p-ISSN 1025-9589, e-ISSN 1819-2718
Indexed in Index Medicus and Medline

JAMC

JOURNAL OF AYUB MEDICAL COLLEGE, ABBOTTABAD, PAKISTAN

Vol.36, No. 4 Oct-Dec, 2024

JAMC

JOURNAL OF AYUB MEDICAL COLLEGE

Vol. 36 (4) **J Ayub Med Coll Abbottabad 2024;36(4)** **Oct–Dec, 2024**

Indexed in Index Medicus and Medline
Approved by Pakistan Medical and Dental Council, and HEC, Registered with the International Serial Data System of France

CONTENTS

ORIGINAL ARTICLE

SUBSCRIPTION

Pakistan:
Annual:
PK Rs. 8000
Single Copy: PK Rs. 2000

Overseas:
Annual: US$ 50
Single Copy: US$ 15.

ORIGINAL ARTICLE

GUIDELINES FOR THE PROCESS OF CROSS-CULTURAL ADAPTATION AND TRANSLATION OF THERAPEUTIC MODULES

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Background: Language is a very important aspect for the adaptation and translation process. For many people, their native language is not just a means of communication but a vessel of cultural identity and emotional expression. When individuals are experiencing the difficulties of life, they should have the chance to address them using a language that truly connects with their personal experiences. Adapting and translating therapeutic modules to align with cross-cultural settings is important to ensure effectiveness and practicality among different populations. The objective of this article is to provide the guidelines for the process of cross-cultural adaptation and translation-back-translation of the therapeutic modules, and also provide the guidelines to test the reliability and validity of the translated version of therapeutic modules. **Method.** The Back-to-Back translation model (10) was used in this study for the guidelines of adaptation and translation of therapeutic modules. Following the instructions in this document made the process of adaptation and translation simpler. **Results.** Results showed that the (10) is a significant model and provided a systematic and comprehensive way for adaptation and translation of therapeutic module with make little changes in reaction to feedback and cultural awareness. **Conclusion.** At the end, it emphasised how important it is to conduct an extensive study to determine the effectiveness and cultural compatibility of the updated modules. However, these principles ultimately enhance effective and inclusive health care, providing health professionals with a foundation for adapting and translating therapeutic processes to diverse cultural conditions.

Keywords: Cross-Cultural Adaptation and Translation; Translation-Back-Translation Model Guidelines; Therapeutic Modules

Citation: Qamar T, Ibrahim N. Guidelines for the Process of Cross-Cultural Adaptation and Translation of Therapeutic Modules. J Ayub Med Coll Abbottabad 2024;36(4):681–5.

DOI: 10.55519/JAMC-04-13584

INTRODUCTION

Language is a very important aspect for the adaptation and translation process. For many people, their native language is not just a means of communication but a vessel of cultural identity and emotional expression. When individuals are experiencing the difficulties of life, they should have the chance to address them using a language that truly connects with their personal experiences.[1] Translating therapeutic modules acknowledges this diversity, affirming the validity of various linguistic and cultural contexts in the realm of healing. The need to translate therapeutic modules into source languages other than the original language is increased with multicultural and global research programmes.[2,3] The majority of the modules were developed by English-speaking countries; however, it is essential to adhere to a specific procedure when adapting and translating a therapeutic module for use in a different country, culture, or language to ensure that it performs as well as the original.

The cross-cultural adaptations and translation of original work are important in many contexts, this is more evident in certain situations than in others. While developing a therapeutic module for use in a foreign region, the challenges of cultural adaptation and language translation are important to keep in mind. In order to avoid the possibility of systematic bias[4,5], there is need to pay attention to the sensitivity of cross-cultural differences. Such as, the most difficult aspects of translating from one language to another are expressing ideas precisely when there are no direct translations available, as well as maintaining consistency and clarity without changing the original meaning. In addition, in order to make therapeutic treatments truly resonate with different people, it is necessary to have a comprehensive knowledge of cultural norms, beliefs, and values.[6] Also, it is important to be sensitive and flexible when developing interventions to address the specific needs of different communities because there are different levels of challenges when considering healthcare systems, socioeconomic problems, and past experiences.

Besides, there is need to overcome these challenges during the cross-cultural adaptation and translation of therapeutic modules. Overcoming challenges in cross-cultural adaptation and translation of therapeutic modules requires collaborative efforts, involving linguists, researchers, and community

workers, considering cultural sensitivity, linguistic accuracy, and contextual relevance in the adaptation and translation process. Literature also identified important considerations for successful adaptation and translation, such as, to identify the ideal approach to intervention modification, all interventions should be linguistically, idiomatically, cognitively, and experientially similar.[7,8] During the cross-cultural adaptation and translation, the validity and reliability of the therapeutic module is also considered as an important aspect.

The International Society for Quality-of-Life Assessment (IQOLA) guidelines is use to assess the translation of a therapeutic module. IQOLA uses a three-stage process, the first of which provides an in-depth explanation of the translation process.[9] The following two stages include the verification and validation of the content, followed by establishing and verifying the normative values of the new edition. It has been seen that in literature, there are many guidelines for the adaptations and translations of different instruments, however, there is not any guideline for the translation and adaptation of therapeutic modules. Thus, the main objective of this study is to provide the guidelines for the process of cross-cultural adaptation and back-to-back translation of therapeutic modules, and, also provide the guidelines to test the reliability and validity of the translated version of therapeutic module.

MATERIAL AND METHODS

Brislin developed a model of back-to-back translation. This study provided the guidelines to use this back-to-back translation model for the adaptation and translation of therapeutic module.[10] The translation-back-translation approach model refers to the process of translating source material into the target language and then back into the original language.[10] In the translation-back-translation method, two or more bilingual translators work independently to translate each step from the source language to the target language. Following that, these translators resolve issues related to the final result in an integrated way.[11] The complete step by step guidelines are provided in the conceptual framework model of the present study. Figure 1 discusses the conceptual framework of the translation-back-translation model's five stages (Figure-1).

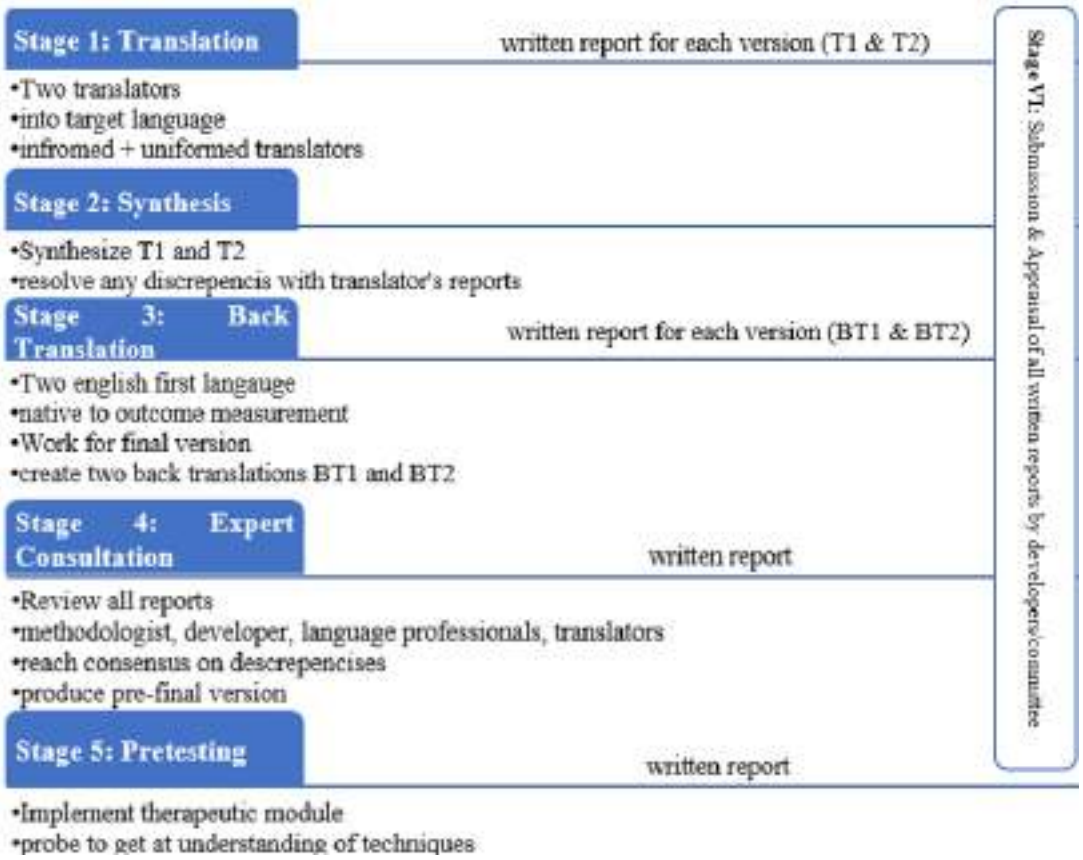

Figure-1: Stages of Translation Back Translation Model of the Present Study

The initial stage of the adaptation process is known as forward translation. We translate the therapeutic module into the target language at least twice from the original (source) language. This process enables the identification of discrepancies between translations, which may indicate linguistic ambiguity in the original text or changes in the translation approach. The translators cast their votes during the discussion about which phrase options they considered to be of lower quality. It is most effective when the translators have therapeutic backgrounds and expertise and fulfil the following eligibility criteria.

(a) Being doctoral candidates in specific therapeutic field; (b) being bilingual in both Native and English language; (c) having therapeutic experience with diverse population; and (d) having translation experience, particularly in native translation. Bilingual translators produce two different versions using their native language as the target language. Translating into one's original language enables a more accurate presentation of language nuances.[5] It is the responsibility of every translator to produce a report detailing their work as a translator. The written report provides detailed explanations for the decisions. The translation includes not only the module text but also the worksheets and instructions.

As the two translators combine their material, an observer records the proceedings. Researchers synthesize these translations using the original module and the versions provided by the first and second translators (T1 and T2) before producing a unified translation. A written report is helpful to learn all about the synthesis method, including the challenges that translators faced and how they overcame them. It is essential to reach a consensus when resolving conflicts, rather than letting one person bottle up their emotions. The therapeutic module, in its second-to-last, final form, completes the following phase.

