related ratios enhance the value of this parameter in bipolar illness, as these are indicative of an inflammatory state in the manic phase. It is hoped that further research will clarify the status of uric acid as a biomarker in BD.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Analysis of Factors Affecting Implant Placement in Posterior Maxilla With Lateral Window Sinus Lift Technique; A CBCT Study

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ABSTRACT

Objective: To identify and analyse factors influencing lateral sinus augmentation for implant placement in the posterior maxillary region.

Study Design: Retrospective cross-sectional study.

Place and Duration of Study: The study was conducted in the Periodontology department at University College of Dentistry, The University of Lahore between January 2024 to June 2024.

Materials and Methods: The study was conducted at the Department of Periodontology, University College of Dentistry. Using CBCT (Cone Beam Computed Tomography) scans from 278 cases with missing posterior maxillary teeth, the study analysed factors like sinus angle, sinus septa presence, angle of sinus, posterior superior alveolar artery (PSAA) visibility and distance of PSAA from the superior and inferior border of the potential window.

Results: Key findings include a predominance of PSAA within the intra-osseous region (92.6%) and variations in distances from the PSAA to the superior and inferior borders of the planned lateral window. Additionally, the study highlighted a low incidence of maxillary sinus septa (5%). Schneiderian membrane thickness was less than 3mm in 79% of the cases, and variations in maxillary sinus shape were noted to be an angle greater than 30 degrees in 90.1% of the cases. The location of PSAA was intraosseous in 75 (92.6%) cases whereas in the remaining 6 (7.4%) cases it was not evident intraosseously.

Conclusion: In conclusion, CBCT proved crucial for treatment planning, and thorough evaluation of PSAA's relationship with sub-antral bone height was emphasized for safe lateral sinus augmentation procedures in posterior maxillary implant placements. The study contributes valuable insights for dental practitioners involved in implant planning and sinus surgeries.

Key Words: *CBCT, Sinus, Dentistry, Dental Implants.*

Introduction

The maxillary sinus, the largest of the paranasal sinuses with an average volume of 12.5 ml, plays a critical role in dental implant placement, particularly in the posterior maxilla. [1] Lined by the Schneiderian membrane—a thin, bilaminar mucoperiosteal layer—the sinus is closely related to several anatomical structures that must be considered during surgical procedures. Sinus pneumatization or depression of the sinus floor often reduces available bone height, complicating implant insertion and necessitating sinus augmentation or lift procedures.[2,3]

The sinus elevation technique, first introduced by Boyne and James in 1980, has since been refined.[4] When residual bone height is less than 5 mm, the open or lateral sinus lift approach is typically recommended, either for simultaneous or staged implant placement. In contrast, when bone height ranges from 5 to 8 mm, a less invasive crestal approach may suffice due to the reduced need for vertical bone augmentation. Literature indicates that sinus augmentation does not compromise implant survival rates.[5,6]

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Cone Beam Computed Tomography (CBCT) has become the preferred imaging modality for assessing the maxillary sinus, aiding clinicians in treatment planning. CBCT provides detailed insights into sinus anatomy, including variations in sinus shape and the location of critical structures like the posterior superior alveolar artery (PSAA).[7,8] While sinus shape variations such as V-shaped or U-shaped configurations are uncommon and usually of limited clinical consequence, they can influence surgical complexity. V-shaped sinuses pose a greater risk of Schneiderian membrane perforation during elevation, while U-shaped sinuses generally offer more space for graft material, facilitating easier procedures.[9]

Histological studies have demonstrated successful bone formation following sinus augmentation with simultaneous implant placement. Additionally, research conducted on the Indian sub-population using CBCT found the PSAA most commonly located within the intra-osseous region. The vessel's distance from the alveolar crest varied by gender but was unaffected by age.[10,11] These findings highlight the importance of identifying the PSAA's position preoperatively to prevent iatrogenic damage during the creation of a lateral window.[12,13]

While concerns have been raised about Schneiderian membrane thickness, a systematic review by Monje et. al.,[12] concluded that membrane thickness does not significantly impact the success of sinus lifts or implant placement. However, anatomical features like sinus septa have been linked to a higher incidence of membrane perforation, as shown in a study by Ghaida et. al.,[14] in Saudi Arabia.

Despite numerous individual studies on maxillary sinus anatomy and augmentation techniques, there remains a lack of comprehensive research evaluating all relevant factors in a single study. Our study aimed to bridge this gap by identifying and analyzing multiple anatomical and procedural variables that influence lateral sinus augmentation for implant placement in the posterior maxilla.

Materials and Methods

The study was conducted at the Department of Periodontology, University College of Dentistry, The University of Lahore during a period of 6 months. A retrospective cross-sectional study was conducted to include the CBCTs fulfilling the inclusion criteria. All CBCTs having one or more unilateral missing maxillary posterior tooth (2nd premolar, 1st molar and 2nd molar) available at the radiology department of University College of Dentistry were included in the study. Any CBCT scan with osseous pathology or defect in the area of interest was excluded from the study. The patient's age was more than 18 years. The sampling technique was non-probability convenience sampling. After approval from the Ethical Review Board of the institute (UCD/ERCA/6/4/23), CBCT images were obtained by Pro Max 3D Mid (Planmeca, Helsinki, Finland). Scanning was performed by fixing the patient's jaw and head support apparatus while the patient was standing. Amongst the total CBCTs gathered since 2018 till 2023, scans were evaluated according to the inclusion criteria. The scans had to have any one or more missing premolars or molars (excluding third molars) in the maxillary region. Cases having any pathology associated with maxillary jaw, incomplete bony healing after tooth extraction or presence of dental implants in the posterior maxilla were excluded.

After placement of a virtual implant of dimensions 5.0 x 8.0 at the selected 1st and 2nd Molar site and 4.5 x 8.0 at a premolar site in a restoratively driven position, following measurements were calculated using the methods explained ahead:

1. A horizontal line was drawn at the apex of the virtual implant and buccal and palatal end points are connected to the most concave part of the sinus floor. This angle is measured to identify the shape of sinus as less than 30 or more than 30-degree angle. [15]
2. Sub-antral bone height was measured starting from the floor of the maxillary sinus to the crest of alveolar bone. The bone height was divided into three groups: less than 5mm, 5 to 8mm and more than 8 mm.[14] Cases with bone height less than 5mm are discussed in this study.
3. A lateral window was planned in cases with sub-antral bone height less than 5mm. An imaginary lateral window was designed on the CBCT. The landmarks of the window were based on the respective sub-antral bone height. The superior window border was designed to be 12mm above the crestal bone level, whereas the inferior window was designed to be 3mm above the

sinus floor for lateral window technique. This design is in accordance with previous literature.[15,16]

Once the window borders were designed and marked on the CBCT, the distance from PSAA is measured by making a vertical line from PSAA to the crestal bone level in the coronal sections and then connecting these lines to the superior and inferior border points. The distance from PSAA to these points on the vertical line was calculated. If the distance from PSAA to the superior border was more than 2 mm or the vessel is not intraosseous it was considered not to affect the window design. On the other hand, if the vessel was within 2 mm of the superior border, it was assumed that the window dimensions would have to be changed and the vessel was affecting the treatment plan.

4. The location of the PSAA was determined either to be intra-osseous or intramembranous based on the CBCT at the given section. Similarly, on the coronal sections, the CBCT sections are analyzed from posterior to anterior to see at what point the PSAA is visible intraosseously, the site of tooth where this occurs is labeled as the first seen sight of the vessel. Similarly, the point where it merges in the soft tissue again on anterior sections is designated as the last seen site of the vessel. The sites were related to the adjacent tooth.
5. The thickness of the Schneiderian membrane was measured from the upper border of the membrane to the lower border and classified according to its thickness. It was divided into two groups namely less than 3mm and greater than 3mm.[14] Similarly, the Schneiderian membrane thickness was calculated on the buccal aspect of the bone as less than 1mm or more than 1mm where the window is to be prepared.
6. The angle formed between the palatal wall and buccal wall was then calculated by connecting the two walls at the level of apex of the implant and connecting both these points on each wall to the most concave point on the sinus floor and measuring this angle. The results were divided into two groups: less than 30^{o} or more than 30^{o}.[17]

Data entry and analysis was done with SPSS version 25. Quantitative variable (distance between PSAA and upper border for the lateral window) were presented with mean ±SD and qualitative variables were presented with frequency and percentage. Chi Square test was applied to see the association between qualitative variables (gender, sinus septa, sinus angle). P-value <0.05 was considered statistically significant.

Results

A total of 278 scans had one or more missing posterior maxillary teeth. Analysis of remaining sub-antral bone height resulted in 81 (29.1%) cases showing less than 5mm of remaining bone thickness, 105 (37.8%) cases showed bone height between 5 to 8 mm and remaining 92 (33.1%) cases had bone height of more than 8 mm. Amongst these, the results of the cases with sub-antral bone height less than 5mm requiring lateral sinus lift are discussed in this study. From the 81 cases evaluated, 41 (50.6%) participants were males and 40 (49.4%) were females. The site distribution showed that 11 (13.6%) sites were missing second premolars, 40 (49.4%) sites showed missing first molars and remaining 30 (37%) sites were related to second molars. Table 1 depicts the various factors along with their measurements. The location of PSAA was intraosseous in 75 (92.6%) cases whereas in the remaining 6 (7.4%) cases it was not evident intraosseously. When the distance of PSAA was calculated from the superior border of the potential window for lateral sinus lift technique, in 13.9% of the cases, presence of the artery hindered the making of ideal dimension window by being too close to the superior border. The mean distance in all the 75 cases was 5.83mm with a range of -2.2 mm to 12.3mm. The average distance of PSAA taken from the inferior border of the lateral window planned was 12.87mm ranging from 6.8mm to 19.3mm. Table 2 shows the relationship of Schneiderian membrane thickness, presence of septa and sinus angle with gender. There is no significant relationship of any of these factors with gender.

Discussion

This CBCT-based study analyzed anatomical factors influencing the lateral sinus lift procedure for dental implant placement in the posterior maxilla. Among cases with sub-antral bone height <5 mm (29.1% of total), we found that 92.6% showed intraosseous

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Table I: Distribution of Tooth No. With Sinus Angle, Presence of Septa and Thickness of Schneiderian Membrane with Chi Square Analysis

Tooth No.	Sinus Angle		Presence of septa		Thickness of Schneiderian membrane at sinus floor	
	Less than 30 degrees	More than 30 degrees	Present	Absent	Less than 3 mm	More than 3 mm
	1 (1.2%)	16 (17.9%)	2 (2.4%)	22 (27.1%)	15 (18.5%)	8 (9.8%)
	3 (3.7%)	30 (45.7%)	1 (1.2%)	21 (25.9%)	19 (23.4%)	11 (13.5%)
	4 (4.9%)	27 (33.3%)	3 (3.7%)	33 (40.7%)	16 (19.7%)	12 (14.8%)
p-value	0.479		0.665		0.752	

Table II: Descriptive Frequencies of Various Factors

Parameters	Categories	N (%)
Sinus angle	<30°	8 (9.9)
	≥30°	73 (90.1)
Sinus septa	Absence of septa	93.7
	Presence of septa	6.3
Schneiderian membrane thickness (at sinus floor)	<3mm	64 (79)
	≥3mm	17 (21)
Schneiderian membrane thickness (at buccal aspect)	≤1mm	70 (86.4)
	>1mm	11 (13.6)
PSAA visibility (origin point)	Not identified (intra-membranous throughout)	6 (7.4)
	Origin at 2nd Molar or posterior to it	65 (80.2)
	Origin at 1st Molar	10 (12.4)
PSAA visibility (termination point)	Not identified (intra-membranous throughout)	6 (7.4)
	Termination at 2nd Pre-molar	12 (14.8)
	Termination at 1st Pre-molar or anterior to it	63 (77.8)
Buccal Bone thickness	Less than 1 mm	60 (74.1)
	More than 1mm	21 (25.9%)

PSAA Posterior Superior Alveolar Artery

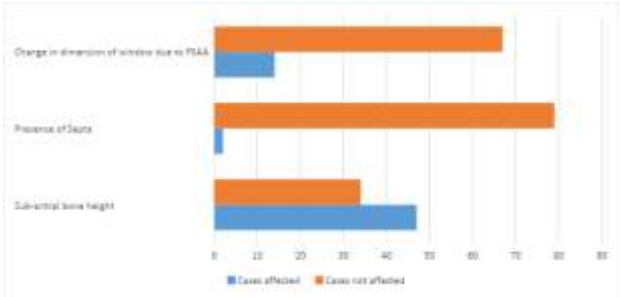

Figure 1: Factors Affecting Implant Placement in Cases With Lateral Sinus Lift

presence of the PSAA, 90.1% had sinus angles ≥30°, Schneiderian membrane thickness was <3 mm in 79% of cases, and septa were present in only 6.3%. These results highlight critical anatomical variables

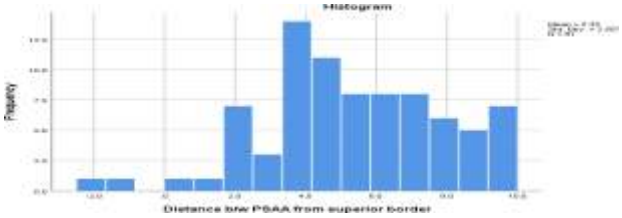

Figure 2: Histogram Showing the Distance of PSAA from the Superior Border of Planned Lateral Window

that can affect sinus augmentation planning.[18]

Sub-antral bone height was found to be <5 mm in 29.1% of cases, necessitating a lateral window approach. Our results reinforce prior findings by Valentini and Atiq et al. who suggested lateral sinus augmentation as a reliable technique when bone height is <8 mm.[19,20,21] However, our study showed a higher frequency of deficient bone height compared to De Souza et al., who reported that 83% of sites had sufficient bone for implant placement.[22] This discrepancy could be attributed to differences in timing post-extraction or population-based variations.

Septa were observed in only 6.3% of cases, significantly lower than the 33% reported in Henriques et al.'s meta-analysis.[23] The low frequency in our sample could reflect population-specific anatomical patterns or a smaller sample size. Despite this low incidence, septa remain clinically significant, as their presence is associated with an increased risk of Schneiderian membrane perforation and complications during sinus elevation, as supported by Ghaida et al.[12] Careful CBCT evaluation remains essential when planning lateral window access.

The PSAA was identified intraosseously in 92.6% of cases, consistent with Godil et. al.,[12] 's findings in the Indian sub-population. Notably, in 13.9% of cases, the artery was within 2 mm of the superior border of the planned lateral window, potentially impacting

the window design. These results emphasize the need for individualized surgical planning. Literature by Iwanaga et al.[24] recommends limiting the superior window border to avoid vessel injury, which aligns with our findings.

Most cases (79%) had membrane thickness <3 mm, similar to results from Monje et. al.,[12] who concluded that Schneiderian membrane thickness does not significantly impact implant success. Our study further confirms that membrane thickness did not vary significantly by gender and posed no procedural limitation in lateral sinus augmentation.

The sinus angle was ≥30° in 90.1% of cases, indicating a predominantly U-shaped sinus morphology, which is generally favorable for graft placement. This supports Cho et. al.,[16] assertion that V-shaped sinuses carry higher perforation risk. The prevalence of wide sinus angles in our cohort reduces intraoperative complications during membrane elevation.

This study is limited by its retrospective design, potential selection bias due to convenience sampling, and lack of surgical outcome correlation. The analysis did not account for time since tooth extraction or sinus pathologies that may affect anatomy.

Prospective studies incorporating surgical outcomes, post-operative CBCT follow-ups, and diverse ethnic populations would strengthen evidence for planning sinus augmentation. Additionally, integrating artificial intelligence in CBCT assessment may improve predictive accuracy for complication risks.

Conclusion

CBCT is an invaluable tool for treatment planning of implant cases requiring sinus augmentation. There are multiple factors that have to be analyzed before placing an implant in the posterior maxillary region. Location of PSAA, height of sub-antral bone, presence or absence of septa and thickness of Schneiderian membrane are some of the more important factors that must be analyzed through CBCT. Each case has variations and must be planned separately but it is suggested that careful evaluation of the relationship of PSAA with sub-antral bone height is necessary for performing a safe procedure.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Predictive Role of Skull Fracture Type and Location in Intracranial Hemorrhage Among Road Traffic Accident Victims: A CT-Based Observational Study

Rukhsana Aziz, Nosheen Noor, Ghazala Naz

ABSTRACT

Objective: To evaluate the predictive relationship between skull fracture types and the presence of Intra cranial Hemorrhage (ICH) in patients with head trauma due to Road Traffic Accidents (RTAs).

Study Design: Retrospective observational cross-sectional study

Place and Duration of Study: The study was carried out during the month of May 2025 at the Radiology Department of Lady Reading Hospital Peshawar

Materials and Methods: Following institutional review board approval, the retrospective study was carried out in May 2025 at the Radiology Department of Lady Reading Hospital Peshawar using data gathered in the Radiology Department's Health Management Information System (HMIS) between January and December 2022. The study analyzed CT brain scans of 300 RTA patients. Data included age, gender, fracture type and site, and presence and type of Intracranial hemorrhage (ICH). Chi-square and logistic regression were used to assess associations.

Results: Out of 300 RTA patients, 246 (82%) were male, with the majority aged 11–30 years. ICH was observed in 126 patients (42%), most commonly extradural hematoma (58.7%). Skull fractures were seen in 154 patients (51%), with parietal bone being the most frequently affected (30.7%). A significant association was found between skull fractures and ICH ($p < 0.001$). Logistic regression confirmed that fracture type independently predicted ICH ($p < 0.001$), with linear fractures showing the highest odds (OR = 5.34), followed by depressed (OR = 4.51) and comminuted fractures (OR = 2.13). Fracture site was also significantly associated with hemorrhage type ($p < 0.001$).

Conclusion: Skull fracture type and location are significant predictors of ICH in RTA patients. Linear and depressed fractures, in particular, are strongly associated with ICH. These findings highlight the importance of detailed CT evaluation for early identification and risk stratification in head trauma cases.

Key Words: *Brain, Computed Tomography; Craniocerebral Trauma, Intracranial Hemorrhage, Road Traffic Accidents, Skull Fracture.*

Introduction

One of the leading causes of mortality and disability worldwide is automobile accidents. RTAs, which cause over 85% of fatalities,[1] are disproportionately common in underdeveloped nations. As the eighth most common cause of mortality worldwide, traffic accidents (RTAs) have emerged as a significant public health concern. Globally, traumatic brain injury (TBI) is a significant health and socioeconomic issue. Out of all trauma-related injuries worldwide, it contributes the most to disability and mortality. In low- and middle-income countries like Pakistan, the burden is exacerbated by limited trauma care infrastructure and poor adherence to safety measures such as helmet or seatbelt use. According to the World Health Organization, approximately 1.3 million deaths occur each year due to RTAs, with many more individuals suffering non-fatal injuries, including head trauma.[2]

Among the spectrum of head trauma, intracranial hemorrhage (ICH) — including extradural hematoma (EDH), subdural hematoma (SDH), subarachnoid hemorrhage (SAH), and intracerebral hemorrhage (ICH) — is particularly critical due to its potential for rapid deterioration. Skull fractures, often resulting from high-velocity impacts, are a key predictor of such hemorrhages.[3-6] Another crucial finding in head injuries linked to RTAs is skull fractures, which

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frequently accompany or increase the risk of ICH. Linear, depressed, diastatic, and basilar fractures are all possible. While depressed and basilar fractures are associated with a higher risk of neurological deterioration and serious intracranial disease, linear fractures are the most common.[7-8] However, not all skull fractures carry the same risk. Fracture characteristics — including type (linear, depressed and comminuted) and location (parietal, frontal, occipital, facial and basal) — may influence the likelihood and severity of ICH. According to studies, the prevalence of different types of ICH varies; epidural hematomas are more common in auto accidents, although subdural and subarachnoid hemorrhages are common.[9-10] Age and gender play significant roles in the severity of outcomes, with the elderly experiencing more severe effects due to bone fragility, and males more frequently involved in RTAs.[9] Although early diagnosis has been enhanced by developments in diagnostic technologies such as computed tomography (CT), the incidence of TBI is still high.[11] While previous studies have established that skull fractures increase the risk of ICH, limited research focuses on how specific fracture types and anatomical sites predict hemorrhagic outcomes. This study investigates these associations in a Pakistani tertiary care setting, aiming to identify fracture characteristics most predictive of ICH and improve early triage and management.

Understanding the predictive value of skull fracture types and locations can refine risk stratification in emergency trauma care. By identifying which fracture characteristics are most strongly associated with ICH, clinicians can prioritize neuroimaging and intervention, especially in resource-limited settings. This study contributes context-specific data to guide trauma management in the local population.

Materials and Methods

This study was conducted following approval from the Institutional Ethical and Research Committee of Lady Reading Hospital, Peshawar (Approval Reference No. 184/LRH/MTI, dated 09.05.2025). As a retrospective observational cross-sectional study using anonymized patient data extracted from the Hospital Management Information System (HMIS) and Radiology PACS, informed consent was not required. All data were handled confidentially, and patient identifiers were removed to ensure privacy. A simple convenient sampling technique was used, including all CT brain scans of RTA patients available in PACS during January –December 2022, ensuring feasibility while capturing consecutive eligible cases. Total 300 patients having history of Road traffic accident in CT Brain report from January, 2022 to December 2022 were included in the study where CT brain was performed using the machine Optima GE 16 slice and reported on PACS system by consultant radiologist (a fellow of CPSP). For reliability, 10% of randomly selected reports were re-reviewed by another senior radiologist; any discrepancies were resolved by consensus. Owing to the large dataset, it was not feasible to re-check all scans; therefore a random sample was used as a quality assurance measure. Repeat/follow-up or post-operative scans from the same episode, known pre-existing intracranial pathology and non-diagnostic image quality scans were excluded.

Using OpenEpi calculator (version 3.01) with 95% confidence level, 19% expected frequency of intracranial hemorrhage among RTA head-injury patients[12], and 5% margin of error, the required sample size was 237. Patients' data was explored from HMIS and entered on a pre-designed proforma having age, gender, type and site of skull bone fracture, any intracranial hemorrhage, its type and site and contusions. Patients were divided into eight age groups based on decades from 0 to +70 years. Data was analyzed using SPSS V 26. Descriptive statistics summarized frequencies. Chi-square test was used to assess categorical associations. Binary logistic regression evaluated fracture type as a predictor of ICH ($p<0.05$ considered significant).

Results

A total of 300 patients involved in road traffic accidents (RTAs) were included in the study. The majority of patients were in the 11–21 years age group (n = 93; 31.4%), followed by the 21–30 years group (n = 68; 22.7%), with a pronounced male predominance (n = 246; 82%). The distribution of age groups and gender is presented in Figure 1A & B.

Intracranial hemorrhages (ICH) were observed in 126 patients (42%). The most common type was extradural hematoma (74 patients; 58.7% of all ICH-positive cases, 95% CI: 50.1–67.3), followed by subdural hematoma (25 patients; 19.8% 95% CI: 12.8–26.8 and other hemorrhages including SAH and

intraparenchymal bleed (27 patients; 21.4%, 95% CI: 14.2–28.6). Age-wise distribution of hemorrhage types is shown in Table I.

Skull fractures were found in 154 patients (51.3%). The parietal bone was the most frequently involved (n = 48; 31.2%, 95%CI: 23.9–38.5; a depiction of linear fracture of parietal bone and associated EDH is presented in Figure 1C & D), followed by the frontal bone (n = 39; 25.3%, 95% CI: 18.5–32.1) and facial bones (n = 34; 22.1%, 95% CI: 15.6–28.6). Multiple skull bone fractures were present in 79 patients (51.3%; 95% CI: 43.4–59.2). The most common fracture type was linear (n = 84; 54.6%, 95% CI: 46.7–62.5), followed by comminuted (n = 57; 37.0%, CI: 29.4–44.6) and depressed fractures (n = 13; 8.4%, 95% CI: 4.0–12.8). The proportion of patients with associated intracranial hemorrhage (ICH) was highest in those with linear fractures (55/84; 65.5%), followed by depressed fractures (8/13; 61.5%) and comminuted fractures (25/57; 43.9%) Table II.

Among the 154 patients with skull fractures, 88 (57.5%) also had ICH, while 42.9% had no hemorrhage. Conversely, isolated ICH (without fracture) was seen in 38 patients (30.2% of ICH-positive cases; data not shown). A statistically significant association was found between skull fractures and ICH (χ^2 = 29.8, df = 1, p < 0.001). Patients with skull fractures had nearly four times higher odds of developing ICH compared to those without fractures (OR = 3.79; 95% CI: 2.33–6.18). Hemorrhagic contusions were observed in 34 patients with skull fractures (22.2% of those with fractures) and in 15 patients without fractures. This difference was not statistically significant (p = 0.4).

Logistic regression demonstrated that the presence and type of skull fracture were significant predictors of intracranial hemorrhage (χ^2 = 36.5, p < 0.001). Compared with patients without fractures, those with comminuted fractures had over two-fold increased odds of ICH (OR 2.13, 95% CI: 1.13–4.04, p = 0.020), while depressed fractures were associated with a more than four-fold increase (OR 4.51, 95% CI: 1.39–14.62, p = 0.012). Linear fractures conferred the greatest risk, with more than five-fold higher odds of ICH (OR 5.34, 95% CI: 2.98–9.56, p < 0.001) Table III.

A significant association was found between the site of skull fracture and the type of intracranial hemorrhage (χ^2 = 107.365, df = 25, p < 0.001). Parietal fractures were most commonly associated with extradural hematoma (54.2% of parietal fracture cases; 35.1% of all EDH cases). Frontal and temporal fractures also frequently resulted in EDH (41% and 45.8% respectively), while subdural and subarachnoid hemorrhages were less common overall but occurred across multiple fracture sites. A majority of patients with facial fractures had no ICH (82.4%), while those with no fractures also occasionally demonstrated various types of hemorrhage, especially subdural and subarachnoid types.

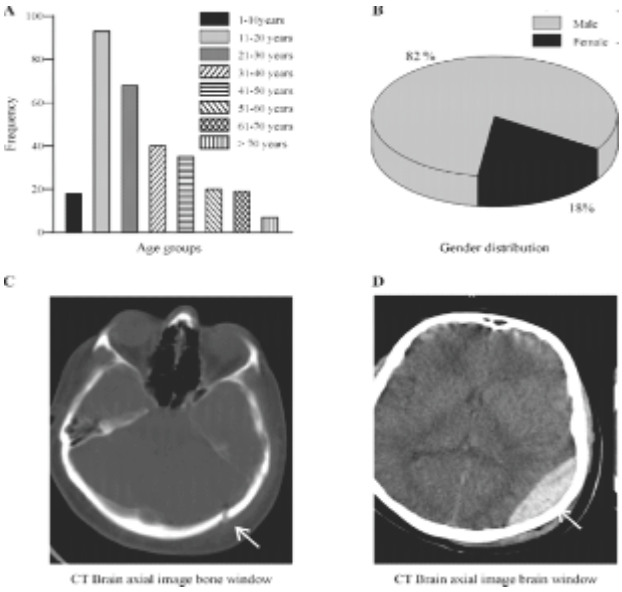

Figure 1. Age (A) and Gender (B) Wise Distribution of The Patients. CT-Brain Axial Image Bone Window (C) And Brain Window (D) Showing Linear Fracture of Left Parietal Bone and Associated Extradural Hematoma.

Table I: Age-Wise Distribution of Hemorrhage Types (n=300)

			Type of Hge					
			Extradural	Mixed	Parenchymal	SubArchnoid Hge	Subdural	Total
Age	1-10 yrs	Count	4	1	0	1	1	7
		% within Age	57.1%	14.3%	0.0%	14.3%	14.3%	100%
	11-20 yrs	Count	29	0	1	0	5	35
		% within Age	82.9%	0.0%	2.9%	0.0%	14.3%	100%
	21-30 yrs	Count	19	2	1	5	9	36
		% within Age	52.8%	5.6%	2.8%	13.9%	25.0%	100%
	31-40 yrs	Count	9	1	2	3	1	16
		% within Age	56.3%	6.3%	12.5%	18.8%	6.3%	100%
	41-50 yrs	Count	8	1	2	0	2	13
		% within Age	61.5%	7.7%	15.4%	0.0%	15.4%	100%
	51-60 yrs	Count	2	2	3	1	1	9
		% within Age	22.2%	22.2%	33.3%	11.1%	11.1%	100%
	61-70 yrs	Count	1	0	0	1	3	5
		% within Age	40.0%	0.0%	0.0%	20.0%	60.0%	100%
	+70 yrs	Count	2	0	0	0	3	5
		% within Age	40.0%	0.0%	0.0%	0.0%	60.0%	100%
Total		Count	74	7	9	11	25	126
		% within Age	58.7%	5.6%	7.1%	8.7%	19.8%	100%

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Table II: Correlation of Intracranial Hemorrhage and Skull Fracture (n=300)

			Skull fracture		Total
			No	Yes	
Intracranial hemorrhage	No	Count	108	66	174
		% within Intracranial hemorrhage	62.1%	37.9%	100.0%
		% within Skull fracture	74.0%	42.9%	58.0%
		% of Total	36.0%	22.0%	58.0%
	Yes	Count	38	88	126
		% within Intracranial hemorrhage	30.2%	69.8%	100.0%
		% within Skull fracture	26.0%	57.1%	42.0%
		% of Total	12.7%	29.3%	42.0%
Total		Count	146	154	300
		% within Intracranial hemorrhage	48.7%	51.3%	100.0%
		% within Skull fracture	100.0%	100.0%	100.0%
		% of Total	48.7%	51.3%	100.0%

Table III: Univariate and Multivariate Logistic Regression Analysis of Skull Fracture Type as a Predictor of Intracranial Hemorrhage

Fracture Type	Univariate OR (95% CI)	p-value	Multivariate OR (95% CI)	p-value
No Fracture	1.00 (reference)	--	1.00 (reference)	--
Comminuted	2.35 (1.31-4.21)	0.004	2.13 (1.13 – 4.04)	0.02
Depressed	4.90 (1.65-14.6)	0.004	4.51 (1.39-14.62)	0.012
Linear	5.62 (3.27-9.64)	<0.001	5.34 (2.98-9.56)	<0.001

Note: OR = odds ratio; CI = confidence interval; Ref = reference category. Univariate ORs were derived from crosstabulated frequencies; multivariate ORs from binary logistic regression including all fracture types simultaneously. Multivariate Model Fit: $\chi^2(3) = 33.77$, $p < 0.001$; Nagelkerke $R^2 = 0.154$; Overall Accuracy = 67.7% (Sensitivity = 50.0%, Specificity = 80.5%).

Discussion

This study aimed to evaluate whether the type and location of skull fractures in road traffic accident (RTA) victims with head trauma are predictive of intracranial hemorrhage (ICH). Our findings demonstrate a clear and statistically significant association between fracture patterns and the occurrence and type of ICH, with important clinical implications for trauma assessment and radiological triage.

In line with global and regional epidemiological trends[13], young adult males were most frequently affected, with the 11–30 years age group comprising over half of the study population. This reflects higher road exposure and risk-taking behavior, consistent with reports from similar LMIC contexts such as Pakistan and Nigeria.[2] Overall, ICH was observed in 42% of patients, with extradural hematoma (EDH) being the most prevalent type (58.7%), followed by subdural hematoma (SDH) (19.8%). These findings differ somewhat from Western literature, where SDH and SAH often predominate, especially in elderly patients.[14] Our younger cohort and high rate of skull fractures may explain the predominance of EDH, which is typically associated with high-impact trauma and arterial injury from fracture lines.

A key focus of this study was the predictive value of fracture types for ICH. Linear fractures were the most frequent (52.9%), followed by comminuted (38.6%) and depressed fractures (8.5%). This finding is similar to other studies where linear fracture was found in 93% of RTA patients.[15-16] Importantly, logistic regression analysis confirmed that fracture type is a statistically significant and independent predictor of ICH ($\chi^2 = 33.77$, $p < 0.001$). Patients with linear fractures had more than five-fold higher odds of ICH (OR = 5.34, 95% CI 2.98-9.56), those with depressed fracture had four-fold increased odds (OR = 4.51, 95% CI: 1.39-14.62) and comminuted fractures carried a two-fold risk (OR = 2.13, 95% CI: 1.13-4.04). These findings emphasize that linear fractures—often regarded as less severe—carry substantial risk of hemorrhagic injury, particularly in the temporoparietal region where the middle meningeal artery is vulnerable. Similar associations have been reported in prior studies, reinforcing the need to avoid underestimating the clinical significance of linear fractures.[17]

Analysis of the anatomical site of fractures revealed strong anatomical correlations with hemorrhage patterns. Parietal bone fractures were the most frequent and most strongly associated with EDH (54.2% of parietal fracture cases; 35.1% of all EDHs). Frontal and temporal fractures also frequently resulted in EDH, consistent with the anatomical course of meningeal vessels. By contrast, facial and occipital fractures were less frequently associated with hemorrhage. This is similar to another study by Hohlrieder et. al.,[18] which showed 14 folds increase in risk of ICH with cranial trauma as compared to facial fractures. A highly significant association between

fracture site and hemorrhage type ($\chi^2 = 107.4$, $p < 0.001$) supports the role of fracture location in guiding clinical suspicion and imaging prioritization.

Interestingly, 30.2% of ICH-positive patients had no radiologically detectable skull fracture, a finding consistent with previous studies[19] that highlight the role of acceleration-deceleration forces in producing coup-contrecoup injuries, diffuse axonal injury, and vascular shearing. These cases reinforce that absence of fracture does not exclude serious intracranial pathology, emphasizing the role of clinical vigilance and liberal CT usage in high-risk trauma scenarios.

The study's findings have direct clinical relevance:

- Skull fracture type and location should be considered early indicators of potential ICH, particularly in resource-constrained settings where rapid triage is essential.
- Linear and depressed fractures, although sometimes underappreciated, demand careful evaluation due to their strong association with hemorrhagic injury.
- CT imaging remains indispensable in all moderate-to-severe head injury cases, regardless of external signs, given the significant number of hemorrhages observed without skull fracture.