The translators then return the therapeutic module to its original language. The translator works on the final pre-version without knowing anything about the source material. The goal of this validation is to make sure the translated version is a true representation of the original module's content. Such as, there is a current trend to use terminology that is difficult to understand while translating. There is no assurance of a high-quality forward translation because of the possibility of mistakes, even though there is consistency in the translation due to the agreement between the back translation and the original source version. However, developers and researchers can use back translation to fix any evident inconsistencies or conceptual errors in a translation. A minimum of two back-translations is recommended. Two individuals, fluent in both the source language and native English, completed the back-translations (BT1, BT2). It is an ideal situation when both translators are completely familiar with the topics under review and has background in therapeutic practice. Literature showed that avoiding information bias and discovering unexpected interpretations in the final version of the translated work is important in improving the probability of finding errors.[6,11]

The cultural equivalency goal depends on the committee's foundation. The expert committee consisted on the small but powerful group includes language experts, researchers, methodologists, and experienced interpreters (in both ways). Along with this, there is constant communication between the expert committee and the people who developed the original module. Every version of the module translated by the translators, including the final therapeutic module ready for the therapeutic evaluation, undergoes a systematic compilation by the expert committee. Therefore, following a comprehensive evaluation of all translations, the committee will write down all discrepancies. The committee received the original module as well as its final pre-versions in both the source language and English, including translations (BT1, BT2).

Moreover, the committee also received written reports explaining all the decisions made in the previous steps. Furthermore, module developers expected from the expert group to provide comprehensive written documentation that explains all factors examined and the logic behind any decisions reached. Moreover, the expert committee must make decisions on four different aspects in order to align the source and target versions. In regard to the following four aspects, the context is very important: Do the ideas have definitions that are completely different and cannot coexist? Can something be reconsidered in the module? Does the translation contain any grammatical errors? Is the translation appropriate with regard to equivalence?

In regard to equivalence, it also has been seen that conceptual definitions of words show cultural changes.[12] Thus, activities that closely resemble and are frequently practiced in the target culture should be replaced with those presented in a proposed therapeutic module. For example, if you have trouble getting up after dancing, then the proposed technique in the module might help you. It's seeming like that the country in which you want to implement the module doesn't use dance activities in its culture; however, uniform equity is important. Depending on the culture, the practice of "visiting your relatives to the extent you desire" varies in regularity. This is due to the fact that cultural norms on the characteristics that differentiate an extended family from a nuclear family vary.

Accordingly, a comparison of the original therapeutic module and back-translated versions is necessary for the committee to reach a conclusion regarding their equivalents. Before proceeding, both parties must reach an agreement; if necessary, they can

use translation and back-translation to establish multiple expressions for each subject. Given the ease of establishing such projects, it would be beneficial for the committee to include all translators. In this scenario, a comprehensive evaluation of easily understandable methods, criteria, and solutions is necessary. However, it is also the responsibility of the module's developers and translators to ensure that the intended audience can understand the final therapeutic module.

During the adaptation and translation phase, the pretest concludes. This field test will involve the participation of patients or participants from the intended location in order to evaluate the final version of the new therapeutic module. A sample size of 10–20 individuals is ideal for the testing, although it depends on the number of participants according to a specific therapeutic module. After completing the module's activities and tasks, the next step is to interview the patients to gain insight into the intended purpose of the activities or procedures and their preferences for specific solutions. Proving the relevance of the responses and activities is important. By doing this, the revised version will maintain its coherence when applied to real-world scenarios.

When adapting and translating a therapeutic module, the final step is to provide all relevant documentation and reports to the group responsible for the translated version, or the individual who developed it. They can then confirm that all necessary steps have been completed and that the generated reports are accurate in relation to the methodology. The procedure can be considered an audit of the process based on the reports produced and the guidelines followed. Following this process, the developers of the module can get a translation that makes sense, but they can't change the text as a group.

RESULTS

This study provided a comprehensive analysis of the process of adaptation and translation of therapeutic modules. Maintaining the module's validity and reliability when translating it from one language to another is the goal of cross-cultural adaptation and translation. The produced version must be valid and reliable in the same way as the original. However, this isn't always the case, possibly due to refined cultural variations in how people go about their daily lives, which may add or subtract complexity to some tasks.[13] These changes could compromise the accuracy and reliability of the module.

After the translation and adaptation procedure, the researchers should conduct tests to ensure the new version meets the requirements for the intended application.[14,15] Not only should the new module incorporate the traits already present at the task and score levels, but it should also add responsiveness, content validity, and reliability. In the final step, the module developer must thoroughly evaluate three critical aspects: respondent validity, reliability, and content validity. The module developers can also look at similar tests conducted within the original module's context. Developers of the module anticipate that the enhanced version will deliver comparable results.

DISCUSSION

This article provided step-by-step guidelines for the translation-back-translation model for adapting and translating therapeutic modules. It also demonstrated that an insufficient translation method could result in a therapeutic module that differs from the original. This article discussed a detailed approach to adapting and translating a module to a novel context. In addition, this article also provided guidelines for testing the reliability and validity of therapeutic modules; however, developers must introduce the new module to ensure the system's validity and reliability. The International Society for Quality-of-Life Assessment (IQOLA) guidelines are consistent with the current study's guidelines and their formal testing suggestions for the final module.[2,11]

Moreover, this article provided a conceptual framework model for five-stage steps that involve adapting and translating to a new culture while simultaneously lowering or replacing certain activities as necessary. Translations at the task or activity level assume that the translated tasks adequately represent the concept of health in a different culture, which researchers should take into consideration. However, a previous study[3] aligns with task equivalency as one of several aspects that require consideration. It is important to understand that a translation cannot be considered a precise measure of a culture's liveliness. Thorough verification is important before and during the final testing phase.[16,17] When working with modules that do not have a specific location for translated versions, it is important to follow the steps provided in this article.

This article also discussed some recommendations for future studies. With the right documentation outlining the adaptation and translation process and the final version of the therapeutic module, the developers may avoid the distribution of several translations and, more importantly, the unnecessary complications of all that hard work. Modifying a therapy module for use in a different setting requires effort and time. Therefore, it is important to consider establishing eligibility criteria for translators in various cross-cultural situations. Additionally, this article discussed the strengths of the adaptation and translation process, which is considered the most effective method for obtaining a uniform value across all report data characteristics. Standardised data collection across cultures makes cross-cultural research more accurate and prevents studies from unfairly eliminating participants who, for whatever

reason, are unable to fill out an English form because there is no translated module available.

CONCLUSION

To conclude, the cross-cultural adaptation and translation of therapeutic modules is important to ensure the applicability, reliability, and resonance across diverse populations. By adhering to rigorous processes such as the translation-back-translation model and engaging experts, the language and culture were preserved. This enhances inclusivity in healthcare and ensures that interventions meet both linguistic and cultural needs effectively. In addition, these guidelines embrace cultural sensitivity, linguistic accuracy, and collaborative approaches; practitioners can bridge cultural gaps and promote the delivery of effective mental health care globally. It is also essential to understand the importance of context, involve developers and translators, and use strict validation methods to make therapeutic modules more useful and acceptable in different cultural settings.

AUTHORS' CONTRIBUTION

TQ: Literature search, write-up. NI: Proof reading, review.

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Submitted: July 12, 2024	*Revised: September 10, 2024*	*Accepted: October 9, 2024*

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ORIGINAL ARTICLE

THE RATE AND TIME TO FIRST READMISSION IN PATIENTS DISCHARGED WITH A DIAGNOSIS OF ACUTE DECOMPENSATED HEART FAILURE ADMITTED TO THE CARDIOLOGY DEPARTMENT, AYUB TEACHING HOSPITAL, ABBOTTABAD

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Background: Admission for heart failure poses a significant risk of readmission. Evaluating readmission rates in settings lacking chronic disease management programs could provide valuable insights to advocate for the establishment of such services. **Methods:** This study focused on patients admitted to the Cardiology Department of Ayub Medical Teaching Institute with acute decompensated heart failure. After excluding patients based on exclusion criteria, demographic and clinical data were recorded, including symptoms, signs, discharge medications, and readmission status within 6 months. Patients not readmitted were contacted via telephone at 1, 3, and 6 months. Readmission rates and time to first readmission or death were documented. **Results:** A total of 222 patients were enrolled, with 60% being males. All patients exhibited pulmonary congestion, with 85% classified as NYHA Class III or IV. Comorbidities included hypertension (59%), history of myocardial infarction (45.49%), and diabetes (38.28%). Within 6 months, 21% of patients were readmitted, and 13% died before readmission, resulting in an overall death or readmission rate of 34% at 6 months. No significant differences were observed between readmitted and non-readmitted patients regarding sex, age, creatinine levels, haemoglobin levels, sodium levels, or ejection fraction. Utilization of guideline-directed medical treatment was low. **Conclusion:** The high rate of readmission or death among patients admitted with acute decompensated heart failure underscores the necessity for implementing multidisciplinary care to closely monitor these patients.

Keywords: Acute Decompensated Heart Failure; Readmission; Heart failure

Citation: Shams S, Khan MI, Afsar R, Javed F, Khan ZU, Ahmad A, *et al*. The rate and time to first readmission in patients discharged with a diagnosis of acute decompensated heart failure admitted to the cardiology department, Ayub Teaching Hospital, Abbottabad. J Ayub Med Coll Abbottabad 2024;36(4):686–91.

DOI: 10.55519/JAMC-04-13550

INTRODUCTION

Heart failure is a clinical syndrome characterized by the heart's inability to provide sufficient blood flow to meet metabolic requirements or accommodate systemic venous return.[1] It has become a global epidemic, affecting an estimated 64.3 million people worldwide.[2] Heart failure imposes a significant burden on healthcare systems, leading to high rates of morbidity, mortality, and poor quality of life.[3]

Hospitalization for heart failure is a pivotal event in its natural history, signalling a worsened prognosis. Despite the availability of evidence-based treatment modalities, hospitalized heart failure patients continue to experience high post-discharge mortality and rehospitalization rates.[4] Factors contributing to hospital readmissions in heart failure are multifactorial, with recent past admissions being strong predictors.[5] Approximately 22% of heart failure patients experience potentially preventable readmissions shortly after discharge, resulting in high costs and a bleak prognosis.[6] Factors such as suboptimal care,[7] comorbidities, and poor compliance[8] also contribute to the risk of rehospitalization.