Limitations and Future Directions

This single-center retrospective design limits generalizability, and important variables such as trauma mechanism, impact velocity, and protective device use were not assessed. Clinical outcomes (neurological status, surgery, mortality) were also not evaluated, and reliance on CT may have missed subtle MRI-detectable injuries like diffuse axonal injury. Future multicenter prospective studies incorporating trauma mechanisms, protective measures, and clinical outcomes, along with comparative CT–MRI assessments, are needed to refine risk models and enhance prognostic relevance.

Conclusion

Skull fracture type and location are strong predictors of intracranial hemorrhage in patients with RTA-related head trauma. These findings highlight the importance of fracture characterization on CT and support its role in risk stratification, triage, and management decisions in emergency settings.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Personality Profiles of Alcohol and Amphetamine Addicts Admitted at Tertiary Care Mental Health Facility

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ABSTRACT

Objective: To determine the personality profiles of alcohol and amphetamine (Ice) users admitted at Armed Forces Institute of Mental Health, (AFIMH) Rawalpindi.

Study Design: A cross-sectional study.

Place and Duration of Study: Armed Forces Institute of Mental Health (AFIMH), Rawalpindi from Nov 1, 2021, till April 30, 2022.

Materials and Methods: We consecutively sampled 222 subjects. Basic demographic data including age, gender, ethnicity and socioeconomic status were recorded. Patients were divided into two groups. Patients with primary alcohol addiction were labeled as Group A, while patients with primary amphetamine (ice) addiction were labeled as Group B. Personality profiles of the patients were assessed using the Urdu version of the Minnesota Multiphasic Personality Inventory- 2 (MMP- 2) and data was analyzed by using SPSS 26.

Results: Out of the total cases, 75 individuals (33.78%) were primarily addicted to alcohol, while 29 individuals (13.06%) had a primary addiction to amphetamines. Among those with alcohol addiction, 26 (34.6%) exhibited hypochondriasis, 54 (72%) showed signs of depression, and 56 (74.6%) scored high on hysteria. Psychopathic deviation was observed in 36 individuals (48%), and 40 (53.3%) had elevated masculinity scores. Additionally, 38 (50.6%) displayed paranoia, 31 (41.3%) had psychasthenia, and 40 (53.3%) showed signs of schizophrenia. Hypomanic traits were present in 10 individuals (13.3%), and 21 (28%) scored high in social introversion.

In the amphetamine addiction group, 10 individuals (34.4%) out of 29 showed hypochondriasis, while 20 (68.9%) experienced depression and an equal number scored high on hysteria. Psychopathic deviation and elevated masculinity were each noted in 14 individuals (48.2%). Paranoia was found in 13 individuals (44.8%), psychasthenia in 15 (51.7%), and schizophrenia in 16 (55.1%). Additionally, hypomania was seen in 8 individuals (27.5%), and 9 (31.0%) scored high in social introversion.

Conclusion: Depression and hysteria are the most common psychiatric disorders among alcohol and amphetamine addicts.

Key Words*: Alcohol, Amphetamine, Drug Abuse, ICE, MMPI, Personality Profile.*

Introduction

Substance use disorders represent a significant global health concern, impacting individuals, families, and communities. Among the diverse range of substances abused, alcohol and amphetamines (ice) stand out due to their widespread availability and profound effects on the central nervous system.[1] Conversely, amphetamines, typically illicit stimulants, are known for their potent psychoactive effects and high potential for addiction, often leading to significant psychological and social disruption.[2] Personality characteristics have long been implicated in the initiation, maintenance, and relapse of substance use disorders.[3] Studies conducted in Iran have shown that personality disorders like hysteria, depression, psychopathic deviation, paranoia and hypomania predisposes individuals to drug dependence.[4] Risk of alcohol use disorder as co morbidity in individuals with personality disorder increase by fivefold while the

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risk of dependence on other drugs increase by twelve fold. It is also important to note that co morbidity depends on the type of personality disorder. It has been observed that substance use disorders are the commonest mental health problem in individual suffering from bipolar disorder, with a lifetime prevalence of around 78% percent.[5]

The Minnesota Multiphasic Personality Inventory-2 (MMPI-2), a widely used and extensively validated psychometric instrument, offers a comprehensive assessment of personality and psychopathology. Its various clinical and supplementary scales provide valuable insights into an individual's emotional functioning, interpersonal relationships, and behavioral tendencies especially in individuals with substance use disorders.[6,7] Investigating the personality profiles of individuals with alcohol and amphetamine use disorders using the MMPI-2 can illuminate potential differences and similarities in their underlying psychological characteristics. Distinct personality profiles associated with each substance can have significant clinical implications. For instance, individuals with different personality patterns might benefit from tailored treatment approaches that address their specific psychological needs and vulnerabilities. Furthermore, understanding these profiles can contribute to the development of more targeted prevention programs aimed at individuals exhibiting predisposing personality traits.[8,9] Other studies have also explored the broader link between personality traits and illicit substance use.[10,11]

The research aimed to explore and compare the personality profiles of alcohol and amphetamine dependence using the MMPI-2. By examining the patterns of elevated scores on the MMPI-2 clinical and supplementary scales, the objective of this study was to identify unique personality characteristics associated with each substance use disorder, ultimately enhancing clinical intervention and future research in the field of Substance abuse.

Materials and Methods

A cross-sectional study was conducted at Armed Forces Institute of Mental Health (AFIMH), after approval of Ethical review committee vide IERC 004/22, Rawalpindi between 1st Nov, 2021 to 30th April, 2022. A total sample size of 222was obtained by using WHO sample size calculator based on the results of study conducted by Al-aghemendan *et. al.,* where anticipated population proportion was 6.5%. We consecutively sampled subjects using convenience nonprobability sampling technique.[4] All patients 18-70 years of age of both genders admitted at AFIMH having drug addiction problems associated with alcohol and amphetamine were included. Patients who have been in rehabilitation and not taken any drugs for the last one month, and patients exhibiting clinical signs of a hangover (running nose, muscular skeletal pains, shivering of the hand and nausea) were excluded.

Basic demographic data including age, gender, ethnicity and socioeconomic status was recorded. Then, the participants were divided into two groups Group A representing patients with primary alcohol addiction and Group B included patients with primary amphetamine addiction.

The Urdu version of the MMPI- 2 was used to determine the Personality profiles of study participants.[12,13] This personality inventory consists of 10 clinical scales. For each clinical scale there are true-false questions to be answered by the participants. Scoring is done to get a total score for all 10 clinical scales by adding the total check marks chosen by participant for each scale separately. These total scores converted to normalized 'T scores' which has a range from 30 to 120. For each scale the cutoff 'T score' is 70 which means that if the score is above cutoff threshold, it is taken as positive or present otherwise it is considered negative or absent for that condition.

Data was analyzed using SPSS version 26.0. To represent “positive” numbers of patients among ten 10 different clinical scales and demographic variables, such as gender, marital status and educational status frequencies and percentages were used while age was represented as mean and standard deviation. Differences in the frequency distribution of the different 10 sub-scales of MMPI-2 between the two groups was assessed, ascertained and compared by applying Chi-squared test. Age, gender, marital status and educational status are confounding variables which were controlled by stratification. The p value of ≤ 0.05 was considered statistically significant.

Results

In this study mean age of participants was 43.56 ± 15.59 ranging between 19 and 70 years while 129 (58.11%) belonged to 18-45 years age group and 93(41.89%)ranged between 46-70 years of age group, 200(90.90%) were males and 22(9.91%) females, 158 (71.17%) married and 64 (28.83%) were un-married, while 77 (34.68%) cases had primary education, 62 (27.93%) cases had middle school to matric degree, 48 (21.62%) were undergraduate and 35 (15.77%) were graduates. A total of 75 (33.78%) cases were with primary alcohol addiction and 29 (13.06%) cases had primary amphetamine addiction (Table-I).There were 73 (32.9%) cases who had hypochondriasis, 164 (73.9%) had depression, 155 (69.8%) had hysteria, 106 (47.7%) cases had psychopathic deviate, 108 (48.6%) had masculinity/femineity, 120 (54.1%) cases had paranoia, 111 (50.0%) had psychasthenia, 124 (55.9%) had schizophrenia, 65 (29.3%) had hypomania and 59 (26.6%) cases had social introversion (Table-II).

When data was stratified for age, gender, marital status and education level psychiatric diseases were statistically same in all other study groups in all strata ($p > 0.05$) with no significant difference observed (Table-III).

Table I: Demographic Variables

S.no	Category	n (%)
1.	**Age** (Mean ± SD)	43.56 ± 15.59
	18-45 years N (%)	129 (58.11)
	46-70 years N (%)	93 (41.89)
2.	**Gender**	
	Male	200 (90.09)
	Female	22 (9.91)
3.	**Marital Status**	
	Married	158 (71.17)
	Unmarried	64 (28.83)
4.	**Education**	
	Primary	77 (34.68)
	Under matric	62 (27.93)
	Under graduate	48 (21.62)
	Graduate	35 (15.7)
5	**Substance of abuse**	
	Alcohol (group A)	75(33.78%)
	Amphetamine (group B)	29 (13.06%)

Table II: Minnesota Multiphasic Personality Inventory Scales (n=222)

S.No	MMPI Scales	Present	n (%)
1	Hypochondriasis	Yes	73 (32.9)
		No	149 (67.1)
2	Depression	Yes	164 (73.9)
		No	58 (26.1)
3	Hysteria	Yes	155 (69.8)
		No	67 (30.2)
4	Psychopathic deviation	Yes	106 (47.7)
		No	116 (52.3)
5	Masculinity/feminity	Yes	108 (48.6)
		No	114 (51.4)
6	Paranoia	Yes	120 (54.1)
		No	102 (45.9)
7	Psychesthenia	Yes	111 (50)
		No	111 (50)
8	Schizophrenia	Yes	124 (55.9)
		No	98 (44.1)
9	Hypomania	Yes	65 (29.3)
		No	157 (70.7)
10	Social introversion	Yes	59 (26.6)
		No	163 (73.4)

Table III : Comparison of MMPI Scales with Demographic Variables (n=222).

	Age (Years)	Present	Group A N (%)	Group B N (%)	P	Gender	Group A	Group B	P	Marital Status	Group A	Group B	P
Hypochondriasis	18-45	Yes	19 (33.9)	8 (36.4)	0.178	Male	23 (32.4)	5 (23.8)	0.006	Married	16 (34.8)	6 (40)	0.051
		No	37 (66.1)	14 (63.6)			48 (67.6)	16 (76.2)			30 (65.2)	9 (60)	
	46-70	Yes	7 (36.8)	2 (28.6)	0.063	Female	3 (75)	5 (62.5)	0.635	Un-married	10 (34.5)	4 (28.6)	0.151
		No	12 (63.2)	5 (71.4)			1 (25)	3 (37.5)			19 (65.5)	10 (71.4)	

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Depression	18-45	Yes	41 (73.2)	15 (68.2)	0.154	Male	50 (70.4)	12 (57.1)	0.496	Married	33 (71.7)	9 (60)	0.800
		No	15 (26.8)	7 (31.8)			21 (29.6)	9 (42.9)			13 (28.3)	6 (40)	
	46-70	Yes	13 (68.4)	5 (71.4)	0.601	Female	4 (100)	8 (100)	-	Un-married	21 (72.4)	11 (78.6)	0.307
		No	6 (31.6)	2 (28.6)			0 (0)	0 (0)			8 (27.6)	3 (21.4)	
Hysteria	18-45	Yes	41 (73.2)	17 (77.3)	0.448	Male	54 (76.1)	14 (66.7)	0.408	Married	33 (71.7)	10 (66.7)	0.486
		No	15 (26.8)	5 (22.7)			17 (23.9)	7 (33.3)			13 (28.3)	5 (33.3)	
	46-70	Yes	15 (78.9)	3 (42.9)	0.164	Female	2 (50)	6 (75)	0.268	Un-married	23 (85.2)	10 (71.4)	0.431
		No	4 (21.1)	4 (57.1)			2 (50)	2 (25)			6 (20.7)	4 (28.6)	
Psychopathic deviation	18-45	Yes	25 (44.6)	12 (54.5)	0.617	Male	33 (46.5)	11 (52.4)	0.410	Married	23 (50)	7 (46.7)	0.734
		No	31 (55.4)	10 (45.5)			38 (53.5)	10 (47.6)			23 (50)	8 (53.3)	
	46-70	Yes	11 (57.9)	2 (28.6)	0.413	Female	3 (75)	3 (37.5)	0.427	Un-married	13 (44.8)	7 (50)	0.366
		No	8 (42.1)	5 (71.4)			1 (25)	5 (62.5)			16 (52.2)	7 (50)	
Masculinity / feminity	18-45	Yes	32 (57.1)	12 (54.5)	0.574	Male	37 (52.1)	12 (57.1)	0.595	Married	24 (52.2)	6 (40)	0.093
		No	24 (42.9)	10 (45.5)			34 (47.9)	9 (42.9)			22 (47.8)	9 (60)	
	46-70	Yes	8 42.1)	2 (28.6)	0.071	Female	3 (75)	2 (25)	0.302	Un-married	16 55.2)	8 (57.1)	0.298
		No	11 (57.9)	5 (71.4)			1 (25)	6 (75)			13 (44.8)	6 (42.9)	
Paranoia	**18-45**	Yes	25 (44.6)	10 (45.5)	0.191	Male	37 (52.1)	9 (42.9)	0.455	Married	25 (54.3)	7 (46.7)	0.911
		No	31 (55.4)	12 (54.5)			34 (47.9)	12 (57.1)			21 (45.7)	8 (53.3)	
	46-70	Yes	13 (68.4)	3 (42.9)	0.310	Female	1 (25)	4 (50)	0.580	Un-married	13 (44.8)	6 (42.9)	0.167
		No	6 (31.6)	4 (57.1)			3 (75)	4 (50)			16 (55.2)	8 (57.1)	

Psychesthenia	**18-45**	Yes	24 (42.9)	11 (50)	0.670	Male	29 (40.8)	10 (47.6)	0.222	Married	18 (39.1)	8 (53.3)	0.508
		No	32 (57.1)	11 (50)			42 (59.2)	11 (52.4)			28 (60.9)	7 (46.7)	
	46-70	Yes	7 (36.2)	4 (57.1)	0.246	Female	2 (50)	5 (62.5)	0.585	Un-married	13 (44.8)	7 (50)	0.261
		No	12 (63.2)	3 (42.9)			2 (50)	3 (37.5)			16 (55.2)	7 (50)	
Schizphrenia	**18-45**	Yes	30 (53.6)	13 (59.1)	0.876	Male	40 (56.3)	12 (57.1)	0.973	Married	22 (47.8)	7 (46.7)	0.877
		No	26 (46.4)	9 (40.9)			31 (43.7)	9 (42.9)			24 (52.2)	8 (53.3)	
	46-70	Yes	10 (52.6)	3 (42.9)	0.929	Female	0 (0)	4 (50)	0.388	Un-married	18 (62.1)	9 (64.3)	0.685
		No	9 (47.4)	4 (57.1)			4 (100)	4 (50)			11 (37.9)	5 (35.7)	
Hypomania	18-45	Yes	2 (37.5)	6 (27.3)	0.360	Male	28 (39.4)	7 (33.3)	0.139	Married	18 (39.1)	5 (33.3)	0.572
		No	35 (62.5)	16 (72.7)			43 (60.6)	14 (66.7)			28 (60.9)	10 (66.7)	
	46-70	Yes	8 (42.1)	2 (28.6)	0.606	Female	1 (25)	1 (12.5)	0.360	Un-married	11 (37.9)	3 (21.4)	0.231
		No	11 (57.9)	5 (71.4)			3 (75)	7 (87.5)			18 (62.1)	11 (78.6)	
Social introversion	18-45	Yes	16 (28.6)	7 (31.8)	0.347	Male	20 (28.8)	5 (23.8)		Married	15 (32.6)	3 (20)	0.412
		No	40 (71.4)	15 (68.2)			51 (71.8)	16 76.2)			31 (67.4)	12 (80)	
	46-70	Yes	5 (26.3)	2 (28.6)	0.749	Female	1 (25)	4 (50)		Un-married	6 (20.7)	6 (42.9)	0.282
		No	14 (73.7)	5 (71.4)			3 (75)	4 (50)			23 (79.3)	8 (57.1)	

Discussion

Addiction is a multifaceted, social, biological and mental illness with an uncontrolled desire to enjoy and reduce stress in a person harboring underlying personality traits of vulnerability.[14,15]

The study results indicate that sample of our participants had mean age of 43.56 ± 15.59 years where minimum age was 19and maximum age was 70 years while 129 (58.11%) participants were 18 to 45 years of age and 93 (41.89%) belonged to ages between 46 and 70 years. Male participants were 200 (90.09%) and only 22 (9.91%) were females while 158 (71.1%) were married and 64 (28.83%) were un-married.