Several studies have demonstrated a decrease in 30-day readmission rates following the implementation of the Hospital Readmission Reduction Program (HRRP), indicating improved care outcomes.[9,10] However, Ayub Medical Teaching Hospital lacks an organized multidisciplinary heart failure management program. We hypothesize that readmission rates for patients with Acute Decompensated Heart Failure (ADHF) in our community are notably high.

The objective of this study is to determine the rate and time to first readmission in patients discharged with a diagnosis of acute decompensated heart failure from the cardiology department at Ayub Teaching Hospital, Abbottabad. If the readmission rates for heart failure are found to be unacceptably high, it would strengthen the case for establishing a multidisciplinary heart failure care team. To our

knowledge, such a study has not been conducted at our hospital before.

MATERIAL AND METHODS

This descriptive case study was conducted in the Cardiology department of Ayub Teaching Hospital, Abbottabad, between April and August 2023. Inclusion criteria comprised patients of both genders aged 20–80 years presenting with acute decompensated heart failure and an ejection fraction of less than 50%. Excluded from the study were patients who developed acute heart failure due to ST-elevation myocardial infarction (STEMI) or non-ST-elevation myocardial infarction (NSTEMI), and those requiring ventilatory or intensive care unit admission. Patients with aortic stenosis, aortic regurgitation, mitral stenosis, or mitral regurgitation were also excluded.

Patients meeting the inclusion criteria and surviving to discharge were included in the study, totalling 222 patients. Basic demographics, medical history, physical examination findings, NYHA classification of shortness of breath, echocardiographic data, and discharge medications were recorded. Patients were provided with a contact number for reporting any unplanned hospitalizations elsewhere, and instructed to retain their unique admission numbers for traceability. All first readmissions were documented, and patients not readmitted were contacted via telephone at 1, 3, and 6 months to assess their status. Time since index admission was recorded for all readmissions.

Data were analyzed using SPSS 22.0. Quantitative variables were described as means, while categorical variables such as gender, comorbidities, NYHA class, and readmissions were presented as frequencies and percentages. Data were stratified by relevant variables, and the significance between percentages was determined using two-proportions t-test and chi-square test

RESULTS

A total of 222 patients admitted to the cardiology department with ADHF constituted the study cohort, all of whom survived to discharge. Sixty percent were males, and baseline characteristics revealed a significant prevalence of hypertension (59%), diabetes (38.28%), history of myocardial infarction (45.49%), and current smoking (8.5%). Peripheral oedema was present in 70% of patients, with over 85% experiencing NYHA Class III or IV shortness of breath. Echocardiography revealed an EF of 30% in 51% of patients, with 96% requiring intravenous diuretics on admission. Atrial fibrillation and uncontrolled hypertension were also observed in 9.5% and 25% of patients, respectively. During the 6 months of follow up 13% of patients died and 21% of patients were readmitted. 18% of patients could not be contacted and the rest (40%) were not admitted. Table-1 presents the baseline characteristics of all patients at index admission. The discharge medications summary is shown in Table 2. Majority were discharge on loop diuretic (92.34%) followed by Beta blockers. Table-3 gives data about readmitted patients. Of the readmitted patients 20.5% were on an ACE-I, 25.6% were on Sacubitril/Valsartan and only half of the patients were on beta blockers Table-4.

Gender wise breakup is given in Table 5. Gender did not confer a risk of death or hospitalization. (p=0.1031) as depicted in Table 5. Outcomes also did not differ based on the Ejection fraction. or age groups. There were no differences in the mean age, creatinine level, ejection fraction, Sodium levels, average Haemoglobin or systolic blood pressure between the patients who were readmitted and those who were not readmitted Table-6.

Only hypertension had a significant effect on the rate of readmission. Readmission rate was more in hypertensive patients. 71.7% readmitted patients had hypertension. All other comorbidities didn't affect the rate of readmission significantly.

The combination of Chronic Kidney Disease and Coronary Artery disease showed the highest re-admission rate with 41% of such patients getting readmitted. The rate of re-admission from other pre-specified comorbid subgroups varied from 12–24%.

Table-1: Baseline characteristics on index admission

Parameters (n= 222)	Value
Mean Age (yrs)	62.43
Males (%)	60.36
Females (%)	39.64
Hypertension (%)	59.00
Diabetes Mellitus (%)	38.28
History of Acute Myocardial Infarction (%)	45.49
Smokers (%)	8.5
History of Percutaneous Coronary Intervention (%)	0.45
History of CABG (%)	0
Impaired Renal Functions on First Admission Cr > 1.5) (%)	22.97
Patients with Oedema on First Admission (%)	69.36
NYHA Class II (%)	4.50
NYHA class III (%)	74.32
NYHA class IV (%)	21.17
Patients with LVEF 40-45% (%)	14.41
Patients with LVEF 30-40% (%)	44.14
Patients with LVEF Less than 30% (%)	51.35
Patients with Hb less than 10mg/dl on first admission (%)	10.36
Patients with Atrial Fibrillation (%)	9.45
Patients requiring Inpatient IV Diuretic (%)	96.84
patients with BP less than 100 systolic (%)	15.31
patients with BP more than 100 systolic (%)	74.77
Uncontrolled HTN on Admission (sys > 140 or dia > 90) (%)	24.77

Table-2: Guideline-directed medical treatment on discharge at index admission.

Guideline Directed Medical Treatment	%	No. out of 222
ACE-I	31.53	70
Betablockers	66.66	148
Loop Diuretics	92.34	205
Valsartan-Sacubitril	24.32	54
SGLT2	23.42	52
Digoxin	16.66	37
Ivabradine	2.7	6
Mineralocorticoid	44.14	98

Table-3: Characteristics of readmitted patients.

Parameters (n=46)	Value
Mean Age	62.72
Males (%)	56.41
Females (%)	43.59
Readmitted within 30 days (%)	46.15
Readmitted within 30-60 days (%)	25.64
1 Readmission more than 60 days (%)	28.21
Hypertension (%)	58.97
Diabetes (%)	41.02
Patients with history of Acute Myocardial Infarction	47.82
Patients with history of Percutaneous coronary Intervention (%)	2.63
Patients with history Of CABG (%)	00.00
Patients with impaired renal functions Cr > 1.5	23.07
Noncompliant with all Medications	17.94
Average Weight gain of all patients readmitted compared to discharge weight	2.92kg
Admission from outpatients (%)	38.46
Admission from Emergency Department (%)	61.54

Table-4: Guideline directed medical treatment of patients on re-admission.

Guideline Directed Medical Treatment on Re-admission	%
Patients on Angiotensin converting enzyme inhibitors (%)	20.51
Patients on Angiotensin receptors blockers (%)	2.56
Patients on Sacubitril/Valsartan (%)	25.64
Patients on Betablockers (%)	53.84
Patients on Mineralocorticoid Inhibitors (%)	51.28
Patients on SGLT 2 Inhibitors (%)	20.51

Table-5: Gender distributions of re-admitted patients.

Sex	n	Re-admitted or dead (%)	*p* value	Not contactable (%)	Not readmitted (%)
Males	135	30	0.1031	23	47
Women	87	40		13	47

Table-6: Average age, Creatinine, EF, Sodium levels, Hb, and Systolic BP of patients admitted vs not admitted.

Parameter	Dead or readmitted	Not readmitted	Not contactable
AGE (mean)	62.12	62.33	61.51
CREATININE (mean)	1.34	1.34	1.3
EF (mean)	29.36	29.36	28
SODIUM (mean)	132.34	132.34	132.65
Hb (gm/dl) (mean)	12.71	12.8	12.7
SYSTOLIC BP (mean)	125.9	125.9	126.3

DISCUSSION

Our study revealed that patients with heart failure receiving treatment and follow-up as part of routine care have a high rate of rehospitalization or death within 6 months, totalling 34%. Specifically, we observed an overall readmission rate of 21%, with 46% readmitted within 30 days, 25% between 30–60 days, and 21% after 60 days. This aligns with previous findings indicating that hospitalization for heart failure carries a grave prognosis. For instance, a study of 40,000 patients with a history of heart failure hospitalization reported a 5-year mortality rate of 75%.[11] While our study's readmission rates were somewhat lower, they still underscore the considerable burden of heart failure management in routine care settings. Large-scale studies have reported higher readmission rates, with 44% of patients readmitted within 6 months.[12] Similarly, research comparing multidisciplinary care to usual care found a 45.7% readmission rate within 90 days for patients under usual care.[13] Another study reported a 47% 90-day readmission rate for patients hospitalized for acute decompensated heart failure.[14]

Regarding risk factors associated with heart failure, our study found a notable prevalence of hypertension (59%), history of myocardial infarction (45.49%), and diabetes (38%). These findings are consistent with previous research showing varying prevalence rates for ischemic heart disease across different populations, [15,16,17] with hypertension occurring in 76% of cases [18] and diabetes in 40%.[19]

While previous studies identified factors such as noncompliance, low haemoglobin levels, and higher NYHA class as significantly associated with rehospitalization,[20] our study did not find any significant differences in these factors between patients who were readmitted and those who were not. However, we observed that self-declared non-compliant patients and those patients with comorbidities such as coronary artery disease and chronic kidney disease were associated with increased readmission rates. The average length of hospital stays in our study (3–6 days) was shorter than the global average (5 to 10 days), indicating potential variations in healthcare practices.[21]

Efforts to prevent hospitalization in heart failure have become a crucial aspect of heart failure management worldwide.[22] Multidisciplinary care programs, including outpatient services led by specialist heart failure nurses, have been shown to reduce mortality and hospital readmissions.[23,24] These programs typically involve patient education, discharge planning, timely follow-up appointments, and tailored discharge instructions. Studies have demonstrated that patient education combined with

follow-up interventions, such as home visits and timely appointments, can significantly reduce readmission rates.[25,26] However, our study revealed gaps in the utilization and up-titration of guideline-directed medical therapy (GDMT) for heart failure, with low adherence to recommended medications such as ACE inhibitors, beta-blockers, and mineralocorticoid antagonists.