The most frequent high scores were observed on sub-clinical scales of depression and hysteria which were 54 (72%) and 56 (74.6%) respectively among alcoholics while among individuals having

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amphetamine addiction 20 (68.9%) scored equally high on depression and hysteria subscales similarly it was noted by Bussone that the most frequent psychological characteristics in these addicts were hysteria and depression.[16] In our study there are higher scores on depression subscale as compared to Alaghemandan *et.al.,*[4] who in his study highlighted that in individuals with risk of addiction there is high proportions of personality disorders with hysteria in 71.1%, depression in 62.7%psychopathic deviation in 60.2%, paranoia 48.3% while hypomania was observed in 53.7%. In current study alcoholics had the lowest scores on clinical subscales of hypomania (13.7%) and social introversion (28%) on the other hand individuals with amphetamine addiction scored more on hypomania subclinical scale (27.5%) and 31% scored for social introversion subclinical scale.

It is noted that both alcoholics and amphetamine addicts with slight difference scored high on clinical subscales of schizophrenia, paranoia and psychasthenia but was less than that of depression and hysteria in contrast to the results observed by Rahimi *et. al.,*[15] who noted that Schizophrenia, hypochondriasis and psychasthenia were the most prevalent clinical scales but this study noted that hypochondriasis was only present in 32.9% of participants.

Marshal *et. al.,*[17] have noted There was a significant correlation between abnormal personal characteristics and demographic variables in addition he also observes that depression and psychopathic deviation have the highest distribution and frequency among personality disorders while when data in this study was stratified for age, gender and marital status the frequency of psychiatric diseases was statistically same in both groups with no significant correlation ($p > 0.05$).

Identification and understanding of behavioral factors are therefore necessary to prevent these problems. In this regard, understanding personality traits of drug addicts is one of the important factors; a better understanding of drug addicts' personality profiling allows for more comprehensive planning to treat these patients according to their dominant personality, and provides policymakers in the health and drug control sectors with opportunities to develop more efficient preventive programs in society. Regarding the importance of the problem of addiction, different approaches have been considered in a macro level.[18] The results of the MMPI-2 test revealed that antisocial personality disorder, schizoid personality disorder, substance-induced mood disorder and somatoform disorder were more prevalent in patients taking methamphetamine.[14]

Conclusion: The most common psychological phenomena observed on MMPI-2 among alcohol and amphetamine addicts was depression and hysteria.

Disclosure: None

Conflict of Interest: None

Limitation of Study: Being cross sectional design of this study, It doesn't help in determining the reasons as to why depression and hysteria is present more frequently in individuals who are alcohol and amphetamine addicts.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Antimicrobial Efficacy of Commercial Dentifrices Containing Triclosan, Chlorhexidine, and Herbal Extracts Against Caries-Associated Pathogens

Maleeha Nayyer[1], Asfia Saeed[2], Syeda Ridaa Fatima[3], Fatima Suhaib[4], Saadia Muneer Malik[5], Muhammad Azhar[6]

ABSTRACT

Objective: To evaluate the antimicrobial potential of four commercial dentifrices against caries-associated microbes and to compare the effectiveness of active ingredients within these dentifrices in preventing the onset and progression of dental caries.

Study Design: In vitro Experimental Study

Place and Duration of Study: Army Medical College from 20th January 2023 to 18th August 2023.

Materials and Methods: The study was performed to compare the antimicrobial potential of four commercial dentifrices against microbes responsible for causing Dental Caries i.e. *Streptococcus mutans* (ATCC 25175) and *Lactobacillus casei* (ATCC 393) using agar well diffusion assay.

Incubations of *S. mutans* were accomplished in aerobic and anaerobic conditions, whereas *L.casei* was incubated in microaerophilic and anaerobic environments. After incubation, the zones of inhibition (ZOI) around the tested dilutions were measured and the mean values of ZOI ± SD were calculated. The plate with no visible growth was considered as MIC. The independent t-test was applied to compare the effectiveness of dentifrice against cariogenic microbes. Inter-group comparisons between dentifrices were conducted through one-way analysis of variance (ANOVA) with significant differences further evaluated by Tukey HSD tests. A *p*-value of ≤ 0.05 was considered statistically significant.

Results: Each dentifrice exhibited antibacterial activity against *S. mutans* and *L. casei*. Chlorhexidine was the most effective agent against both *S. mutans* and *L. casei,* while herbal dentifrices exhibited the least efficacy. In addition, for each formulation, *S. mutans* showed significantly higher susceptibility.

Conclusion: All four dentifrices showed antimicrobial effectiveness against key cariogenic pathogens. Chlorhexidine emerged as the most potent in preventing both the initiation and advancement of dental caries due to its strong antibacterial efficacy against *S. mutans* and *L. casei.*

Keywords: *Chlorhexidine, Dentifrice, Herbal, Lactobacillus Casei, Streptococcus Mutans, Triclosan.*

Introduction

Accumulation of plaque on tooth surfaces and crevices is a natural process, representing a complex community of microorganisms and their by-products, embedded within an organized extracellular matrix.[1] Among these, the colonization of cariogenic bacteria, including *Streptococcus mutans* and to a lesser extent *Streptococcus sanguis, Streptococcus sobrinus, Lactobacillus casei* and *Lactobacillus acidophilus,* on the tooth surfaces may lead to demineralization of teeth, cavitation and ultimately pulp necrosis.[2]

Global prevalence of dental caries and periodontal diseases, with caries ranked as first among 328 diseases by Global Burden of Disease (GBD) affecting 2.3 billion adults, is 532 million.[3] Maintenance of good oral hygiene and limiting dietary sugars are essential for preventing the onset and advancement of dental caries. Tooth brushing and flossing are considered standard tools for maintaining oral hygiene. Furthermore, globally, dentifrices containing chemical agents designed to inhibit the initiation of caries and promote remineralization are used.[4] A study conducted in Spain found that maintaining good oral hygiene played a superior role in decreasing caries prevalence than modifying diet.[5] A variety of dentifrices are available worldwide.

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Fluoride was the first and the most widely used therapeutic agents, and is incorporated into most dentifrices.[6] It is usually added in the form of sodium fluoride (NaF), stannous fluoride (SnF_2), or sodium monofluorophosphate (Na_2PO_3F).[7] Fluoride interferes with bacterial metabolism and acid production, preventing demineralization, and promoting remineralization, thereby creating an acid-resistant enamel surface, ultimately reducing the likelihood of developing caries.[8]

However, in conditions like xerostomia and hypo salivation, fluoride alone may not be adequate.[9] Therefore, incorporating antimicrobial agents has been suggested to improve plaque control and reduce colonization of cariogenic bacteria. Hashmat *et al*. compared the amount of fluoride released and antimicrobial activity of commercial and experimental dentifrice formulations containing fluoride-doped nano bioactive glass (F-nBG) and zinc oxide nanoparticles. They observed that the combination of F-nBG and ZnO nanoparticles provides plaque control by reducing the growth of *S. mutans* and *L. Casei*.[10] Triclosan is another common antibacterial agent that is commonly used in toothpaste. Triclosan is a non-ionic phenolic derivative with the ability to block fatty acid synthesis in bacterial cells, leading to their death.[11] Similarly, chlorhexidine, a cationic compound which damages the bacterial cell membrane, causing ions' leakage and eventual cell death are often used in dentifrices.[12] It has an antiplaque effect due to its ability to block salivary glycoprotein groups, along with reducing the bacteria's ability to adhere to the tooth structure.[13] Despite the improved antimicrobial properties of these dentifrices, there is an increased demand for the utilization of natural compounds to improve oral health and to avoid the potentially harmful effects of synthetic compounds.[4] These herbal dentifrices usually contain varied ingredients from neem, camomile, mint, meswak, etc.[14]

Serdar *et al.* reported that dentifrice based on natural products exhibits varied antimicrobial efficacy depending on the nature of the herbal extract. In a study comparing herbal dentifrice containing calendula and sage clay extract with a chemically composed dentifrice against *L. bacillus* and *C. albicans*, it was observed that both formulations exhibited similar antimicrobial effects at higher concentrations. However, a reduction in the concentration of the herbal extract resulted in decreased antimicrobial efficacy of the herbal dentifrice.[15]While various in vitro studies have explored the antiplaque effects of experimental dentifrices, limited data is available on the comparative analysis of commercial dentifrices. Considering the availability of abundant toothpaste brands in the market, addressing this gap is crucial for identifying the most effective formulation for patients with increased susceptibility to dental caries. Therefore, this study compared the antimicrobial efficacy of commercial dentifrices containing fluoride, triclosan, chlorhexidine, and plant extracts against caries-associated microbes. The results of this study will make it possible to select an effective dentifrice formulation for high-risk caries patients.

Materials and Methods

This in vitro experimental study was conducted at Army Medical College from 20th January 2023 to 18th August 2023 after obtaining approval from the Ethical Review Board (10/11/22). Four commercial dentifrices were tested for which three dilutions were prepared for each dentifrice, each at a two-fold concentration (1:1, 1:2 and 1:4). Antimicrobial analysis was performed against two lyophilized microbial strains. The microbial strains were obtained from the American Type Culture Collection (ATCC, Manassas, USA). Freeze-dried vials of *Streptococcus mutans (S. mutans)* (ATCC 25175) and *Lactobacillus casei (L. casei)* (ATCC 393) were revived in Brain Heart Infusion (BHI) broth and de Man, Rogosa and Sharpe broth (MRS) broth respectively. Following the incubation period (24 h for *S. mutans* and 48 h for *L. casei*) at 37°C, microbes were cultured on selective culture media, and their growth was confirmed by observing colony morphology and performing biochemical tests and gram staining. Nutrient agar and Chocolate agar were employed for *S. mutans* and *L. casei* respectively.

The agar well diffusion assay was performed according to the guidelines provided by the European Committee on Antimicrobial Susceptibility Testing (EUCAST). Briefly, inoculum was prepared by transferring three to five well-isolated colonies of microbes to test tubes containing 5 ml Normal saline

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(0.9%) (Sterifluid NS, Frontier Dextrose Ltd, Lahore, Pakistan) to obtain a turbidity of 0.5 grade on the McFarland Turbidity Scale. Within fifteen minutes of inoculum preparation, swabbing was evenly performed on the respective agar plates. On each agar plate, four wells (diameter: 8mm, depth: 4mm) were punched at an equidistance of 20 mm using a sterile cork borer as represented in Figure 1.

A total of six agar plates were used for each dentifrice. Wells were filled with 0.2 ml of prepared dilutions (1:1, 1:2, 1:4) through a micropipette (Genex Beta, Guangdong, China). Distilled water was taken as a negative control. *S. mutans* were incubated in both aerobic and anaerobic conditions, whereas for *L. casei*, a candle-jar (microaerophila) and an anaerobe jar (Gas-Pak sachet-Oxoid AnaeroGen, Thermo Fisher Scientific) were used. Following incubation (24 h for *S. mutans* and 48 h for *L. casei*), the resultant ZOI around the tested dilution were measured using a Vernier caliper. Mean ZOI was calculated by performing triplicate tests. Broth dilution method was adopted to determine the minimum inhibitory concentration as illustrated in Figure 2.[16] Five (two-fold) dilutions, i.e. 1:1, 1:2, 1:4, 1:8 and 1:16 of dentifrice in respective broth (BHI for *S. mutans* and MRS for *L. casei*) were used in the experiment (2 g/2 ml gave a 1:1 dilution). A control test tube containing 2 ml of distilled water with no dentifrice was used as a reference.

Microbes were inoculated in test tubes with a sterilized wire loop. *S. mutans* and *L. casei* were incubated at 37°C for 24 h and 48 h, respectively. Following incubation, the test tubes were sub-cultured on selective media in duplicate. The lowest concentration (highest dilution) in which no growth of bacteria was visibly appreciated, was considered the MIC. [17] Data was analyzed using SPSS version 21, IBM, Corp. Armonk, NY, USA. Shapiro-Wilk test *(p* = 0.20) was used to evaluate the normality of data. The mean value ± SD was calculated for the ZOI. Levene's test of equality was checked, and an independent t-test was subsequently applied to compare the effectiveness of dentifrice against cariogenic microbes and assess if different environments impact antimicrobial efficacy. Inter-group comparisons of dentifrice were conducted through a one-way analysis of variance (ANOVA) followed by Tukey HSD tests. A *p* value of ≤ 0.05 was considered significant.

Results

Agar well diffusion method

Figure 3a and b show distinct inhibition zones observed after incubation for *L. casei* and *S. mutans* on the agar plate respectively. No inhibitory effect was observed on either bacterium in the negative control wells. Comparison of mean ZOI for *S. mutans* and *L. casei* in the dentifrices are shown in Figure 3c and d.

Mean values of ZOI for all dentifrices at each dilution are enlisted in Table II. The results indicate that the ZOI inhibition acquired from each dilution for both bacteria across all environments decrease as dilution of the dentifrice increases. This points towards a dose- dependent relationships. Figures 4 and 5 depict graphical comparison of *S. mutans* and *L. Casei* susceptibility in each formulation in different environments. A significant difference in susceptibility between *S. mutans* and *L. casei* is observed. *S. mutans* consistently shows higher susceptibility irrespective of incubation condition or dentifrice formulations.

Table III shows a comparison of dentifrices in inhibiting *S. mutans* in different environments. Chlorhexidine was the most effective while herbal dentifrice exhibited the least efficacy. In aerobic conditions, pair-wise comparisons using a post hoc Tukey's test revealed statistically significant differences among all dentifrice formulations except triclosan and chlorhexidine.

In anaerobic conditions, the ZOI was statistically similar for herbal and fluoride dentifrice, triclosan and fluoride, and triclosan and chlorhexidine, respectively.

A comparative evaluation of the effectiveness of dentifrices in inhibiting *L. casei* in various environments are listed in Table IV. A similar trend was observed, with chlorhexidine being the most effective while herbal dentifrice exhibited the least efficacy. One-way AVOVA (analysis of variance) results showed that herbal and fluoride dentifrice had statistically significant comparable results in each environment, while all other formulations had statistically significant differences.

MIC revealed that Clinica (chlorhexidine) was bactericidal even at the dilution of 1:16 for *S. mutans* and at the dilution of 1:8 for *L. casei*. This finding

correlated with the smallest mean ZOIs observed for microbes using agar well diffusion assay (Tables III and IV). Distinct growth was observed on the control plates for both bacterial strains.

Table I: List of Dentifrices and Their Characteristics

Commercial Dentifrice	Active agent	Conc. of Active Ingredient	Fluoride	Conc. of Fluoride	Manufacturer
Bannet	Triclosan	0.3% w/w	Sodium Monofluorophosphate (MFP)	0.76% w/w	Platinum Pharmaceuticals (Pvt) Ltd. Pakistan
Clinica	Chlorhexidine	0.2% w/w	Not present	-	Platinum Pharmaceuticals (Pvt) Ltd. Pakistan
Colgate Herbal	Mint, clove, Neem and eucalyptus in addition to Fluoride	Not specified	Sodium Monofluorophosphate (MFP)	0.76% w/w	Colgate- Palmolive Pakistan
Colgate Cavity Protection	Fluoride only	No other agent	Sodium monofluorophosphate (MFP)	0.76% w/w	Colgate- Palmolive Pakistan

Table II: Mean ZOI for the Dentifrice Slurries at the Dilution of 1:1, 1:2, 1:4

Dentifrice	Dilution	*S. mutans*				*L. casei*			
		Aerobic		Anaerobic		Microaerophilia		Anaerobic	
		Mean	S.D.	Mean	S.D.	Mean	S.D	Mean	S.D
Colgate Herbal	1:1	24.67	0.57	25.00	1.00	13.33	1.15	16.00	2.00
	1:2	20.00	1.00	19.50	0.50	10.07	2.10	13.00	1.00
	1:4	15.83	0.76	15.83	0.76	10.00	2.00	9.83	0.29
Bannet (Triclosan)	1:1	37.73	0.46	36.00	1.00	19.00	1.00	22.67	1.15
	1:2	34.80	0.72	31.17	1.04	17.33	0.57	20.33	0.57
	1:4	28.83	1.04	25.83	0.28	15.33	0.57	18.16	0.29
Clinica (Chlorhexidine)	1:1	41.26	1.10	40.67	1.15	31.16	1.04	34.83	0.76
	1:2	35.50	0.50	34.16	1.61	24.50	0.50	27.50	1.32
	1:4	34.33	0.57	31.16	0.76	20.33	0.57	25.67	0.57
Colgate Cavity Protection (Fluoride)	1:1	29.83	0.28	29.83	0.28	16.33	1.52	17.67	0.57
	1:2	25.83	1.60	26.50	1.80	11.33	0.76	14.33	0.57
	1:4	21.00	1.00	20.73	1.10	10.40	0.53	11.33	0.57

*Zones of Inhibition (ZOI)

Table III: Comparison of Dentifrices in Inhibiting S. Mutans in Various Environments

Condition	Dentifrice	ZOI (mm)		F(p-value)	Post-Hoc Tukey test	p-value
		Mean	S.D.			
Aerobic	Colgate Herbal	20.17	3.89	37.075 (≤0.001)	Herbal vs Triclosan	≤0.001
					Herbal vs Chlorhexidine	≤0.001
					Herbal vs Fluoride	0.024
	Bannet (Triclosan)	33.80	3.99		Triclosan vs Herbal	≤0.001
					Triclosan vs Chlorhexidine	0.284
					Triclosan vs Fluoride	≤0.001
	Clinica (Chlorhexidine)	37.06	3.32		Chlorhexidine vs Fluoride	≤0.001
	Colgate Cavity Protection (Fluoride)	25.67	4.03			
Anaerobic	Colgate Herbal	20.11	4.04	21.514 (≤0.001)	Herbal vs Triclosan	≤0.001

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Table IV: Comparison of Dentifrices in Inhibiting L. Casei in Various Environments

Condition	Dentifrice	Zone of inhibition(mm)		F (p-value)	Post-Hoc Tukey test	p-value
		Mean	S.D.			
Aerobic	Colgate Herbal	11.13	2.27	37.155 (≤0.001)	Herbal vs Triclosan	≤0.001
					Herbal vs Chlorhexidine	≤0.001
					Herbal vs Fluoride	0.72
	Bannet (Triclosan)	17.22	1.72		Triclosan vs Herbal	≤0.001
					Triclosan vs Chlorhexidine	≤0.001
					Triclosan vs Fluoride	0.022
	Clinica (Chlorhexidine)	25.33	4.78		Chlorhexidine vs Fluoride	≤0.001
	Colgate Cavity Protection (Fluoride)	12.78	2.86			
Anaerobic	Colgate Herbal	12.94	2.89	51.397 (≤0.001)	Herbal vs Triclosan	≤0.001
					Herbal vs Chlorhexidine	≤0.001
					Herbal vs Fluoride	0.738
	Bannet (Triclosan)	20.44	2.01		Triclosan vs Herbal	≤0.001
					Triclosan vs Chlorhexidine	≤0.001
					Triclosan vs Fluoride	0.002
	Clinica (Chlorhexidine)	29.39	4.37			≤0.001

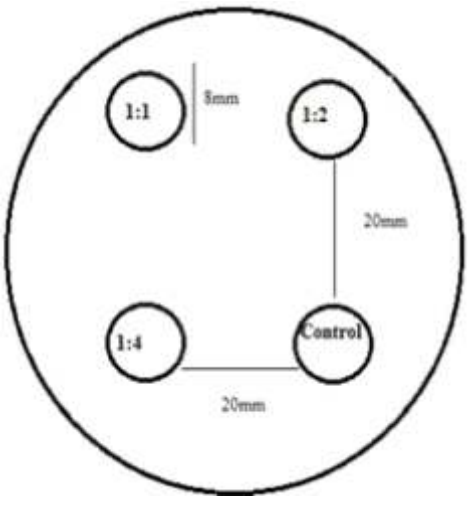

Figure 1: Diagrammatical Representation of Agar Plate for Antimicrobial of Agar Plate for Antimicrobial Susceptibility Testing

Figure 2 : Steps to Evaluate Minimum Inhibitory Concentration (MIC) Of Commercial Dentifrice Against Cariogenic Microbes

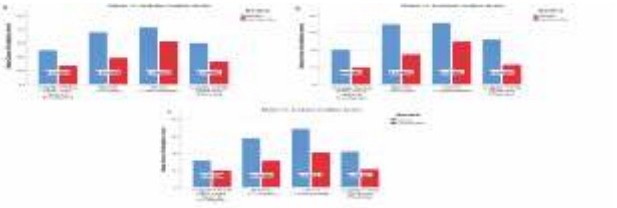

Figure 3: ZOI Following Incubation, (A) L. Casei After 48 Hours of Incubation, (B) S. mutans after 24 Hours of Incubation, (C) Mean ZOI for L. casei, (D) Mean ZOI for S. mutans

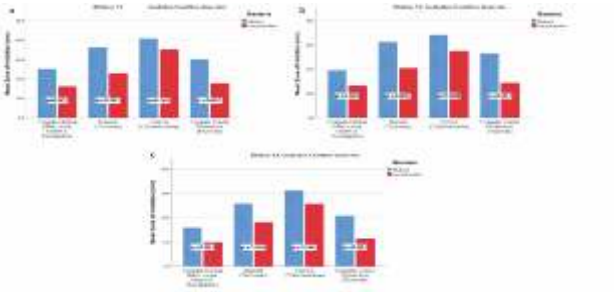

Figure 4: Comparison of Microbial Susceptibility at 37°C Under Aerobic Conditions at Various Dentifrice Dilutions: (A) 1:1 Dilution, (B) 1:2 Dilution, And (C) 1:4 Dilution

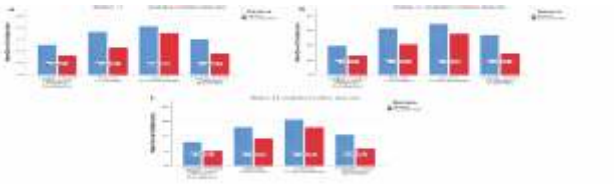

Figure 5: Comparison of Microbial Susceptibility at 37°C Under Aerobic Conditions at Various Dentifrice Dilutions: (A) 1:1 Dilution, (B) 1:2 Dilution, And (C) 1:4 Dilution.

Discussion

Globally, caries is considered one of the most prevalent oral diseases. The primary culprit for dental caries is *Streptococcus mutans* while lactobacilli are considered secondary invaders, mostly involved in the progression of the disease.[18] The first line of defence against dental caries is the maintenance of good oral hygiene. This largely involves tooth brushing and flossing.[19] With so many options of dentifrices available in the market, it is imperative to educate the masses about their caries' preventive potential. This study focuses on the antimicrobial capacity of four commercial dentifrices which are easily available in Pakistan.

A dentifrice mostly contains abrasive, binder, detergent, flavour, and any antibacterial agent.[20] Fluoride is also present in most conventional dentifrices. Herbal dentifrices have also been researched to showcase antibacterial potential against cariogenic bacteria.[21] In this research, Colgate Herbal, Colgate Cavity Protection, Bannet and Clinica toothpaste were evaluated. As mentioned in Table I, the active ingredients in Colgate Herbal include mint, clove, Neem, eucalyptus, and Fluoride. Mint leaves are known to exert an antibacterial effect through their components such as menthol, methyl esters and terpenoids.[22] Eucalyptus is also known to be effective against *S. mutans*. Fluoride is an active agent in both Colgate Herbal and Colgate Cavity Protection. The two toothpastes are well established as having antibacterial activity against several pathogens such as *E. coli, S. aureus,* and *C. albicans.*[23, 24] In addition, research has proven the antimicrobial prowess of triclosan and chlorhexidine, which are the main antibacterial agents in Bannet and Clinica dentifrices.[25,26] Three dilutions for each dentifrice (1:1, 1:2, and 1:4) are prepared and tested for antibacterial activity. This is done to somewhat mimic the salivary dilution of dentifrice in the oral cavity.[27] As depicted in Figure III, a ZOI is formed for both *S. mutans* and *L. casei* for each dilution of each dentifrice.

The study indicates that chlorhexidine shows the highest antimicrobial activity across all formulations. It is widely used in dentifrices and is the gold standard of antiplaque agents.[28] De Rossi *et al.* in their research proved that dentifrice containing chlorhexidine showed comparable antibacterial activity to those containing triclosan or natural components.[29] Racheli *et al.* published research concerning chlorhexidine's biocidal zombie effect in 2019. This effect involves the biocidal effect of bacterial cells that have been killed by chlorhexidine by acting as a reservoir for the antibacterial agent.[30]

Colgate Herbal exerted the least antibacterial effect on the tested bacteria. Another study comparing Colgate Herbal with other herbal dentifrices has documented relatively diminished antibacterial activity.[31] A study conducted in Iran found that chemical and herbal dentifrices exert the same antibacterial effect, however, the efficacy of herbal dentifrice is highly sensitive to its concentration.[15] Similar results were found from Patil *et al.* who proved that the herbal dentifrices containing neem

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have the same antibacterial potential as fluoride-containing dentifrice.[32]

It is evident from the results that the antimicrobial activity varies in a dose-dependent manner. Sarembe *et. al.,*[27] explored the effect of dentifrice's concentration on oral hygiene, concluding that increased concentration leads to higher antimicrobial activity. Another study found that the ZOI for any dentifrice diminishes as its dilution is increased.[33] It is further noted from Figures 4 and 5 that *S. mutans* was much more susceptible to all dentifrice formulations as compared to *L. casei.* This finding was consistent irrespective of dentifrice's dilution or bacteria's incubation conditions. Several studies have indicated the increased sensitivity of *S. mutans* against antibacterial agents.[34] Although there is data that *L. casei* is more sensitive to Neem-containing dentifrice than *S. mutans*, the results of this study indicated that Colgate Herbal containing Neem also exerted a much more pronounced antibacterial effect against *S. mutans* than *L. Casei.*[35] Another research conducted in India suggests that the Neem-containing dentifrices are just as effective against *S. mutans* as Fluoride-containing ones.[32]

It is evident from the intergroup comparison between active ingredients of dentifrices that both chlorhexidine and triclosan were more effective antimicrobial agents against *S. mutans* as compared to herbal ingredients or fluoride. This is in line with previous research that has shown comparable antimicrobial potential of the two active ingredients.[29] Therefore, both can be used in patients where the goal is to prevent the onset of dental caries. Although triclosan is an effective antibacterial agent, its use in soaps specifically has been banned by FDA since 2016.[36] This decision came after raising public concerns over the toxicity of triclosan and its extended effect on the human body. It is now classified as 'not generally recognized as safe and effective (GRASE)'. Despite this, its use in toothpastes is not banned as many products containing triclosan slip past the regulation process.[37] Therefore, further research exploring health effects of triclosan in toothpaste will add valuable information.

For *L. casei*, chlorhexidine showed greater antimicrobial activity than all other active components. These results suggest that dentifrices containing chlorhexidine (Clinica) as the active ingredient is most effective against both onset and progression of dental caries. This finding is in line with previous research that has proven chlorhexidine to be either just as effective or more effective than triclosan.[38] However, research has shown that antiplaque efficacy of chlorhexidine is reduced when used with Sodium Lauryl Sulphate (SLS) containing toothpaste.[13,39] This is due to the anionic nature of SLS surfactant that inhibits the antiplaque effect of the cationic chlorhexidine. Although most commercial toothpastes contain SLS, it is recommended to use a non-ionic surfactant to maintain the antibacterial activity of chlorhexidine.[40]

As the study was done to compare commercial dentifrices, it would be interesting to note the effects of antimicrobial agents in novel materials compared with commercial products. The authors suggest that the new formulations may be experimented with lower concentrations of the antimicrobial agents to eliminate any toxic effects associated with these agents.

Conclusion

Thus, in conclusion, the four dentifrices used in this study all showed antimicrobial activity against *S. mutans* and *L. casei* in both aerobic and anaerobic conditions across all formulations. However, the antimicrobial effect of the dentifrices was found to be dose dependent. Moreover, Chlorhexidine containing dentifrice was found to be best suited to prevent the onset and progression of dental caries.

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CONFLICT OF INTEREST

Authors declared no conflicts of Interest.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

ORIGINAL ARTICLE

Prevalence of Urinary Tract Infection (UTI) In Malnourished Children Aged 1 Month to 5 Years: A Study from The Children's Hospital and Institute of Child Health, Multan

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ABSTRACT

Objective: To identify the prevalence of urinary tract infections in malnourished children and the predominant pathogens and assess their antibiotic sensitivity pattern.

Study Design: A retrospective observational study.

Place and Duration of Study: Conducted at Nutritional Stabilization Centre of The Children's Hospital and The Institute of Child Health Multan, from 01.01.2023-31.12.2023.

Materials and Methods: Children aged 1 month to 5 years with severe acute malnutrition (weight-for-height < –3 SD with or without complications or bilateral pedal edema) based on WHO criteria were included. Urine samples were collected by age-appropriate methods; midstream clean-catch for children >3 years and pediatric urine collection bags for younger children, after proper perineal hygiene and analyzed by the hospital's pathology department through routine examination and culture. Results were analysed by using SPSS version 23.0. with frequency distributions and paired t-tests applied; significance was set at $p < 0.05$.

Results: A total of 247 patients were included in study. Of these, 62 children (33%) had culture positive UTI. *Escherichia coli* was the most frequently isolated pathogen (64.5%), followed by *Klebsiella* species (19.3%). Antibiotic sensitivity varied by organism, indicating the need for pathogen-specific treatment protocols.

Conclusion: Urinary tract infections (UTIs) are highly prevalent among children with severe acute malnutrition, with *Escherichia coli* identified as the predominant pathogen, followed by *Klebsiella*. Routine screening for UTIs in malnourished children admitted to nutritional stabilization centers is recommended to facilitate timely interventions, improve clinical outcomes, and reduce morbidity.

Key Words: *Bacterial Infection, Severe Acute Malnutrition, UTI, Urine Examination.*

Introduction

Urinary tract infections are very frequent in children with severe acute malnutrition than the children with normal weight for height percentiles. The chances of urinary tract infections increase with the severity of malnutrition.[1] Severe acute malnutrition (SAM) is a serious issue with a broad spectrum of morbidities, and it has been linked with increased risk of mortality especially in children under five years of age. In the third world countries the prevalence of SAM is much higher with up to 41% children suffering from SAM and 230 million children being stunted.[2,3] The National nutritional survey 2018 of Pakistan states that currently 40.2% of under five years children are stunted and 17.7% are struggling with wasting whereas 28.9% children in our country are underweight.[4]

Furthermost researches conducted on children with severe acute malnutrition with complications who were admitted for treatment in in-patient facilities shows that these children frequently suffer from urinary tract infections, the frequencies reported were 11% in Nigeria, 17% in The Gambia, 23% to 42% in South Africa (highest in HIV infected children and in those with marasmic-kwashiorkor) and approximately 30% in Turkey and Uganda.[5-9] In the above-mentioned research, the clinical signs associated with urinary tract infections were quite low or almost unnoticeable however another study conducted in Kenya revealed that a positive dipstick

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test for urine analysis was mostly likely linked to higher mortality rates in under five children with SAM.[10]

In another study conducted on autopsies revealed that 15-71% SAM children suffer from renal infection: abscesses or pyelonephritis.[11] Children with malnutrition are more prone to develop Urinary tract infections (UTI) with prevalence of about 8 to 35% as compared to normal healthy children.[12] Its occurrence depends on several predisposing factors and immune competency of individual. Children with severe malnutrition have low resistance to bacteria due to impaired immune function. Thus, it is essential that SAM children should be screened and treated for urinary tract infections as earliest as possible to avoid further morbidities and mortality.[1,13]

There is a strong relation between severe acute malnutrition and frequent infections. Infections can lead to malnutrition and vice versa. Malnourished children may not present with typical symptoms and signs of UTI. The typical triad of fever, vomiting and abdominal pain is usually absent. It is therefore necessary to investigate all children with malnutrition for UTI. Swift and proper management and treatment will prevent malnourished children from recurrent UtI infections and complications.[14]

Dependable urine culture testing facilities are typically absent in the majority of health units where children with severe acute malnutrition are treated so the diagnosis is highly dependent on dipstick test and microscopy. Another study reported that testing for UTI with microscopy, Gram stain to visualize bacteria is 96% accurate and urine microscopy for leucocytes is 91% accurate as compared to dipstick testing which is only 88% accurate for UTI.[15] In Pakistan, there is shortage of data available on urinary tract infection in malnourished children.

Despite urinary tract infection (UTI) being a declared comorbidity among malnourished children, current literature on the topic in Pakistan is scarce Majority of the local reports report the prevalence of general pediatric UTI with no stratification according to the nutritional status even though malnutrition is very common and is associated with a known effect of immunocompromising the child. As a result, the reality regarding the burden of UTI in malnourished Pakistani children is not well-documented. This absence of context-specific information restricts the capability of clinicians to come up with specific screening and management approaches for this marginalized group. Malnourished children require timely diagnosis and proper management of UTI because poor diagnosis can increase morbidity and result in chronic infections and kidney damage. Malnutrition is not only a predisposing factor to infections, but it also distorts typical clinical manifestations and UTIs are more difficult to identify in this population. The aim of this study was to find UTI Prevalence and to screen UTI in malnourished children for empirical therapy and hospital infection control policies.

Materials and Methods

It was retrospective observational study done at Nutrition Stabilization Centre of CH & ICH, Multan dated 1st January 2023 to 31st December 2023. Ethical approval was obtained from institutional ethical committee (2462, dated: 25.11.2022).

Patients with severe acute malnutrition (Weight/Height less than -3SD for that age and sex with some complications like hypoglycaemia, anaemia, hypothermia or other co-morbid conditions and or bilateral pedal edema) of age 1 month to 5 years who fulfilled the inclusion criteria were included in this study. Children with congenital anomalies of kidneys and urinary tract like hydronephrosis, dysplastic kidneys, vesicoureteral reflux, neuropathic bladder, children with chronic diseases like tuberculosis and AIDS and children taking antibiotics prior to admission in hospital were excluded from our study. All particulars were added in a predesigned structured Performa. Informed written consent was taken from guardians of minors. History was taken and detailed physical examination including genital area examination was done. Genital and perineum were washed with soap and water. For children more than 3 years of age a freshly voided clean mid-stream urine was collected in sterile containers and for children who were aged less than 36 months, their urine sample was collected in paediatric urine collection bag. Urine sample was then shifted to laboratory within half an hour for examination. In all children with evidence of UTI on complete urine examination, such as the presence of pus cells, bacteria, red blood cells, albuminuria (++), nitrite positivity, and leukocyte esterase, a urine

culture and sensitivity test was performed. Abdominal ultrasonography of the kidneys, bladder, and ureters were conducted in all patients showing signs of UTI on urine analysis.