Transition from hospital-based treatment to ongoing ambulatory care has many essential steps. None of which exist in our hospital. Studies have shown that specialized inpatient heart failure treatment cannot prevent acute events post-discharge including death if the outcomes of excellent inpatient treatment are not maintained during ambulatory care. 95% of our patients on their index admission were in NYHA class III or IV. On discharge from their index admission, 98% of our patients had improved to NYHA class II. The majority of them had lost weight. Our patients still showed a 21% readmission and a 13% mortality rate over 6 months, strikingly similar to the results of a 20-year-old Euro heart failure survey program of 2003 when chronic disease management programs were not widely established, which showed a 24% readmission rate and a 13.5% mortality rate over 12 weeks.[27]

A pioneering study by McDonald K *et al* showed that patients who were stable at discharge with freedom from intravenous diuretics for two days and on maximally up-titrated disease-modifying drugs showed a 25.5% mortality rate in patients undergoing usual care compared to only 7.8% in patients subjected to multidisciplinary care. Multidisciplinary care included inpatient and outpatient education and close telephonic and clinical follow-up.[28]

The rate of GDMT usage was low in our patients with 56% patients on Angiotensin-converting enzyme inhibitors (ACE-I) or Sacubitril/Valsartan (ARNI) combination and 66% on betablockers (BB). 44% on Mineralocorticoid antagonists (MRA) and only 24% on Sodium Glucose cotransporter 2 inhibitors (SGLT2I) at discharge following index admission. On readmission 65% were taking either ACE-I, Angiotensin Receptor blockers (ARB), or ARNI, 51% were taking MRA and 53% were taking BB. Only 20% were taking SGLT2 inhibitors. Current guidelines recommend inpatient initiation of GDMT in patients admitted with acute decompensated heart failure. There are however still barriers to initiation and up-titration of inpatient GDMT which vary from socioeconomic (affordability), patient-related barriers (hypotension, bradycardia, reduced renal function, etc.), tolerability and side effects, or simply inertia on the part of clinicians.[29] Previous data derived from real-world registries show similar gaps between real-world vs clinical trial data. Data from CHAMP-HF, one such registry showed in 2018, ACE/ARB/ARNI usage of 27%, BB usage of 33%, and MRA in 67% of patients.[30] Medication up-titration which has been shown to improve outcomes,[31] is another important aspect of ambulatory care in patients with heart failure which cannot be undertaken in a timely fashion as a part of usual care. None of our patients underwent any dose up titration of their GDMT. A meta-analysis of studies involving nurse-led up titration of beta blockers and angiotensin-converting enzyme inhibitors found that patients enrolled in such programs were 21% less likely to be readmitted and 34% less likely to die.[32] Early follow-up likewise has been shown to lower the risk of 30-day readmission rates.[33] A substantial body of evidence points to the usefulness of disease management programs in reducing readmission and mortality. Such disease management programs combine patient education, early follow-up, telemonitoring, and promotion of self-care activities including exercise and dietary advice.[34–37]

One limitation of our study is the inability to account for 18% of the study population, potentially affecting the accuracy of our findings. Additionally, despite efforts to track acute readmissions through telephone calls, some hospitalizations may have been missed, particularly for patients admitted to other hospitals within our catchment area. Another limitation of the study worth mentioning was the lack of an active intervention arm which would have compared the results of patents managed in heart failure clinic and usual care.

CONCLUSION

Patients with chronic heart failure managed outside of chronic disease management programs face a high risk of readmission or death, coupled with suboptimal utilization of guideline-directed medical therapy. Given the suboptimal outcomes of patients followed up as a part of usual care, our study opens up an opportunity to study the outcomes of these high-risk patients in a disease management program. Improved outcomes of heart failure patients followed up in a disease management program would make a strong case for developing such a program in our hospital.

AUTHORS' CONTRIBUTION

SS: Data Collection and data interpretation. MIK: Study Design, Data Analysis, write up. RA: Data collection. FJ: Data collection. ZUK: Data collection. AA: Data collection. MK: Proof reading.

No funding was received for this study

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Submitted: August 1, 2023	*Revised: December 22, 2023*	*Accepted: July 1, 2024*

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ORIGINAL ARTICLE

BASAL CELL CARCINOMA EXCISION INTRAOPERATIVE FROZEN SECTION FOR TUMOUR CLEARANCE RATE AND RECONSTRUCTIVE SURGERY

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Background: Basal cell carcinoma (BCC) is the most common skin cancer. Its annual incidence in US is 2 million per year with an increase of 0.87%. The objective was to report intraoperative frozen section clearance rate of tumour margins and depth for excised basal cell carcinoma in a tertiary care centre and find the frequency of tumour in surgical margins with respect to location, size, and surgical reconstruction technique. **Method:** It was a prospective open-label interventional study conducted at the Dermatology department of tertiary care hospital Rawalpindi (Pakistan) in liaison with the histopathology department from January 2023 to April 2024. The patients with clinical diagnosis of basal cell carcinoma, of 10–35 mm located on the face were included as per inclusion/ exclusion criteria. An intraoperative frozen section for tumour margins and depth was taken from a histopathologist. The surgical defect was reconstructed after the negative report. *p*-value of <0.05 was considered significant for margin involvement, surgical technique, and location. **Results:** A total of 36 patients of BCC were enrolled. Tumour-free margins and depth were attained in 77.77% of cases. Tumour excision with a frozen section concerning surgical technique had a chi-square *p*-value ≤0.51, location ≤0.24, and size ≤0.84. **Conclusion:** Intraoperative frozen section for basal cell carcinoma is a reliable technique for complete tumour excision. This technique is resource-intensive and time-consuming. It should be reserved for tumours at high-risk sites, and require complex reconstruction. Patients should be educated for follow up in case of induration, morphological changes, or new developments in surgical scar.

Keywords: BCC frozen section; BCC face reconstruction technique and tumour free margin; Tumour free margin, BCC excision

Citation: Tahir M, Bashir U, Akhtar A, Javaid S, Ansari Z, Ansari S. Basal cell carcinoma excision intraoperative frozen section for tumour clearance rate and reconstructive surgery. J Ayub Med Coll Abbottabad 2024;36(4):692–7.

DOI: 10.55519/JAMC-04-13800

INTRODUCTION

Basal cell carcinoma (BCC) is the most common skin cancer. The majority of BCC are in Europe, US and Australia. Annual incidence in US is 2 million per year with an increase of 0.87%.[1] In skin of color (SOC) sun exposure causes photodamage, dyschromia and BCC. Photoprotection in SOC is primarily focused on dyschromias and photoaging, with comparatively less emphasis on the prevention of BCC. [2] Women are now affected more than man. The nodular BCC is more common on the head and neck while superficial spreading BCC is on the torso [3]. BCC is the most common skin cancer in Pakistan.[4,5]

National Comprehensive Cancer Network (NCCN) guidelines state low-risk BCC, as nodular, superficial spreading, and primarily located on sites L (trunk and extremities), <20 mm in size, or on sites M (cheeks, forehead, scalp, neck, and pretibial) and <10 mm in size. BCC located on sites L (trunk and extremities) >20 mm or/ and M (cheeks, forehead, scalp, neck, and pretibial) >10 mm in size, H (central face, eyelids, eyebrows, periorbital skin, nose, lips, chin, mandible, preauricular and postauricular skin/ sulci, temple, ear, genitalia, hands and feet), at radiation site, in patients on immunosuppression and with pathologic pattern of morpheaform or basisquamous are as high risk [6]. Mohs micrographic surgery (MMS) or margin control techniques are the gold standard, especially in high-risk BCCs offering maximum cure[7]. The European Dermatology Forum (EDF) guidelines recommend a safety margin of 3mm for an 85% cure rate, whereas NCCN recommends 4 mm for low-risk and 6 mm for high-risk BCC. An elliptical excision with a safety margin of 4 mm of normal skin is often not possible because of cosmetic and functional limitations of the face. A narrow safety margin can be kept for small, well-demarcated pigmented BCC located in more cosmetic and sensitive anatomical sites.[8] However, margin involvement after BCC excision results in recurrence only in a proportion of patients.[9] The excision margin

of 1–5 mm has been described as safe with no statistically significant recurrence.[8] Mohs micrographic surgery (MMS) and tissue processing techniques has subjective variations in approach with the highest cure rates.[10,11] Rehman SH et al in quantitative analyses of skin cancer research in Pakistan reported cancer publications as 2.7 per year. Punjab Cancer Registry (PCR) has reported skin cancer as the 9th, and the Karachi Cancer Registry (KCR)reported it as the 8th common cancer. There is a need for appropriate diagnostic, therapeutic, and prognostic evaluation for skin cancers.[12] The present study aims to report the utility of intraoperative frozen section (FS) histopathological clearance rate for excision of BCC in a tertiary care center and find the frequency of tumours in surgical margin with reference to location, size and reconstruction technique.

MATERIAL AND METHODS

This Prospective study was conducted at a tertiary care hospital of Rawalpindi Pakistan from 1st Jan 2023 till 16th May 2024. The institutional ethical review board approved the study. A sample size of 36 was calculated with a 95% confidence interval, the margin of error 5%, population proportion of 2% with Epi Info sample size calculator.[13,14] Patients with a clinical diagnosis of primary BCC on the head and neck were enrolled in the study by purposive sampling technique after informed consent. Patients with BCC size greater than 35 mm, recurrent lesions, past history of treatment such as cryotherapy, electrocautery, topical 5FU, Imiquimod cream, non-melanoma skin cancer (NMSC) surgery, patients on anticoagulants, and BCC involving eyelids and ears were excluded. All patients underwent SE of BCC with a margin of 2–3 mm under infiltrative local anaesthesia (lignocaine hydrochloride 2% with adrenaline 1 in 80 000) at the Dermatology Department by a consultant Dermatologist. A prior appointment with a histopathologist was made for frozen section (FS) analysis on the telephone. Intraoperative FS consultation for margin and depth clearance by liaison with a histopathologist was again done on the telephone. Margins of the resected lesion were tagged as 6, 9, 12 & 3 'o'clock and sent in normal saline, with documentation of the patient's particulars, site, and morphology of BCC. After the clearance report from the histopathologist surgical defect was reconstructed by primary closure, rotation, or advancement flaps and sec intention under aseptic measures with proline 4/0. Haemostasis was secured. Anti-septic dressing was employed and patients were reviewed on 2nd post-op day. Stitches were removed on the 7th post-operative day. The final histopathology report was re-examined on the 10th day for margin and depth clearance.

Data was analyzed by SPSS 27. Descriptive statistics were calculated for age, gender, reconstructive technique, location, tumour-free margin rate, involved margins, and depth involvement report on frozen section analysis. The chi-square test was employed for statistical significance of the involvement of surgical margin rate concerning location, size, and reconstructive surgical technique, *p* value of <0.05 was considered significant.

RESULTS

A total of 36 patients of BCC were enrolled**,** males 12 (33.3%) and females 24 (66.6%). Age ranged from 45 years to 80 years mean of 58.36±SD 7.8. The size of BCC ranged from 5 mm to 35 mm mean of 25 mm ±SD 0.63. The anatomical location of BCC is shown in table 1. Morphology was as nodular in 18 (50%), superficial spreading in 11 (30.6%), morphoeic in 1 (2.8%), and ulcerative in 6 (16.7%) cases**.** Six patients (16.7%) had hypertension, and 29 (80.6%) had no comorbid. Nine (25%) were graduates, 9 (25%) completed primary school and 18 (50%) secondary school**.** Fourteen (38.9%) had office jobs, and 22 (61.1%) had fieldwork. Two (5.6%) were residents of Gujranwala, 9 (25%) were from Kashmir, 20 (55.6%) Rawalpindi, and 5 (13.9%) were from Muzaffarabad.

Primary closure was performed in 15 (41.7%), advancement flap was performed in 10 (27.8%), rotation flap in 9 (25%), and the surgical defect was left open to heal by secondary intention in 2 (5.6%) cases. The morphology of BCC and tumour-free margin is shown in Figure-1

Excised tumour depth was uninvolved in all cases. There was no statistically significant relationship of tumor margin involvement with its size chi-square *p*-value of 0.84, location chi -square *p*-value of 0.24, and reconstruction technique *p*-value of 0.515.

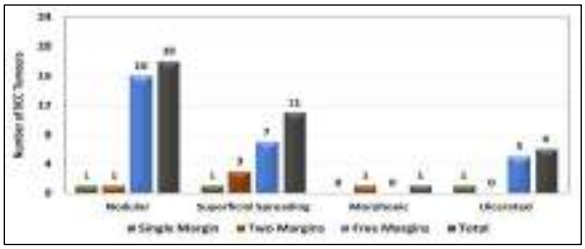

Figure-1: Tumour-free margins rate in various types of BCC

Table 1: Frequency of BCC Locations of Face

Anatomical Location	No (Total: 36)
Forehead	6 (16.7%)
Temple	3 (8.3%)
Nose	9 (25%)
Cheek	14 (38.8%)
Lip	1 (2.7%)
Infraorbital	4 (11.11%)

Table-2: Chi-square *p*-value for intraoperative Frozen section marginal clearance rate and its correlation with location, size, and reconstruction technique.

Parameter	Tumour involvement of margin				
Size (mm)	**All Tumour Margins (n)**	**Single Margin (n)**	**Two Margins (n)**	**Total (n)**	**Chi-square *p*-value**
10	1	0	0	1	0.84
15	3	0	0	3	
20	9	0	1	10	
25	4	1	0	5	
28	1	0	0	1	
30	8	2	3	13	
35	2	0	1	3	
	28	3	5	36	
Location					
Forehead	5	0	1	6	0.24
Temple	1	1	0	2	
Nose	4	1	1	6	
Cheek	14	1	3	18	
Lip	0	0	0	0	
Infraorbital	4	0	0	4	
Reconstruction Technique after the Intraoperative Frozen section for tumour margin clearance rate					
Prim closure	13	0	2	15	0.515
Rotation Flap	5	2	2	9	
Advancement Flap	8	1	1	10	
Healing by secondary intention	2	0	0	2	

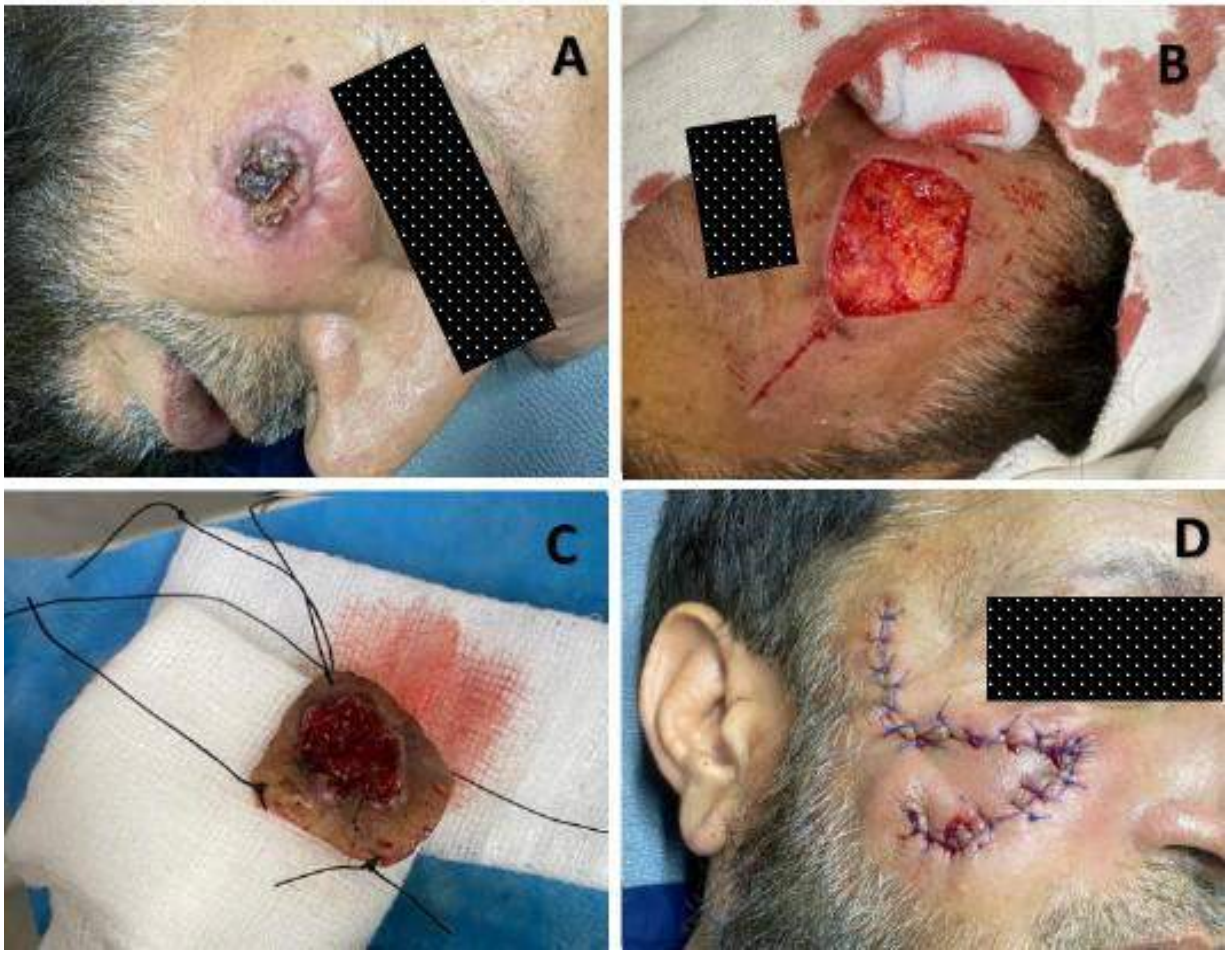

Figure-2: A. Nodulo-ulcerative BCC B. Excised under local anaesthesia C. BCC margins are tagged with threads at 12, 3, 6 and 9 'o' clock position for frozen section clearance D. Surgical defect is reconstructed after FS Histopathology report

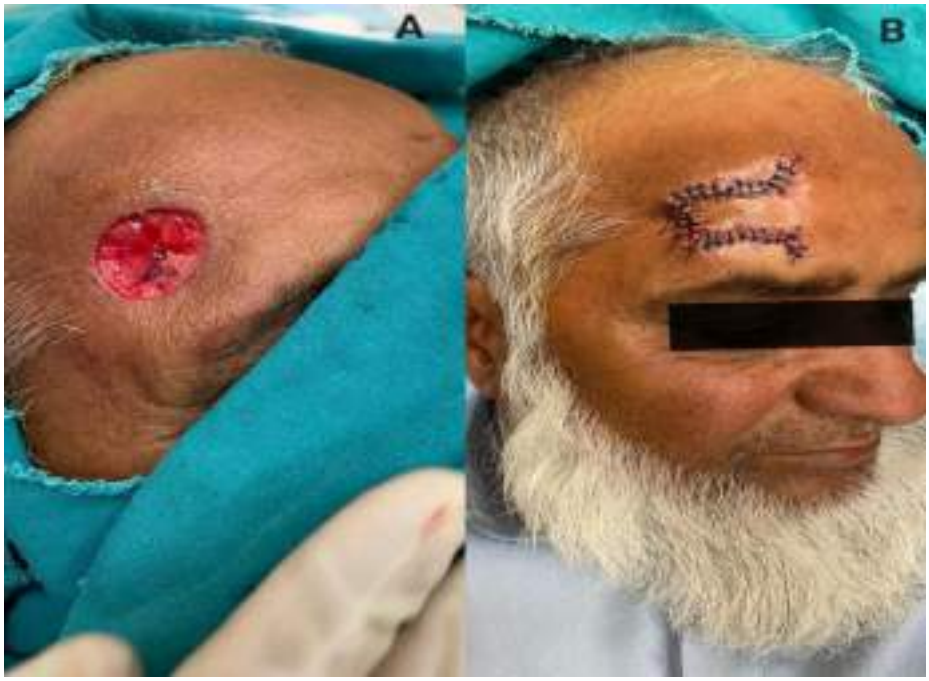

Figure-3: (A) BCC surgical defect (B) Single advancement flap

DISCUSSION

Basal cell carcinoma subclinical extension is observed in high-risk sites, tumour recurrence, size >10 mm, and aggressive subtype. Well-defined BCC may need excision of small margins for clearance but relatively larger margins are required for superficial, micronodular, infiltrative, and morphea form BCC. It is important to classify BCC as low and high risk for management plan.[15] Training in Mohs Micrographic Surgery (MMS) is in demand in Pakistan.[16] Recommended follow-up for primary BCC is 10 Years considering the probability of recurrence in 4.4% after MMS and 12.2% after surgical excision (SE). Recurrence may occur earlier than 5 years, especially for BCC at H sites of the face, positive excision margins in previous resections, or with an aggressive histological growth pattern.[17] SE is the gold standard treatment for BCCs, post-surgical recurrence is seen in 2–8% after 5 years. A safety margin of 2–5 mm and 5–15 mm are recommended for low- and high-risk tumours respectively.[18] BCC was frequent in (53.2%) of males and (46.8%) of females (1.2: 1), the excision margins were reported as clear in 82 (34.9%) cases and involved in 55 (23.4%) cases.[19] Hidayat Ullah *et al* in a descriptive cross-sectional study of 88 cases of low-risk BCC at Hayatabad Peshawar, found a frequency of 63.6% in males and 36.4% in females.[20] In a retrospective study of 382 patients of BCC in Bangladesh there was a preponderance of females (59%), as compared to males 41%.[21] This is in comparison to our study where BCC was frequent in females. This difference is due to women's UV exposure in fields in rural areas of Punjab, UV triggers skin carcinogenesis, and inflammation.[22] Weshah *et al* in a retrospective study of 76 patients in King Hussein Medical Center (KHMC), Jordan found nodulo-ulcerative (42.1%) BCC commonest morphology and nose (46.0%) was the commonest site.[23] Aandani A. *et al*. in the retrospective study reported 53 BCC at the plastic surgery department of Civil Hospital Karachi; the nose (43.40%) was the commonest site and the most frequent clinical type was ulcerative (83.02%).[24] Jaffer N *et al* in a retrospective study of 142 NMSC, at Jinnah Post Graduate Medical Center, Karachi reported nodular variant in 56 (65.1%) cases, as the commonest.[25] This morphological pattern is consistent with our findings. cheek as the commonest anatomical site where as the nose was reported by Afridi RAK *et al* to be the commonest site.[26] Differences in sites may be due to differences in sun exposure of enrolled participants in study.