The data was collected and entered in SPSS version 23.0. The frequency distribution of qualitative variables is presented into tabulated form. The mean ± SD of quantitative variables are distributed. The paired t test was used to analyse the correlation among UTI and non-UTI patients, and level of significance was determined at p-value <0.05.

Results

A total of 260 children were analyzed at nutrition stabilization center of Ch & ICH, Multan. Out of 260, 13 patients were excluded who did not fulfil the inclusion criteria. Remaining 247 patients were included in study. Male to female ratio were 1.35:1. The male 142(57.5%) was predominant to the female 105(42.5%), 21.2% children belonged to less than 12 months of age. Most of the patients 108 (43.7%) belonged to 13-36 months of age. Out of 247 patients, 144 (58%) belonged to rural areas (Table: I).

Table I: Gender and Age Distribution of Malnourished Children (n=247)

Characteristics	Frequency (n)	Percentage (%)
Gender		
Male	142	57.5
Female	105	42.5
Age groups		
Less than 12 months	52	21.2
12-36 months	108	43.7
36 months -59 months	87	35.2
Residential status		
Urban	103	42
Rural	144	58

Urine samples were collected using the clean-catch midstream method and by applying a sterile urine collection bag. Total 62 urine samples were positive out of total 247 representing presence of UTI 33%. (Table II).

Fever was most common presentation 34(89.47%) in children with UTI followed by diarrhea 29 (76.31%) and vomiting 26(68.42%) (Table II).

Blood investigations were also performed in admitted children. Out of total 62 patients with UTI, anemia was present in 40(88.89%) children, leucocytosis in 23(51.11%) children, elevated renal function was detected in 12(26.67%) children and positive blood culture was found in 21(46.67%) children.

Table II: Common Symptoms in Children with Urinary Tract Infection (UTI)

Common symptoms	Non-UTI Patients (n=185)	UTI Patients (n=62)
Fever	125 (52.3%)	55 (89.47%)
Vomiting	72 (19.90%)	42 (68.42%)
Diarrhea	95 (25%)	47 (76.31%)
Cough	48 (19.90%)	12 (18.4%)
Convulsions	22 (13.63%)	06 (10.5%)
Abdominal pain	35 (3.97%)	20 (26.31%)
Urinary bladder tenderness	0 (0%)	10 (7.89%)
Urinary symptoms	27 (1.7%)	23 (28.9%)

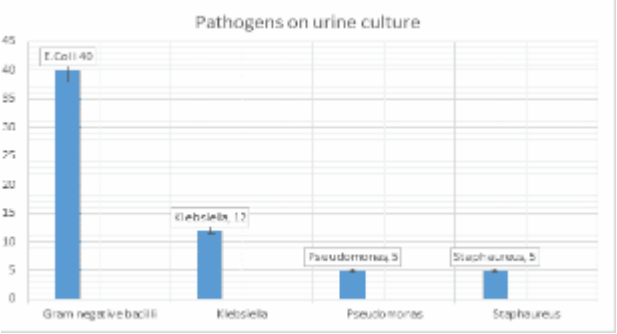

Figure 1. Pathogens Identified on Urine Culture Reports of the Children of Severe Acute Malnutrition

In the current study, urine examination revealed albuminuria in 22 children (48.89%), pyuria in 26 children (57.78%), and a positive urine culture in all 62 children (100%) as shown in Table III.

Discussion

UTIs cause a significant burden of childhood morbidity in children under five years of age , second only to respiratory tract infections. UTIs can present with both symptomatic and asymptomatic forms, with the latter being more frequent in SAM children.

In the current study, 274 cases of malnourished children were investigated and most of them were under the age of three years (mean age 16.7 ± 11.1 months). Similar findings were also reported by Kumar et. al.,[16] and Choudary et. al.,[17] who also found higher percentage of UTIs in children under 20 months of age. Male dominance was observed in our study (57.5) with the male to female ratio 1.35:1. This is in line with the findings reported by Gopal et. al.,[14] and Rehman et al but Sharma et. al.,[19] reported a higher percentage of female cases.[13,18] Those discrepancies might represent gender differences in biological vulnerability, cultural beliefs, and health seeking behavior in different regions.[14,16]

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Table III: Urine and Blood Reports of Children with Urinary Tract Infection (UTI)

Examination type	Findings	Total number (n=62)	Percentage (%)
Urine protein +	Positive	30	48.89
	Negative	32	51.11
Pyuria	Positive	35	57.78
	Negative	20	42.22
Urea culture	Positive	20	33.33
	Negative	42	66.67
Blood examination	Anemic	55	88.89
	Non-anemic	7	11.11
Leukocytosis	Yes	32	51.11
	No	30	48.89
RFT	Elevated	17	26.67
	Normal	45	73.33
Blood culture	Positive	29	46.67
	Negative	33	53.33

The prevalence of UTI in this study was 18.2%, lower than that reported by Sharma et. al.,[16] and higher than the prevalence described by Kumar et. al.,[18] in their cohort.

The differences in prevalence could be explained by the variability in the study design, diagnostic criteria and nutritional status of enrolled children. Urine examination shows that pyuria was present in majority of samples. Similar study was conducted by Kumar et. al.,[16] where pyuria presence was significantly lower than our findings. There were clinical characteristics, including fever (75.6%), vomiting (48.9%), and diarrhea (42.2%), which are consistent with Robino et. al.,[17] and Choudary et. al.,[20] who also reported the gastrointestinal symptoms among the frequent presenting complaints.

The laboratory tests showed that there were high rates of anemia (88.9%) and leukocytosis (51.1%) and high levels of renal functions (26.7%) and positive blood cultures (46.7%) children respectively. These were significantly more than the results of Kumar et. al.,[16] this could indicate the significant effect of severe acute malnutrition on the study population whereby they are prone to systemic infections and hematological abnormalities.

Escherichia coli was identified as the most common organism with a rate of 64.5%, then *Klebsiella* (19.3%), *Pseudomonas* and *Staphylococcus aureus* (8%) each in terms of pathogen profile. Such results are in line with other studies such as those conducted by Bhuiyan et. al.,[21] and Sharma et. al.,[18] that also reported *E. coli* as the most common pathogen in pediatric UTIs. This fact is underscored by the fact that gram-negative organisms are predominant in nature, and thus they require specific empirical therapy, especially in resource-limited environments, where culture facilities might be limited.[15,20,21]

Altogether, the results of the current research support the idea that UTIs are a severe under-diagnosed issue in children with severe acute malnutrition. Morbidity and the possibility of developing long-term renal complications can be minimized through the early diagnosis and regular check-ups at nutritional rehabilitation facilities.[20] Enhancing diagnostic capacity in the lab, prompting antimicrobial coverage, and incorporating malnutrition management protocols with the UTI screening could help to decrease the outcome in this highly susceptible group. UTI screening in nutritional rehabilitation centers should thus be given priority in order to timely detect and intervene. Malnutrition management protocols should incorporate urine cultures testing and reinforcement of antimicrobial stewardship that can possibly lead to morbidity and long-term complications. The results of this research necessitate an aggressive strategy in pediatrics in resource-constrained areas such as Multan where key diagnosis and the limited treatment of UTIs can make a significant impact on the health outcomes of malnourished children.

Conclusion

Urinary tract infections (UTIs) are highly prevalent among children with severe acute malnutrition, with *Escherichia coli* identified as the predominant pathogen, followed by *Klebsiella*. Routine screening of UTIs in malnourished children admitted to nutritional stabilization centers is recommended to facilitate timely interventions, improve clinical outcomes, and reduce morbidity.

Limitation of the Study and Recommendations

There are certain limitations to the current study, it was done in one tertiary care unit only, a multi-centre study will validate the results and support the findings, also follow-ups of the enrolled children can provide insights into reoccurrences of UTI and other infections in malnourished children.

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CONFLICT OF INTEREST

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

REVIEW ARTICLE

Bibliometric Evaluation of Dental Research Productivity and Assessment of Influencing Factors in Pakistan

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ABSTRACT

Objective: This study aimed to evaluate the dental research productivity of Pakistan-based authors and assess the factors that can influence their performances.

Methods: The bibliometric analysis was carried out to examine dental research contributed by Pakistani authors from 1993 to 2022. The bibliographic details of all the relevant published articles on dentistry were extracted from the Scopus database. The search strategy was built using pertinent keywords connected with different Boolean Operators. After applying the inclusion/exclusion criteria, 2859 articles were included in the final analysis. Micro-soft Excel and VOS viewer software were used to analyze the data.

Results: Overall, Pakistan contributed 0.72 percent of the global dental research, however in the last five years, this ratio reached 1.56 percent. A slow research progress was recorded in the first 15 years, whereas exceptional growth was found in the last five years of study. The research impact analysis showed that the selected articles were cited with an average of 7.68 citations per article. Moreover, dental research co-authored with international authors had a higher citation impact than nationally collaborated or single-authored articles. The highest number of articles were found on *Dental Education*, followed by *Oral Pathology/Medicine* and *Dental Public Health*, however, the articles on *Periodontics* gained the highest citation impact. Most of the articles were published in locally published journals, and Saudi Arabia was found to be a vital partner in dental research.

Conclusion: The research activities increased over time, and dental research with international collaboration had a better impact.

Keywords: *Academics; Bibliometric Database; Dentistry; Developing Countries; Pakistan; Research Activity.*

Introduction

Academic and clinical research require a lot of effort and consistency, whereby educators and institutions must strategize the curricula, develop programs, and conduct activities such that both undergraduate and postgraduate students are engaged towards a research-oriented approach.[1,2] The innovative advances in operating techniques and contributions to dentistry revolutionized oral health therapy and greatly extended life expectancy.[3] As a far-reaching consequence, the research activities aim to improve the standards of oral health care provided to patients. Both preventive and curative dental treatments aim to improve patients' quality of life.[4]

According to the United Nations, nearly forty-five countries worldwide have been classified as least developed. Most African nations fall within the low-income category according to the World Bank's criteria, while South Asian countries are classified as lower-middle-income. Predominantly, all the research and data analysis on oral health and disease is concentrated in high-income countries.[5]

According to the United Nations, Pakistan is classified as a lower-middle-income country. A healthy community can significantly contribute to the nation's progress.[6] Numerous universities, dental

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colleges, dental hospitals, and oral health research facilities in Pakistan are involved in dental research. Ever since the restructuring of the higher education system in Pakistan, research publications have become mandatory for promotion and upgradation.[7] This altered the mindset and provided an innovative insight. An extraordinary growth in research activities has been observed over the last two decades.[8]

Being the fifth most populous country in the world, the share in global research has been unsatisfactory.[9] Haq[10] reported that only 731 papers on medical sciences were produced by Pakistan in 2001, reaching 6685 in 2020. Furthermore, the study deduced that more than one-third (27%) of the total research in Pakistan was conducted in medical sciences, however, the ratio of dental research was nominal.

Literature also revealed the trend of subject-wise publication related to dentistry in Pakistan and reported the scarce situation, thereby creating a substantial knowledge gap.[11,12,13,14] This limited output not only underscores the uneven distribution of scholarly focus but also reveals significant gaps in evidence-based resources necessary for advancing academic inquiry. Consequently, the lack of comprehensive and balanced research creates a substantial knowledge gap that warrants urgent attention from researchers, academicians, and policymakers alike. Though, bibliometric studies evaluated the research output in dentistry, and reported that globally dental research makes limited contributions in biomedical sciences.[15,16] It is essential to highlight Pakistan-based dental research through quantitative analysis. To the best of the author's knowledge, no quantitative study to date has documented the global contribution of dental research originating from Pakistan.

Therefore, this study aimed to do a comprehensive bibliometric analysis of Pakistan-based dental research published in the Scopus-indexed journals and addressed the methodological gap. The study is based on the research questions, including (i) what was the contribution of Pakistan to global dental research, and how did dental research and its metrics progress from 1993 to 2022? (ii) What was the proportion of research collaboration at national and international levels? (iii) Which were the preferred patterns of authorship and what were the most favorite and the least researched areas of dental research in Pakistan? (iv) Which were the most frequently used sources of publications, and which were the most research collaborative countries to Pakistan in dentistry?

Methodology

This study employed a bibliometric method to evaluate research progress in dentistry produced by Pakistan over 30 years, from January 1, 1993, to December 31, 2022. The study examined the data obtained from the Scopus database.

The study used these keywords: dentistry, dental, orthodontic*, prosthodontic*, periodontic*, pedodontic*, oral surgery, maxillofacial surgery, restorative dentistry, endodontic*, oral hygiene, and oral health. These keywords were used by Alonaizan et. al.[17] to analyze Saudi Arabia's research output in dentistry. Further, only original research articles and reviews were selected from the filter of the document type, and all the other types of documents were excluded. Pakistan was selected from the country/territory filter. Microsoft Excel (Microsoft 365, Microsoft, USA) and VOSviewer software (*version* 1.6.20) were used to analyze the data.

Results

The initial search query generated 398,624 articles (articles and reviews only) on various dental specialties published between January 1, 1993, and December 31, 2022. However, after selecting Pakistan from the country/territory filter, only 2,859 articles were left (Figure 1). From 1993 to 2022, Pakistan subsidized 0.72 percent of the world's dental research. The periodic distribution revealed that from 2018 to 2022, Pakistani authors contributed 1.56% of the global dental research (Table I).

Progress was plodding (n=120; 4.19%) during the first 15 years (1993 to 2007), however, in the next 10 years (2008 to 2017), the growth of dental research appeared to be picking up, and more than one-third of the articles (n=972; 34%) were published. A phenomenal growth (n=1767; 61.81%) was recorded over the past five years (2018 to 2022). The articles published between 2008 and 2012 had the highest citation impact (12.60 citations/article), whereas overall, all the articles gained an average of 7.68 citations per article (Figure 2).

The analysis (Table II) of national and international research collaboration showed that Pakistani authors produced more than two-thirds of articles by collaborating at the national level. In contrast, almost one-third of the articles were the outcome of international research collaborations. Over time, the proportion of international collaboration increased, and from 2018 to 2022, 37 % of articles were co-authored with international authors. A sharp contrast in citation impact between national and international collaboration was found. The articles produced with international collaboration gained an average of 14.10 citations per article compared to those produced nationally, which received 4.62 citations per article (Table II).

The analysis of authorship patterns revealed that 97% of the articles were written by a collaboration of two or more authors, and the six-author pattern was found to be most proffered, followed by three-author patterns (Figure 3). The nine-author pattern gained the highest citation impact (14.25 cites/article), and the six-author pattern gained the lowest citation impact (4.86 cites/article). The average number of authors per article was 3.18 during the first 15 years (1993-2007), while this ratio increased to 4.15 authors per article in the next 10 years (2008-2017), and the highest proportion, an average of 6.10 authors per article, was found during the last five years of study (2018-2022).

The subject dispersion of dental research exposed that apart from miscellaneous articles that were related to more than one dental specialty or minutely related to dentistry, the highest number of articles were written on the topic of *Dental Education* (468), followed by *Oral Medicine/Oral Pathology* (330) and *Dental Public Health* (312). *Pediatric Dentistry* (47) and *Oral & Maxillofacial Radiology* (38) had the lowest number of articles. The articles on *Periodontics* had the highest citation impact, followed by Restorative Dentistry. The ratio of citable articles is expected to be higher in these two dental specialties. The articles on *Pediatric Dentistry* had the lowest citation impact (Figure 4 & Table III).

Twelve of the top 15 most preferred sources of publications are being published from Pakistan, and 57% (n=1632) of the total articles were published in these top 15 journals. The highest number of articles was published in *Medical Forum Monthly,* followed by the *Pakistan Journal of Medical and Health Sciences*. The top six journals published more than 100 articles each. *The European Journal of Dentistry* was found to be the most preferred international source of publication. Among the top 15 sources, Photodiagnosis and Photodynamic Therapy had the highest citation impact (24.03 citations/article), followed by the *European Journal of Dentistry* and the *Pakistan Journal of Medical Sciences*. *Journal of Islamic International Medical College* and *Medical Forum Monthly* received the lowest citation impact.

The examination of international research collaboration exposed that Saudi Arabia surpassed the rest of the world with 527 articles co-authored with Pakistan. Malaysia came in second with 152 articles, followed by the United Kingdom and the United States with 139 and 122 articles, respectively. Amongst the top 15 collaborating countries, the dental research co-authored with Canada gained the highest citation impact with an average of 30.81 citations per article, followed by Italy (29.72 citations per article) and the United Kingdom (22.33 citations per article). The research articles jointly written with India had the lowest citation impact (Figure 5 & Table 5).