T Ito *et al*. in an observational study of excision of pigmented BCC 288 at Dermatology Department Kyushu University Japan reported 95.3% clearence with 2-mm margins and 100% with 3 mm margin.[27] Otsuka *et al*. in 542 skin carcinomas in intraoperative 'en face' frozen section analysis found 98% clearance of margins. We reported 77.8% clearance with 2–3 mm margin with FS followed by histopathology report.[28] Baber *et al* in a cross-sectional study of 51 cases found tumour-free margins in 84.3% of cases.[29] Intraoperative FS analysis is an acceptable

alternative to MMS as it allows a comprehensive assessment of all margins.[30]

The inherent limitation of our study was that follow up for tumour recurrence wasn't included in the study. The study findings of margin clearance were based on BCC lesions up to (35 mm) only. Consequently, a prospective multicenter study with a longer follow-up period is necessary to further validate and enhance our research findings. Frozen section histopathology in future may be interpreted with artificial intelligence (AI). The primary benefit of utilizing frozen sections in AI training is that it enhances the diversity of pathology-based AI training sets.

CONCLUSION

Intraoperative frozen section for excision of basal cell carcinoma is a reliable technique as it achieved tumour-free margins in 77.7%cases, with a safety margin of 2–3 mm.

Although this technique is resource-intensive and time-consuming, patients achieve complete excision and better aesthetic outcomes. The frozen section is available in tertiary care hospitals in Pakistan. It is resource-intensive for patients living in remote areas. The frozen section for basal cell carcinoma may be reserved for patients with tumours located at high-risk sites and requiring complex reconstruction after tumour excision. Patients should be educated for follow-up visits for induration, morphological change, or new lesions or developments in previous scar.

ACKNOWLEDGMENT

Authors acknowledge participation of patients, skin trained technicians Mohsin, Emanuel and Ahsan for their unconditional support in the study.

Conflict of interest; None

AUTHORS' CONTRIBUTION

MT: Study design, Conception, Data Collection, Analysis, manuscript writing. UB: Data Collection, Analysis, manuscript editing, intellectual input. AA: Data Collection, Analysis, manuscript editing, intellectual input. SJ: Data Collection. ZA: Zainab Ansari, data collection, manuscript writing, editing, statistical analysis of data. SA: Data collection, Manuscript writing, editing, statistical analysis of data

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Submitted: September 2, 2024	*Revised: October 2, 2024*	*Accepted: November 20, 2024*

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ORIGINAL ARTICLE

AN AUDIT OF OXYGEN PRESCRIBING PRACTICES IN RESPIRATORY WARDS OF A TERTIARY CARE HOSPITAL IN NOTTINGHAMSHIRE, UK

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Background: This audit primarily assesses compliance with the British Thoracic Society guidelines (BTS) for oxygen prescriptions in the Respiratory Department at King's Mill Hospital. The results of this audit aim to guide the strategies to improve the oxygen prescription practices in the Trust. **Methods:** We collected the data on oxygen prescriptions, from the electronic prescribing system, of all the patients admitted in the three respiratory wards of King's Mill Hospital over the period of one week. This data was then recorded and analysed using Audit management and Tracking© (AMAT). **Results:** The overall compliance score to BTS guidelines for oxygen prescription was 12.2%. Out of the 152 patients, only 8 (5%) had oxygen therapy prescribed and a target oxygen saturation range was identified. No patient had an identifiable oxygen delivery method on their prescription. **Conclusion:** The current practices of oxygen prescription at the respiratory department of King's Mill Hospital are suboptimal. These findings highlight the risk of serious potential consequences and the opportunity to implement safe prescribing measures for oxygen, like other prescribed medications.

Keywords: Oxygen inhalation therapies; Respiratory failure; Electronic prescribing

Citation: Ahmed H, Nataraju K, Elmahdy AA. An audit of oxygen prescribing practices in respiratory wards of a tertiary care hospital in Nottinghamshire, UK. J Ayub Med Coll Abbottabad 2024;36(4):698–701.

DOI: 10.55519/JAMC-04-12375

INTRODUCTION

Oxygen is essentially a medicine, used to correct hypoxia. Like other medications, it has a therapeutic range and over/under oxygenation can lead to serious adverse effects.[1] It is well known that low oxygen levels cause tissue hypoxia interfering with all essential physiological processes while higher than necessary oxygen levels, especially in patients with COPD lead to respiratory depression, and causes oxidative stress among other things, all of which increase mortality.[1,2] Systematic review and meta-analysis of randomized controlled trials have shown that liberal oxygen therapy increases mortality in a dose-dependent fashion.[3] For that reason, it must be used with caution and prescribed appropriately. Correct and complete prescriptions ensure that an effective dose/quantity of oxygen is delivered to the patient to obtain the desired physiological effects.

For most of the patients, the recommended target oxygen saturation is 94–98%, except in COPD and other conditions with chronic hypercapnia, where the target is 88–92% to avoid respiratory depression and increased patient mortality.[2] British Thoracic Society (BTS) advises that all admitted patients should have an oxygen prescription, with a clearly outlined saturation goal, and signed, except in emergencies in which oxygen should be given without delay.[4] This ensures that appropriate oxygen levels can be administered if acute hypoxemia develops at any point during the inpatient stay. Despite these guidelines, it is widely recognized that oxygen prescriptions in hospitals are often inadequate.[5] With this audit, we aim to assess compliance with the BTS guidelines for oxygen prescription, in the respiratory wards at King's Mill Hospital (KMH).

MATERIAL AND METHODS

This was an observational, single-centre study. A proposal for conducting this study was discussed with the audit and improvement committee and respiratory audit lead at KMH, where it was approved. Since the study involved collecting anonymized data from electronic prescriptions, a formal institutional review board or ethics committee appraisal was not suggested.

King's Mill Hospital has a total of three respiratory wards. Data was collected over a period of one week from 29/03/2023 to 04/04/2023 for all the patients admitted to these respiratory wards. Consecutive sampling was applied to collect data. The inclusion criteria for the study encompassed all adult patients over the age of 16 admitted to any of the three respiratory wards at KMH during the specified week. This included all inpatients, regardless of whether they required oxygen upon admission, as well as patients receiving non-invasive ventilation. However, the study excluded patients admitted to departments other than the adult respiratory department to maintain focus on this specific population. Additionally, patients on invasive ventilation were not included in the study.

Audit standards were agreed beforehand. (Table-1) This audit mainly focused on whether the oxygen prescription with a target oxygen saturation has been completed or not. We did not investigate if that target was appropriate for the patient. A questionnaire was developed to standardize data collection based on BTS guidelines for oxygen prescription Table-2.

Table-1: Audit standards

Audit standards
A prescription for oxygen should always be provided.
Doctors and other prescribers should prescribe oxygen using a target saturation range and sign the electronic prescribing order.
An oxygen target saturation range should be prescribed for all patients who are admitted to the hospital.
A prescription should also have oxygen flow rate and delivery devices identified.

Table-2: Oxygen prescription questionnaire

Please circle Yes or No for each of the following:
Has oxygen therapy been prescribed?
2. Has the person prescribing signed the prescription?
Has target oxygen saturation been identified?
4. Has the oxygen flow rate and appropriate delivery systems been identified?
5. Has the respiratory model been updated on the nerve centre?

King's Mill Hospital uses Nerve Centre™ electronic prescribing system for all in-patient prescriptions. We examined electronic orders for a valid oxygen prescription for all patients in the respiratory department and checked if it meets all the essential criteria. On day one of data collection, data was collected from all the admitted patients and then newly admitted patients were added each day. In total, data was collected from 152 patients. Nursing and medical teams were not informed of the start date or duration of the audit.

All data was recorded and analyzed using Audit Management and Tracking (AMAT™)

RESULTS

Of the 152 patients in the study, only eight (5%) had oxygen prescribed Figure-1. Thankfully, these prescriptions were electronically signed, which is automatically done by the system based on the details of the logged-in user. The same eight patients had target oxygen saturation identified on the prescription.

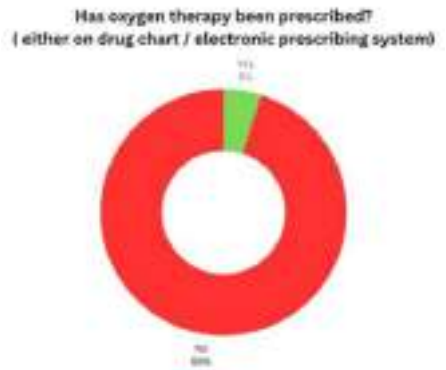

Figure-1: Percentage of patients with oxygen prescription

However, the oxygen flow rate and appropriate delivery system were not identified in any of the cases, which made all the prescriptions inadequate. In King's Mill Hospital's electronic prescribing system, i.e., Nerve Centre™, the section for recording observations has a preset "respiratory model". If this preset is turned on, the system will not trigger an alert to medical staff if oxygen saturation falls between 88–94%. This is quite useful for COPD patients where a lower saturation target is preferred and prevents unnecessary alerts. The respiratory model was turned on for 69 of the 152 patients (45%). This was a secondary observation and isn't necessarily a requirement of BTS guidelines.