Table I: Contribution of Pakistan in the Global Dental Research

Intervals	Total dental articles at the Global level	The share of Pakistan in dental articles	%
1993-1997	35803	8	0.02
1998-2002	39964	35	0.09
2003-2007	50705	77	0.15
2008-2012	71359	303	0.42
2013-2017	87449	669	0.77
2018-2022	113344	1,767	1.56
Total	398624	2859	0.72

Table II: Comparison of National and International Collaboration in Dental Research

	Total			National Collaboration			International Collaboration		
Intervals	TP	TC	CI	TP	TC	CI	TP	TC	CI
1993-1997	8	59	7.38	4	22	5.50	4	37	9.25
1998-2002	35	390	11.14	24	130	5.42	11	260	23.64
2003-2007	77	811	10.53	65	624	9.60	12	187	15.58
2008-2012	303	3819	12.60	247	2,165	8.77	56	1654	29.54
2013-2017	669	7289	10.90	491	2,825	5.75	178	4464	25.08
2018-2022	1767	9584	5.42	1106	3,182	2.88	661	6402	9.69
Total	2859	21952	7.68	1937	8948	4.62	922	13004	14.10

TP: Total Publications; TC: Total Citations: CI: Citation Impact

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Table III: Distribution of Articles, Citable Articles, Citations and Citations Impact by Dental Sub-Categories of Dentistry

Dental Sub-Categories	Total Articles	Percentage of citable Articles	Total Citations	Citation Impact
Dental Education	468	61.11	3258	6.96
Oral Medicine/Oral Pathology	330	67.58	3013	9.13
Dental Public Health	312	58.65	1962	6.29
Orthodontics	266	56.02	1235	4.64
Restorative Dentistry	220	69.09	2609	11.86
Periodontics	215	73.49	3004	13.97
Endodontics	186	63.44	1143	6.15
Oral and Maxillofacial Surgery	162	51.85	709	4.38
Prosthodontics	145	57.93	956	6.59
Pediatric Dentistry	47	57.45	192	4.09
Oral and Maxillofacial Radiology	38	68.42	299	7.87
Miscellaneous	470	52.34	3572	7.60

Table IV: Top 15 Most Frequently Used Sources of Publications

S. No.	Name of Journal	Total Articles	Total Citations	Citation Impact
1	Medical Forum Monthly	332	52	0.16
2	Pakistan Journal of Medical and Health Sciences	290	200	0.69
4	Journal of the Pakistan Medical Association	199	967	4.86
3	Journal of the College of Physicians and Surgeons Pakistan	183	1196	6.54
5	Pakistan Armed Forces Medical Journal	150	69	0.46
6	Journal of Ayub Medical College Abbottabad JAMC	103	393	3.82
7	Pakistan Journal of Medical Sciences	88	1474	16.75
8	Rawal Medical Journal	58	23	0.40
9	Journal of the Liaquat University of Medical and Health Sciences	56	49	0.88
10	European Journal of Dentistry	32	708	22.13
11	Photodiagnosis and Photodynamic Therapy	32	769	24.03
12	Biomed Research International	30	204	6.80
13	Journal of Postgraduate Medical Institute	29	58	2.00
14	Journal of Medical Sciences Peshawar	25	12	0.48
15	Journal of Islamic International Medical College	25	1	0.04

Discussion

Research in dentistry encounters particular difficulties in developing nations, such as a lack of funding, poor infrastructure, and regulatory barriers.[18] It later affected the quality, quantity, and extent of research due to a shortage of finances and resources.[19] At an institutional level, research orientation and competence gain accreditations and attract talented students. It opens a channel through which innovative progress and impactful research for societal progress can be generated.[20, 21] As educational institutions bear the responsibility of laying the foundation, delving into prospective research work both as a student and academician is the only way to support society as a whole.[22]

Concerning Pakistan, the first dental college, de'Montmorency College of Dentistry, was established in 1934 in Lahore. Later, public-sector

Table V: Frequency of Articles its Impact Co-Authored with Top 15 Countries

S. No.	Country's Name	Total Publications	Total Citations	Citations Impact
1.	Saudi Arabia	527	6829	12.96
2.	Malaysia	152	1157	7.61
3.	United Kingdom	139	3104	22.33
4.	United States	122	2069	16.96
5.	China	56	1142	20.39
6.	India	55	234	4.25
7.	Germany	34	449	13.21
8.	United Arab Emirates	34	342	10.06
9.	Australia	32	548	17.13
10.	Canada	31	955	30.81
11.	Egypt	25	424	16.96
12.	Italy	25	743	29.72
13.	Thailand	19	332	17.47
14.	Sweden	17	320	18.82
15.	Oman	16	321	20.06

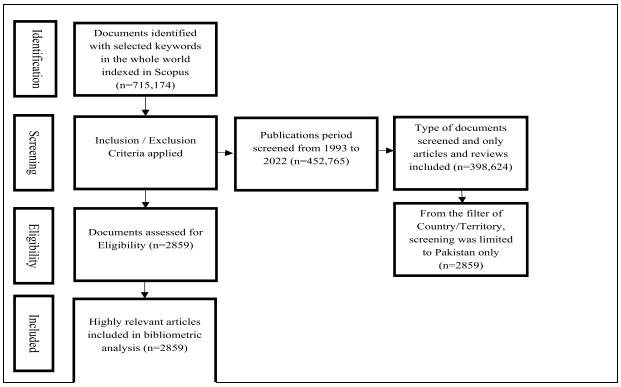

Figure 1: Screening Process of Articles on Scopus Database

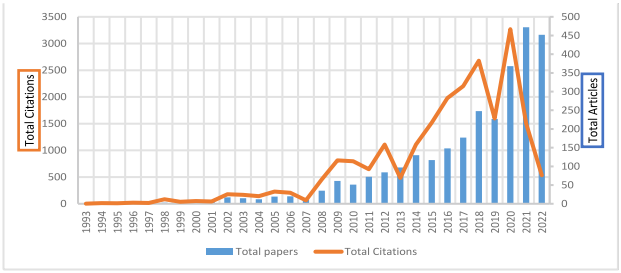

Figure 2: Distribution of Articles and Citations by years

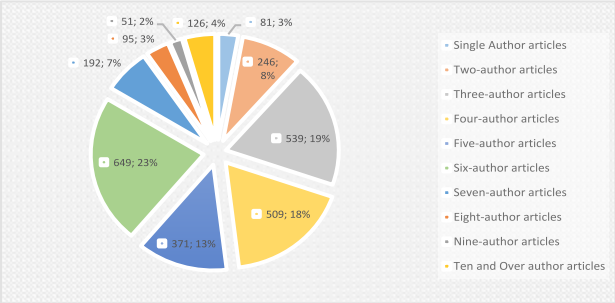

Figure 3: Distribution of Articles by Authorship Pattern

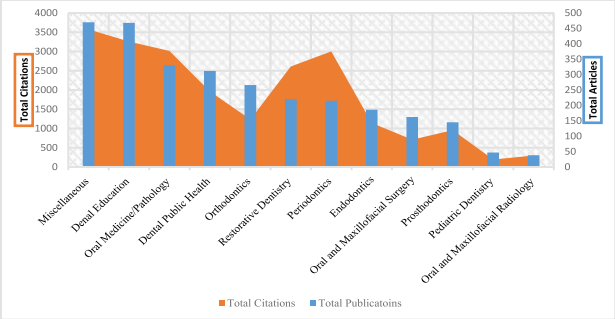

Figure 4: Distribution of Articles and Citations by Sub-Categories of Dentistry

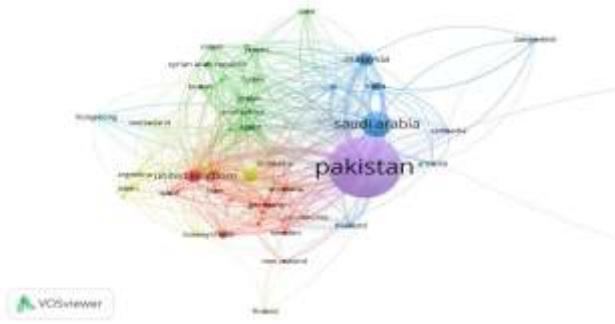

Figure 5: Co-Occurrence Network of Countries

medical colleges at Hyderabad, Peshawar, Multan, and Quetta commenced their dental sections in 1963, 1964, 1974, and 1985, respectively, while the first private dental college started at Baqai Medical University in 1992.[19] Currently, 18 public sector dental colleges/sections and 43 private dental colleges/sections are recognized by the Pakistan Medical & Dental Council (PM&DC).

According to the present study, it is unfortunate that Pakistan's research production in dentistry is minuscule (0.72%) compared to global output. The quantity of publications at national and international levels is highly unsatisfactory, indicating the conventional non-research-based approach despite an upward trend (1.56%) over the past few years (2018-2022). This stands in contrast to other Middle Eastern, Arab, and African countries, where Saudi Arabia contributes almost 3.63% of global dental research,[23] and Brazil, Egypt, Malaysia, and Iraq are also major contributors.[24-26]

There is a concerning issue that Pakistan is trailing behind its neighboring countries. Iran produces substantially more dental research, as indexed in PubMed, despite having a far lower population than Pakistan.[15] India, being a populous country, still produces an average output in terms of research articles; however, the trend is on the rise, and currently, it is contributing almost 1.21% in dental research around the world.[27]

Since the first dental article was published in 1902, the trend towards dental research was stagnant till the late 1950s, after which both article publications and citations increased significantly. Another interesting finding is that research follows certain dynamics, such as economic stability and resource availability.[28] Therefore, the highest contribution towards dental research comes from Scandinavian countries, with Sweden on top; next is the United Kingdom, followed by New Zealand, Israel, Australia, Canada, Germany, Belgium, and the USA; however, the most cited articles come from the United States (US).[29] There is only marginal participation by underdeveloped countries. Developed countries like the US, the United Kingdom (UK), China, Japan, etc., have successfully devised a functional system to engage in research with a focus on addressing and overcoming upcoming challenges.[30] In an attempt to innovate the latest and safest methods of treatment, nations have worked together to fight the odds[31].

Moreover, in developed countries, the research is more coherent with contemporary treatment modalities and futuristic approaches in utilizing artificial intelligence and robotics for diagnosis and treatment planning.[29] Although it is to the advantage of humankind for a small population, in the larger context, all the low- and lower-middle-income countries shall be brought at par with high-income countries in terms of both at the best level. For developing countries, matters are more complex regarding human resource development, infrastructure provision, specifying target areas of concern, generating a loop of finance and collaboration, dealing with the process of patency and publications, and creating a vicious research cycle.[32]

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Since the advent of the internet and consequential globalization, all fields have been moving fast towards the internationalization of efforts. Similarly, in dental research, scientists work collaboratively at inter-university and interdepartmental levels to broaden the impact of their studies. In the Pakistani research scenario, about one-third (32.24%) of articles were the results of international research collaboration. These articles gained 14.10 citations per article compared to the articles that collaborated nationally or single author that received an average of 4.62 citations per article. Likewise, it was studied in Saudi Arabia that international collaboration significantly increases publications in international journals as well as citations for an article.[17] Another relevant example is that of India working in close association with Australia in all fields of dentistry, with a special focus on research, which gave exponential upward growth for India and a more stable output for Australia as well.[33] In fact, collaborative research in terms of bilateral, trilateral, and quadrilateral papers has become so prevalent that a Collaborative Category Normalised Citation Impact (Collab-CNCI) was developed to ensure transparency among the authors for citation scores.[34] Another key factor is access to indexed journals for researchers and academicians. Issues like findability, reusability, interoperability, and accessibility pose critical problems for authors and researchers. According to a study, compliance with the FAIR principles is only 32.6%, with data sharing being more plausible in open-access journals than in non-open-access journals.[35] Presumed Predatory journals, high article processing charges, and non-acceptance of students' articles are also issues that hinder greater productivity.[36]

Based on the author's perspective, involving multiple co-authors, especially foreign colleagues, in an article has numerous benefits, such as a greater target audience, broader demographic data collection, quicker ethical issues resolution, sharing the processing charges, faster data analysis, strategic cross-checking, and better peer review. One may have to share the ownership; however, responsibilities are also divided. Although interactive hassles or disinterested participants can cause unnecessary delays, teamwork can resolve issues.[37]

There was an increase in citations and publications overall from 2017 to 2020 as the Pakistan Higher Education Commission (HEC) started multiple dentistry-related post-graduation in both public and private sectors, encouraged students to go abroad for the same, and extended fellowship programs by the College of Physicians and Surgeons Pakistan, along with an extension for current students. As per the current data, around 1000+ dentists have Fellowships from the College of Physicians and Surgeons, Pakistan, which is expected to increase with time. Subsequently, the research productivity will increase. Many private and public sector institutes offer PhD, MPhil, and MDS programs in clinical and basic sciences. The authors do not have exact data about currently enrolled postgraduate students.

In recent times, almost all technical expertise has shifted towards utilizing artificial intelligence (AI) to perform tasks and projects efficiently, as is the case in dentistry and dental research.[38] As a proficient game-changer, AI has emerged as the most researched domain worldwide, be it data analysis or digitalization of clinical skills. Moreover, 3-D printing technology, stem cell regeneration, and tele-dentistry have also gained immense attention.[39] However, this present study found that periodontology is the most citable topic in Pakistan. Ever since the focus of dental treatment has shifted from curative to preventive, periodontology has become a center of attention for clinicians, academicians, and researchers altogether. The probable cause can be poor oral hygiene conditions and low access to technological advancements in the masses. However, the trend varies in other countries; for example, in Saudi Arabia, the most developed field is implant dentistry in research, and restorative dentistry is the most funded field. A study showed that the trend of dental research focused more on implants, tissue engineering, and bioactive restorative materials.[40]

Another research indicates the direct relationship between political stability, economic development, and financial proficiency with research productivity.[41] It can partially explain the low output from Pakistan, and oral & dental research is not a priority in the health policy, subsequently affecting the research foci. Therefore, it is a dire need of the

hour to focus more on contemporary research fields in basic and clinical sciences. Undergraduate and postgraduate programs shall encompass research and publications as an obligatory part of their courses. The authorities must undertake individual and collective projects, with inter-departmental and inter-institutional collaboration. Academicians and journals should ensure high-impact publications and cater to a larger target population that can contribute to increased citations. It was observed in the present study that the majority of articles published in international journals have been co-authored with Saudi Arabia. A possible explanation could be based on the fact that a large number of dentists have migrated to Saudi Arabia and the Middle East for professional purposes. While working there, they maintained working relations with their colleagues in Pakistan and managed to get publications in international journals.

Nevertheless, it was observed that the overall citation impact for these articles was much lower than that of articles that were published with Canadian collaboration. The reason could be that Canada is a developed country, and the state-of-the-art facilities and interdepartmental collaborations resulted in a much higher citation impact for asmaller number of articles. Co-authorship with Malaysian institutes has also increased, and this may be due to the fact that many Pakistani dentists have recently opted for Malaysian universities for postgraduate studies and developed their research collaborations.

In last decade, many Pakistani dentists obtained postgraduate degrees, especially master's level, from the UK, Malaysia, Hong Kong, and the USA. However, very few pursued it for the doctoral program. One possible reason could be limited financial resources and the availability of scholarships. Higher Education Commission (HEC) Pakistan initiated many programs to provide international and indigenous scholarships, funding, and grant opportunities. Furthermore, Fulbright, Commonwealth, Deutscher Akademischer Austauschdienst (DAAD), Third World Association of Science (TWAS) PhD Fellowships, US-Pakistan Knowledge Corridor, Faculty Development Program, etc., scholarships are also available, which should be explored to enhance the research culture. These scholarships do not directly cater to clinical dentistry programs; however, one can apply in basic science subjects.

Recently, several dental and medical institutes, including Khyber Medical University, Peshawar, National University of Medical Sciences, Rawalpindi, Shifa Tameer-e-Milat University, Islamabad, Jinnah Sindh Medical University, Karachi, and Baqai Medical University, Karachi, are offering doctoral programs in dental subjects. However, they are still in the infancy stage. Some Pakistan-based universities, such as the National University of Science & Technology and COMSATS University Islamabad, have developed their research laboratories and provided services to other institutes. It has been observed that dentists recently joined their PhD program in basic sciences such as biomaterials, nanotechnology, biotechnology, molecular sciences, etc., which will eventually help to promote further research in the field of dentistry. As discussed earlier, research in dentistry is not a priority at a national level; still, a few dental institutes (such as Dow Dental College) have developed their research laboratories; however, they are still scarce. It is recommended that dental institutes utilize indigenous resources, develop their research laboratories, and encourage their faculty to indulge in research activities. It has been observed that the Pakistan-based dental journals are not Scopus-indexed. Therefore, the articles published in those articles were not included. The editorial boards and administration of national journals should try to index their journals in globally accepted databases like Scopus, Web of Science, and PubMed.

The study has some limitations; only one database, Scopus, has been used to extract the publication data on dentistry produced by authors affiliated with Pakistan. Web of Science, PubMed, and Google Scholar results could produce different research outputs. The citation metrics were also collected from Scopus; the ratio of metrics on other databases would be different. Some data may not be added to this study because many Pakistani journals, especially two dental journals, i.e, The Journal of Pakistan Dental Association and Pakistan Oral and Dental Journal, are not indexed in Scopus.

The findings indicated that all stakeholders, including HEC, PM&DC, institution administrators, and other

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healthcare policymakers, need to revisit research policies to raise faculty research growth. Support from financial sources, provision of modern high-tech technology, professional growth, and collaboration with researchers from talent-rich countries are required to achieve high-impact research. The results of this study may be helpful to dental practitioners, researchers, and academicians who wish to evaluate the patterns of dental research in Pakistan. Some convenient conclusions can be drawn from this research, such as that this study has the potential to identify influential topics and collaborative countries, which can support making decisions about future prospects. The dental community of Pakistan might benefit from recognizing top research trends and identifying gaps.