The overall compliance score to National British Thoracic Society guidelines (BTS) for oxygen prescription was 12.2% as calculated by AMAT™, a stark divergence from the expected standards. The prescription rate is also much lower than other comparable healthcare systems in the UK.[6]

A summary of the results is as followed Table-3:

Table-3: Results

Question	Choice	Responses	%
Has oxygen therapy been prescribed?	Yes	8/152	5.3%
	No	144/152	94.7%
Has the person prescribing signed the prescription?	Yes	8/152	5.3%
	No	144/152	94.7%
Has target oxygen saturation been identified?	Yes	8/152	5.3%
	No	144/152	94.7%
Has the oxygen flow rate and appropriate delivery systems been identified?	Yes	0/152	0.0%
	No	152/152	100.0%
Has the respiratory model been updated on the nervecentre?	Yes	69/152	45.4%
	No	83/152	54.6%

The results compiled from the data showed that we have failed to meet the standards and criteria being set by the British Thoracic Society by a wide margin leading to a significant portion of patients being potentially exposed to adverse outcomes.

DISCUSSION

British thoracic society is the leading organization working to improve standards of care for people who have respiratory diseases and to support and develop those who provide that care. It routinely publishes evidence-based guidelines including that for supplemental oxygen. Respiratory is a well-established department at King's Mill Hospital, the hospital has embraced a consensus to adhere to the BTS guidelines concerning the delivery of supplemental oxygen, underlining the hospital's dedication to providing the highest level of care to its patients. However, this audit has now shown that compliance remains very poor.

The idea of an oxygen prescription has been introduced in guidelines to highlight the significance of oxygen as a formally prescribed medication.[7] This also aims to highlight like other medications, it has a therapeutic index and potential for adverse effects. The lack of oxygen prescription is a multifaceted issue. At the crux of this issue lies the complexity of oxygen prescription, which junior doctors typically carry out, and in our experience, many of whom are unfortunately unaware of the hospital's policy mandating comprehensive oxygen prescriptions for all patients. This lack of awareness signifies an information gap that, when bridged, can lead to significant improvements in compliance. During our study, we found that none of the patients had a specified flow rate or oxygen delivery devices indicated in their prescriptions. This appears to be an oversight in the electronic prescribing system at KMH, where the option to define a flow rate and oxygen delivery method is missing. Currently, this information is shared verbally between doctors and nurses, increasing the possibility of errors since the number of delivery devices, and the lack of accompanying information with many, make it difficult to choose the correct one.[8] Since the accurate selection of the proper flow rate and device significantly influences patient outcomes, it is crucial that this issue is promptly rectified.[9] This study is a critical call to action, highlighting the urgent need for improved adherence to evidence-based guidelines. To improve oxygen prescribing we are recommending a multidisciplinary approach to educate medical and nursing staff for which different avenues like teaching sessions, posters etc can be explored to re-enforce the oxygen prescription guidelines and to highlight the importance of oxygen toxicity.[10] Ward consultants' enthusiasm to uphold these guidelines is essential. The way the messenger is perceived can impact how well the message or clinical guidelines being conveyed are accepted and adopted by juniors.[11]

Recognizing the pivotal role of technology in contemporary healthcare, we recommend collaboration with the hospital's electronic prescribing leadership. This collaboration aims to integrate reminders into the electronic prescription system, which is known to boost prescription rates and reduce errors through automated prompts.[12] There are also certain areas of limitation within this study. Although the study gives a good snapshot of the rate of oxygen prescriptions, it doesn't investigate if the prescriptions were medically accurate. We didn't assess if the target saturations on the prescription were appropriate given the patients' comorbid like COPD, etc. like we have seen with similar audits.[13] The study also doesn't correlate arterial blood gases with oxygen therapy, which is considered the gold standard to see if a patient has the correct target saturations prescribed.[14] This data was collected only from respiratory wards which is not necessarily reflective of the practices at the entire hospital, although it was assumed that the oxygen prescription rates would be better compared to other wards. Our study was conducted in a district general hospital, which is a smaller setup compared to some tertiary care centres, so should be generalized nationally with caution. A multi-centre study including more hospitals is needed to improve generalizability of current findings. The data collection spanned for one week only and may not capture the practices throughout the year. Potential bias arising from the doctors involved in the study working on those wards during that time period leading to an increase in prescription cannot be ruled out. Our sample size was small and there was no categorization of patients into comorbid subgroups, which helps identify patients more at risk of adverse outcomes. An audit with a much wider scope would be needed before we make any vast generalizations. Additional audits are also warranted to examine any adverse effects stemming from the current poor prescription rate. Following the implementation of our recommendations, a follow-up audit will be conducted to evaluate the effectiveness of our interventions. The recommendations include educational sessions and posters aimed at enhancing prescription standards among medical and nursing staff. Progress will be assessed through regular Plan-Do-Study-Act (PDSA) cycles at King's Mill Hospital, with the expectation that continuous reminders and active measures will lead to sustained improvements in prescription practices. Our study findings will be presented at the hospital's monthly respiratory meeting, attended by all departmental stakeholders. This forum will facilitate the dissemination of best practices for oxygen prescription across all respiratory wards, ensuring that key insights and recommendations are shared widely within the department. We are collaborating with the electronic prescribing team to make oxygen prescription mandatory within the system. This update would prevent users from prescribing other medications unless a valid oxygen prescription is in place. The benefits and potential drawbacks of this approach are currently under discussion.

CONCLUSION

In summary, oxygen serves as a vital therapeutic tool to address hypoxia, functioning similarly to and should be treated like any other drug and prescribed appropriately. The study's findings shed light on the concerning disparity between oxygen prescription practices at King's Mill Hospital and the established British Thoracic Society (BTS) guidelines. Only eight (5%) out of the 152 patients included in the study had an oxygen prescription. This may potentially lead to poorer patient outcomes.

Comprehensive training and strict adherence to these guidelines are pivotal in guaranteeing patient safety within the hospital. This can be achieved through educational sessions aimed at reinforcing the existing guidelines for oxygen prescription and emphasizing the significance of being cautious about oxygen toxicity. Once these suggestions have been put into effect, a subsequent audit will be needed to evaluate whether there has been an enhancement in the quality of prescriptions. A multidisciplinary willingness to improve service provision is essential if we are ever to achieve 100% compliance. It's crucial to bear in mind that oxygen is a critical life-saving intervention, and the potential damage caused by tissue hypoxia far surpasses the risks associated with type 2 respiratory failure. For that reason, refraining from administering oxygen to a hypoxic patient solely due to the absence of a prescription is not advisable.

Conflicts of interest:

All authors have confirmed that there is no conflict of interest.

Research and Publication Ethics:

A proposal for conducting this study was discussed with the audit and improvement committee and respiratory audit lead at King's Mill Hospital, where it was approved. Since the study involved collecting anonymized data from electronic prescriptions, a formal institutional review board or ethics committee appraisal was not suggested. There is no formal approval number given for this study.

Acknowledgements

The authors would like to thank Dr Khaled Amsha (Respiratory Medicine, King's Mill Hospital, Nottinghamshire, GBR) for his supervision during this audit. We would also like to thank Dr Shaheen Shahid (Respiratory Medicine, King's Mill Hospital, Nottinghamshire, GBR) for his valuable insight and guidance.

AUTHORS' CONTRIBUTION

HA: Contributed to this write up, proof reading, data collection and coordinating with other authors. KN: Contributed to literature search and formulating results. AAE and MAC: Contributed to the data collection and discussion section of this publication

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Submitted: August 18, 2023	*Revised: November 2, 2024*	*Accepted: November 4, 2024*

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ORIGINAL ARTICLE

HEPATOPROTECTIVE EFFECT OF MINT AGAINST HEPATOTOXICITY, INDUCED BY CHLOROQUINE, IN MALE ALBINO MICE: RCT

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Background: Many drugs have been associated with hepatotoxicity worldwide. This hepatotoxicity occurs due to oxidative stress generated by those drugs. Hence, different plants, which have antioxidant effects, can be used to prevent hepatotoxicity. The objective was to find out the hepatoprotective effect of mint, against chloroquine induced hepatotoxicity, due to its antioxidant potential. **Methods:** For that randomized controlled trial study, ninety male albino mice were obtained and were divided randomly into three groups, with each group containing 30 mice. Group A was the control group. So, no intervention was done on mice of Group A. Group B and C were the experimental groups. Group B mice were given chloroquine only. The mice of Group C were given both chloroquine and mint extract. The single oral dose of chloroquine, 970 mg/ kg of body weight, was given to the mice of group B, on the 9th day of the experiment. The ethanolic extract of mint, at the dose of 1 gm/kg, was given consecutively from day 1 to day 8 of the experiment to Group C mice. Then chloroquine (970 mg/kg of the body weight) was given on nineth day to Group C. The ethanolic extract was then continuously given from day 10 to day 16 of the experiment, followed by chloroquine administration, to those mice. The blood samples were collected on 17th day by terminal intracardiac sampling technique. Data analysis was done by SPSS version 20. **Results:** Group B mice showed highly significant rise in serum ALP and significant decrease in serum albumin, as compared to those of group A. Serum AST and ALT, however, raised insignificantly. Hence, mild hepatotoxicity was induced in group B mice. On the other hand, malondialdehyde, was found to be highly significantly raised in group B mice. While, serum glutathione peroxidase was found to be declined highly significantly in group B mice, which showed oxidative stress induction. The mice of group C showed highly significant decrease in serum ALP and significant decline in serum AST. They showed significant raise in serum albumin. Serum malondialdehyde, however, declined highly significantly and serum glutathione peroxidase raised highly significantly in group C. These results in group C occur due to antioxidant action of mint. **Conclusion:** Mint revealed hepatoprotective effect due to its antioxidant potential, against chloroquine induced mild hepatotoxicity.

Keywords: Chloroquine; Mint; Hepatotoxicity; Oxidative stress; Hepatoprotective; Antioxidant

Citation: Khalid S, Fazal A, Kanwal S. Hepatoprotective effect of mint against hepatotoxicity, induced by chloroquine, in male albino mice: RCT. J Ayub Med Coll Abbottabad 2024;36(4):702–6.