Conclusion

Pakistan's contribution to overall global production is insignificant (0.72%), despite a rising trend toward research output, particularly over the past five years. The citation index is higher with international collabroators compared to national collaborators. The highest number of publications is related to Dental Education; however, the percentage of citable articles is for Periodontology. Most of the articles were published in collaboration with Saudi institutes/authors.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

CASE REPORT

Beyond Acute Appendicitis: A Rare Case of Preoperative Diagnosis of Appendiceal Intussusception on Ultrasound Imaging

Maria Niaz Khan[1], Saman Afraz[2], Momina Waqar[3], Ayesha Imran[4]

ABSTRACT

Appendiceal intussusception is an uncommon and often misdiagnosed condition due to its nonspecific clinical presentation. We document the case of a 40-year-old female presenting with right iliac fossa pain, in whom ultrasonography revealed doughnut sign suggestive of appendiceal intussusception—a rare finding on this imaging modality. This case underscores the significance of considering a broad spectrum of differential diagnosis in abdominal pain and reinforces the diagnostic value of ultrasonography in identifying rare surgical pathologies.

Key Words: *Intussusception, Appendix, Ultrasonography.*

Introduction

Appendiceal intussusception is an exceptionally rare and often overlooked clinical entity, with the earliest documentation dating back to McKidd et. al.,[1] in 1858. Clinically deceptive, it can mimic acute appendicitis, present as a caecal polyp, or remain entirely asymptomatic making diagnosis challenging.[2] The condition results from the appendix telescoping into the caecum, often triggered by underlying anatomical or pathological factors. It occurs more commonly in adults (76%) than children (24%), with a notable female predominance in adult cases (72%). In contrast, male patients constitute a higher proportion (58%) in the paediatric age group.[3] Owing to its infrequency and diverse clinical presentations, it remains a significant diagnostic and therapeutic challenge. We report the case of a female patient who presented with right iliac fossa (RIF) pain, where appendiceal intussusception was diagnosed on ultrasonography, an uncommon diagnostic route for this condition.

Case Report

A previously healthy 40-year-old female arrived at the emergency department complaining of abdominal pain for the last 10 days that had initially started in the epigastric region and subsequently localized to the RIF. It was characterised as dull, continuous, and non-radiating, associated with anorexia, nausea, and vomiting. She also reported intermittent low-grade undocumented fever but denied any history of dysuria, menstrual irregularities, vaginal discharge, or tuberculosis contact.

On initial assessment, the following vitals were recorded: temperature 98.8°F, heart rate 95 bpm, and blood pressure 130/80 mmHg. Abdominal examination demonstrated localised tenderness in the RIF with positive Blumberg's and Dunphy's signs. Systemic examination was unremarkable. Laboratory investigations showed leukocytosis (12,500/mm³) with neutrophilia (74.2%). The detailed laboratory findings are given in the Table I. The patient's Alvarado score was calculated as 9/10, as presented in Table II. However, what followed next was a remarkable and completely unexpected ultrasound finding, transforming this seemingly routine case into a surgical rarity: an adynamic, non-compressible, blind-ending structure in the right iliac fossa, measuring 55 mm in length, 11 mm in width, and 4 mm in wall thickness. A doughnut sign (19 × 17 mm) was visualized at the caecal end, suggestive of acute appendicitis with appendiceal intussusception. (as shown in Figure 1)

Based on the clinical assessment and supporting laboratory and imaging findings, a provisional diagnosis of acute appendicitis with appendiceal intussusception was made. After obtaining informed

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consent, an emergency open appendectomy was planned. The patient was prepared for surgery according to hospital protocol. Intraoperatively, findings consistent with the ultrasound report were noted i.e. an acutely inflamed appendix with its base buried into the caecum. (as shown in Figures 2, 3) The appendix was gently released, the intussusception was reduced, and a standard appendectomy was performed. The patient had an uncomplicated postoperative recovery, and she was safely discharged in a stable condition and healthy wound on the third postoperative day. Histopathological analysis of the resected specimen revealed an acutely inflamed appendix, with no evidence of malignancy.

Table I: Laboratory Findings of the Patient

Parameters	Measured Values	Normal Values
Haematocrit	36.5%	35-49%
Haemoglobin	12.3g/dl	12.0-15.0 g/dl
Platelets	201x10^3/ml	150 – 400 x10^3/ml
TLC	12.5x10^3/ml	4 – 11.0 x10^3/ml
Neutrophils	74.2%	40-70%
CRP	15.6 mg/dl	<0.7 mg/dl

TLC: Total Leucocyte Count CRP: C-Reactive Protein

Table II: Alvarado Score Calculation of the Patient

Symptoms	Score
Migratory RIF Pain	1
Anorexia	1
Nausea	1
Signs	
RIF Tenderness	2
Rebound Tenderness in RIF	1
Elevated Temperature	0
Laboratory Findings	
Leucocytosis	2
Neutrophilia	1
Total	9

Figure 1: Ultrasound Image Demonstrating Appendiceal Intussusception

Figure 2: Intra-operative Image of Acutely Inflammed Appendix with its base buried into caecum

Figure 3: Intra-operative Image Showing Appendiceal Intussusception

Discussion

Appendiceal intussusception is an exceedingly uncommon phenomenon, with an incidence estimated at around 0.01%. [1] It is characterised by invagination of appendix into caecum due to disruption of normal peristalsis caused by anatomical or pathologic factors.[2] Chaar et. al.,[4] analysed the pathological findings of 151 reported cases of appendiceal intussusception and identified association with inflammation (29%), endometriosis (26%), mucocele (18%), adenoma (9%), carcinoid (6%), adenocarcinoma (5%), and other less common conditions (6%). The clinical presentation of appendiceal intussusception can vary significantly, with four distinct types described: the first resembles acute appendicitis, the second features classic intussusception symptoms, including several days of abdominal pain, vomiting, and sometimes diarrhoea or melaena. The third type involves months of recurrent right lower quadrant pain, vomiting, and melaena. The fourth type is asymptomatic and typically diagnosed incidentally.[2]

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Due to its rarity, appendiceal intussusception presents as a diagnostic challenge to radiologists as well as clinicians. When suspected, ultrasonography and computed tomography (CT) serve as the preferred diagnostic modalities. Ultrasonography may reveal characteristic "target" or "doughnut" signs. On contrast enema studies, though now infrequently used, the absence of contrast filling in the appendix along with the appearance of a coiled spring pattern may suggest intussusception.[5, 6] In addition to imaging, there are documented cases in literature where appendiceal intussusception was identified during colonoscopy. It often presents as a polypoid lesion, which can lead to diagnostic uncertainty. Insufflation during the procedure may cause spontaneous reduction of the intussusception, revealing a halo-like erythematous ring around the appendiceal orifice. However, such findings are not always conclusive, as some cases have been mistakenly interpreted as caecal polyps or even malignancies on endoscopy.[2]

Surgical intervention remains the primary treatment approach for appendiceal intussusception. While appendectomy is the most frequently performed procedure, cases with intraoperative features suggestive of malignancy or lacking a definitive preoperative histological diagnosis may necessitate a right hemicolectomy. Beyond addressing acute conditions like appendicitis or intestinal obstruction, surgeons should remain alert to the possibility of underlying malignancy, it is therefore critical that surgeons conduct a meticulous intraoperative assessment.[1,3]

Conclusion

This report emphasises the indispensable role of imaging in detecting rare variations of common surgical emergencies. The doughnut sign on ultrasonography, a diagnostic gem, proved to be a crucial clue that set this case apart, highlighting the importance of vigilance in abdominal imaging and timely surgical intervention.

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Conflict of Interest: none

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- If reviewers and editors are satisfied with the changes, the manuscript is accepted and assigned to the future issue for publication.
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- The editor may reject manuscripts without outside review, for example if the subject matter is outside the purview of the journal, a manuscript on the same topic is just about to be published, the quality of the manuscript is poor, or criteria for the submission of manuscripts are not met.

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A corrigendum refers to a change the authors wish/want to make to their article at any time after its acceptance by the journal. Corrigenda submitted by the authors are published if scientific accuracy or reproducibility of the original paper is compromised. In case of an error in the published author list, JIIMC will publish a Corrigendum but not usually for overlooked acknowledgements. Authors should contact the editor JIIMC, who will determine the impact of the change and decide on an appropriate course of action.

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An addendum is decided on the significance of the addition to the interpretation of the original publication. Addenda do not contradict the original publication, but if the authors inadvertently omitted significant information available to them at the time of submission. This material will be published as an addendum after peer review.

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JIIMC can consider issuing an Expression of Concern (EOC) if editors have well-founded concerns and feel that readers should be made aware of potentially misleading information contained in an article. JIIMC will consider an expression of concern if they receive inconclusive evidence of research or publication misconduct by the authors, there is evidence of unreliable findings, or an investigation is underway, but a judgement will not be available for a considerable time.

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- It has been published solely on the basis of a compromised or manipulated peer review process.
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At times the article may occasionally be retracted for correction of errors in submission or publication and will be replaced with the corrected one.

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3. JIIMC Publication & Research Integrity Committee will evaluate the evidence of misconduct and response of the authors. Based on the findings, the committee will recommend a final decision whether to retract the publication or otherwise.
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5. The retraction-note titled "**Retraction: [article title]"** will be published in the paginated part of a subsequent issue of the journal and listed in the contents list.

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MATERIAL FOR PUBLICATION

The material submitted for publication may be in the form of an original research (Randomized controlled trial – RCT, Meta-analysis of RCT, Quasi experimental study, Case Control study, Cohort study, Observational Study with statistical support, etc.), a Review Article, a Case Report, Recent Advances, New Techniques, Debates, Book/CDs Review on Clinical/Medical Education, Adverse Drug Reports or a Letter to the Editor. Survey Articles and Studies more than five years old at the time of submission are not accepted for publication in JIIMC. Non-English articles are not accepted for publication in JIIMC.

ORIGINAL ARTICLES should report original research of relevance to clinical medicine and may appear either as papers or as short communications. The original paper should be of about 2000-2500 words excluding abstract and references. The abstract should be structured of about 250 words. Three to 10 keywords should be mentioned at the end of the abstract as per MeSH (Medical Subject Headings). There should be no more than four tables or illustrations. The data should be supported with 20 to 25 locals as well as international references. More than 50% of the references should be from the last five years.

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REVIEW ARTICLE should consist of structured overview of relatively narrow topic providing background and recent development with reference of original literature. An author can write a review article only if he/she has written a minimum of three original research articles and some case reports on the same topic. Review articles should be of 2500 to 3000 words with a non-structured abstract of 150 words and minimum 3 key words.

LETTERS TO THE EDITOR should normally not exceed 400 words, have no more than 05 references and be signed by all the authors-maximum 3 are allowed. Preference is given to those that take up points made in contributions published recently in a journal. Letters may be published with a response from the author of the article being discussed. Discussions beyond the initial letter and response will not be entertained for publication.

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- When reporting the results of a randomized trial, JIIMC requires a completed CONSORT 2010 checklist and flow diagram as a condition of submission.
  - o CONSORT 2010 checklist
  - o CONSORT 2010 flow diagram
- Templates for these can be readily accessible here or on the CONSORT website, which also describes several CONSORT checklist extensions for different designs and types of data beyond two group parallel trials
- Authors should ensure that your article, at minimum, reports content addressed by each item of the checklist. Meeting these basic reporting requirements will greatly improve the value of your trial report and may enhance its chances for eventual publication.
- As per recommendation of ICMJE, Journal of Islamic International Medical College requires registration of clinical trials in a public trials registry as a prerequisite for publication of all clinical trials.
- **Clinical Trials:** Clinical Trials submitted for publication must be registered in public registry, e.g., http://clinicaltrial.gov/ , must provide registration proof & all RCTs must be based on CONSORT statement. Unregistered trials will not be published.

  A clinical trial is any research study that prospectively assigns human participants or groups to one or more health-related interventions to assess their effects on health outcomes. These interventions can include drugs, surgical procedures, devices, behavioral treatments, dietary changes, and modifications in care processes. Health outcomes encompass any biomedical or health-related measures collected from patients or participants, including pharmacokinetic data and adverse events. Purely observational studies (those in which the assignment of the medical intervention is not at the discretion of the investigator) do not require registration.

GENERAL ARCHIVAL INSTRUCTIONS

The manuscript should be typed in MS Word. Each manuscript should include a title page (containing email address, cell numbers, institution, and postal address of the corresponding author), abstract, key words, text, acknowledgements (if any), references, tables (each table, complete with title and footnotes) and legends for illustrations and photographs. Each component should begin on a new page. Sub-headings should not be used in any section of the script except in the abstract.

TEXT ORGANIZATION

All manuscripts except Short Communication and Letter to the Editor should be divided into the following sections.

ABSTRACT

Abstracts of original article should be in structured with following sub-headings:

- Objective
- Study Design

- Place & Duration of Study
- Materials & Methods
- Results
- Conclusion

Four elements should be addressed: "why did you start?", "what did you do?", "what did you find?" and "what does it mean? “.” Why did you start?" is addressed in the objective. "What did you do?" constitutes the methodology and could include design, setting, patients or other participants, interventions, and outcome measures. "What did you find?" is the 'results', and "what does it mean?" would constitute the conclusions. Please label each section clearly with the appropriate sub-headings. Structured abstract for an original article, should not be more than 250 words. At least 3 key words should be written at the end of the abstract. Review articles, case reports and others require a short, unstructured abstract. Commentaries do not require an abstract.

INTRODUCTION

Write this section with references as per following instructions:

1. Give background information about the subject matter and the issues your study intends to address. Only strictly pertinent references should be cited, and the subject should not be extensively reviewed.
2. Describe what is known (in the literature) and what is not clear about the subject with reference to relevant literature thus identifying the literature gap.
3. You write the rationale (justification) of your study.
4. Finally, you mention the objective of your study

MATERIALS AND METHODS

Methodology is written in past tense.

Follow this sequence **without headings:**

- Study design
- Place and Duration of Study
- Sample size
- Sampling technique
- Mention about permission of the ethical review board and other ethical issues addressed.
- Inclusion and Exclusion Criteria
- Data collection procedure-
- Type of data: parametric or nonparametric
- Data analysis: including Statistical Software used, and statistical test applied for the calculation of p value and to determine the statistical significance. Exact p-values and 95% confidence interval (CI) limits must be mentioned instead of only stating greater or less than level of significance. All percentages must be accompanied with actual numbers.

RESULTS

These should be presented in logical sequence in the text, tables, and illustrations. All the data in the tables or illustrations should not be repeated in the text; only important observations should be emphasized or summarized. No opinion should be given in this portion of the text.

DISCUSSION

This section should include the author's comments on the results. Write in present tense, active voice except for results, which are written in past tense. It should be written in following sequence:

- First, very briefly summarize, Interpret and discuss main results and don't merely repeat the results.
- Discuss key studies relevant to your study.
- Compare your work with other's work.
- Describe limitations of your study.
- Suggest future work if necessary.

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Conclusion should be provided under a separate heading. It should be in congruence with the objective. No recommendations are needed under this heading.

REFERENCES

References must be written in Roman Number and in the Vancouver Style only. References should be numbered in the order in which they are superscripted in the text. At the end of the article, the full list of references should give the names and initials of all authors (unless there are more than six when only the first six should be given followed by et al). The author's names are followed by the title of the article; title of the journal abbreviated according to the style of the Index Medicus (see “List of Journals Indexed”, printed yearly in the January issue of Index Medicus); year, volume, and page number, e.g., Hall, RR. The healing of tissues by C02 laser. Br J. Surg: 1970; 58:222-225. References to books should give the names of editors, place of publication, publisher, and year. The author must verify the references against the original documents before the

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Tables and illustrations should be merged within the text of the paper, maximum number of tables and illustrations should not exceed four, and legends to illustrations should be typed on the same sheet. Tables should be simple and should supplement rather than duplicate information in the text; tables repeating information will be omitted. Each table should have a title and be typed in double space without horizontal and vertical lines on an 8 ½” x 11’ paper. Tables should be numbered consecutively with Roman numerals in the order they are mentioned in the text. Page number should be in the upper right corner. If abbreviations are used, they should be explained in footnotes and when they first appear in text. When graphs, scattergrams, or histograms are submitted, the numerical data on which they are based should be supplied. All graphs should be made with MS Excel and be sent as a separate Excel file even if merged in the manuscript. For scanned photographs the highest resolution should be used.

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System International (SI) Unit measurements should be used. All drugs must be mentioned in their generic form. The commercial name may however be mentioned within brackets, if necessary.

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- JIIMC Checklist
- JIIMC Conflict of Interest Performa
- JIIMC CopyRight and Undertaking Agreement
- IRC Certificate
- Bank draft as initial processing fee (Original bank draft send in JIIMC office)

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- Author will describe the role of the study sponsor (s), if any, in study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.
- If there is no Methodology section, the role of the funding source should be stated as an acknowledgment.
- The corresponding author should confirm that he/she had full access to all the data in the study and had final responsibility for the decision to submit for publication.
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