DOI: 10.55519/JAMC-04-13443

INTRODUCTION

It has been found that about 50% of the cases of liver failure in the world, occur due to hepatotoxicity, induced by drugs.[1] Drug induced hepatotoxicity is one of the most common causes of liver failure.[2] Those drugs caused hepatotoxicity due to the induction of oxidative stress in the subjects.[3]

In oxidative stress induction, various free radicals are generated, which can attack the lipids of the membranes.[4] As a result of this attack, various secondary metabolites are formed. Malondialdehyde is one the secondarily metabolites, which is formed during lipid peroxidation process.[5] So, the increased levels of malondialdehyde are indicative of oxidative stress induction.[6] When this damage occurs in the liver cells, various enzymes, which are present inside the hepatic cells such as ALP, AST and ALT are released into the blood.[7] Raised levels of liver enzymes in the blood indicate hepatotoxicity.[8] Due to this damage, the function of the liver, such as formation of proteins, is comprised. Hence, the level of albumin is declined in hepatotoxicity.[9]

A study conducted by Edeordo Gianini *et al*, (2005) revealed that the magnitude of changes in the ALT and AST can be classified into three types i.e. mild, moderate and marked changes. Mild alteration indicates that ALT and AST changes are less than five times the upper limit of normal. Moderate alteration

means changes in the level of ALT and AST are between five to ten times the upper limit of normal. And marked changes are labelled when alteration occurs more than the ten times of the upper limit of normal. Acute liver injury is labelled when alteration of ALT and AST occurs more than the ten times of the upper limit of normal.

It has been studied previously that chloroquine, when given at the dose higher than the therapeutic dose (<2gm), can induce hepatotoxicity.[10] This hepatotoxicity occurs due to oxidative stress induction.

There are various antioxidants, enzymatic and non- enzymatic, which are produced in our bodies.[11] These antioxidants scavange free radicals, that are generated during lipid peroxidation process. They have the ability to lose electrons due to which they are able to stop free radical chain reactions. The phenolic acids inhibit the conversion of Fe^{+3} into Fe^{+2}. Hence, they end non-enzymatic lipid peroxidation process. Antioxidants balance the increased formation of free radicals.[12] Due to the excessive utilization of antioxidants, their levels are declined in the body.[13]

Worldwide, a lot of research is going on to find such herbs and plants, which contain antioxidants.[14] For that purpose, mint (mentha) is being widely studied.[15] Mint (mentha) contains abundant number of antioxidants.[16] Flavonoids and polyphenols are the two important antioxidants, which are present in the mint. These antioxidants have the ability to make further new antioxidants and even, they can activate the existing antioxidants.[17] They can scavenge free radicals generated in lipid peroxidation process. [18] Due to their antioxidant potential, they can be used for prevention of hepatotoxicity.

About 20 different species of mentha has been discovered so far in the world.[19] Various species of mentha have been found widely in Pakistan. Mentha arvensis is one of them, which has been used in the current study.[20] So, the current study has been conducted to determine antioxidant and hepatoprotective potential of mentha arvensis. Mentha arvensis can be used for therapeutic purposes against hepatotoxicity induced by different drugs.

MATERIAL AND METHODS

For this randomized controlled study, ninety male albino mice were included. Those mice were bought from University of Veterinary and Animal Sciences, Lahore. The selection of Mice for the study was done by non- probability consecutive sampling method. Those 90 mice were divided into three groups of 30 each. Group A was selected as control, in which no intervention was done. The mice of group B were given chloroquine orally only, at the dose of 970 mg/kg of body weight on the 9th day of the experiment. The mice of Group C were given both chloroquine and mint. The ethanolic extract of the mint, at the dose of 1 gm/kg of the body, was given from day 1 of experiment to day 8 of experiment. Then, on nineth day of the experiment, the chloroquine, at the dose of 970 mg/kg of body weight was given. The ethanolic extract of mint was continued to be given to the mice of that group from day 10 to day 16 of the experiment, followed by chloroquine. Blood samples of the mice were collected on the 17th day of experiment by terminal intracardiac sampling technique. Data analysis was done by SPSS version 20.

RESULTS

The mean values of ALT, AST, ALP, albumin, total proteins, malondialdehyde and glutathione peroxidase, in controlled group A mice, are 9.73±4.35, 57.20±22.50, 106.47±10.87, 2.70±0.75, 6.21±1.79, 0.12±0.37 and 1.03±0.13 respectively.

One way ANOVA was applied to compare the mean values of those three groups. One way ANOVA showed that the difference of serum ALP was highly significant (p=0.000) among all the three groups. While significant difference (p=0.05) was found in the mean values of serum AST and albumin. However, serum ALT and total proteins depicted no significant difference (p>0.05) among the three groups (Table 1).

While table 2 shows highly significant (p=0.000) difference in the mean values of serum malondialdehyde and serum glutathione peroxidase among all the three groups, when one way ANOVA was applied.

Post hoc Tukey's test was then applied to compare significant results of the two groups. Post hoc Tukey's test depicts that when results were compared between group B, in which hepatotoxicity was induced by chloroquine with group A, in which no intervention was done, they showed highly significant (p<0.000) rise in the mean value of serum ALP (234.77±100.14) in group B as compared to that in group A (106.47±10.87. While significant (p=0.05) decline in serum level of albumin (2.30±0.28) observed in group B as compared to that in group A (2.70±0.75). But, serum AST level (61.13±14.10) did not rise significantly (p>0.05) in group B as compared to that in group A (57.20±22.50).

Table 4, however, revealed that serum level of malondialdehyde (0.22±0.12) rose highly significantly (p<0.000) in group B as compared to that in group A (0.12±0.037). While, serum glutathione peroxidase level declined highly significantly (p<0.000) in group B than in group A (0.12±0.037).

Similarly, results of group C, in which mint along with chloroquine was given, were compared by Post hoc Tukey's test with those of group B, in which only choroquine was administered. The comparison

revealed highly significant (p<0.000) decline in the value of ALP (104.57±20.34) in group C as compared to that in group B (234.77±100.14). Serum level of AST (43.63±25.74) declined significantly (p=0.05) in group C as compared to that in group B (61.13±14.10). Serum level of albumin (2.65±0.39) raised significantly (p=0.05) in group C as compared to that in group B (2.30±0.28).

Table-4, showed highly significant (p<0.000) fall in the serum level of malondialdehyde (0.18±0.05) in group C as compared to that in group B (0.79±0.12). While, serum glutathione peroxidase level (0.94±0.17) rose highly significantly (p<0.000) in group C than that in group B (0.79±0.12).

Table-1: Comparison of serum ALP AST, ALT, albumin and total proteins among groups A, B and C by one way ANOVA test. Values are given out here as mean±SD

Values are given out here as mean±SD Parameters	Group A (n= 30)	Group B (n=30)	Group C (n=30)	*p*-value
ALT (U/L)	9.73±4.35	11.47±5.96	10.00±2 63	0.285
AST (U/L)	57.20±22.50	61.13±14. 20	43.63±25.74	0.005
ALP (U/L)	106.47±10.87	234.77±100.14	104.57±20.34	0.000*
Albumin (g/dl)	2.70±0.75	2.30±0.28	2.65±0.39	0.007
Total proteins (g/dl)	6.21±1.79	6.10±0.37	6.41±0.37	0.530

Values are given out here as mean±SD, *p<0.001= highly significant

Table-2: Comparison of serum malondialdehyde and glutathione peroxidase among groups A, B and C by one way ANOVA test. Values are given out here as mean±SD

Parameters	Group A	Group B	Group C	*p*-value
Serum malondialdehyde (ng/ml)	0.12±0.37	0.22±0.12	0.18±0.05	0.000*
Serum glutathione peroxidase (ng/dl)	1.03±0.13	0.79±0.12	0.94±0.17	0.000*

Values are given out here as mean±SD, *p<0.001= highly significant

Table-3: Comparison of serum ALP, AST, ALT, albumin and total proteins among groups A, B and C by Post hoc Tuckey's test. Values are given out here as mean ± SD

Group comparisons	AST(U/L)	ALP (U/L)	Albumin (g/dl)
Between group B and A	0.756	0.000*	0.10
Between group C and B	0.006	0.000¨	0.27

Values are given out here as mean±SD, *p<0.001= highly significant

Table-4: Comparison of serum malondialdehyde and glutathione peroxidase among groups A, B and C by Post hoc Tukey's test. Values are given out here as mean ± SD

Group comparisons	Serum malondialdehyde (ng/ml)	Serum glutathione peroxidase (ng/dl)
Group B and A	0.000*	0.000*
Group C and B	0.000*	0.000*

Values are given out here as mean±SD, *p<0.001= highly significant

DISCUSSION

The above data suggest that hepatotoxicity induced in the present study was mild in nature. So, in the present study minor elevation of ALT and AST indicate mild damage of hepatocytes. While, for declaring acute liver injury, marked elevation of ALT and AST was required.

Raised in the levels of serum alanine aminotransferase and aspartate aminotransferase was found due to their release into the circulation, after the damage of the hepatocytes. Lipid peroxidation caused the cell membrane to lose its integrity. ALT and AST, which were present in the cytoplasm of hepatocytes, released into the circulation. The magnitude of elevation of serum ALT and AST was directly correlated to the number of the hepatocytes that were damaged.

Alkaline phosphatase was present in the cytoplasm of canalicular or biliary cells. So, when damage occurred to cell membrane due to lipid peroxidation, ALP was released into the circulation. In the present study, highly significant elevation of serum ALP indicates damage to biliary cells.

Most of the plasma proteins are formed by the liver, including albumin. Albumin makes up the major bulk of plasma proteins. About 60% of plasma proteins are albumin.[21] In the present study, damage to hepatocytes resulted in reduced synthesis of total proteins and albumin. Serum albumin depicted highly significant decline but the total proteins did not decline significantly in group B when results were compared with those of control group (group A).

These results are contradictory to those obtained by Pari L *et al*, (2005), who had used the same dose of chloroquine, i.e., 970 mg/kg in female wister rats. Significant elevation of ALT, AST and ALP was noticed in their study. Chloroquine caused damage to hepatocytes. As a result, enzymes were released into

the circulation. But, compared to that study, mild hepatotoxicity has been induced in the current study with the use of same dose of chloroquine, i.e., 970 mg/kg. Which shows that higher doses of chloroquine must be tested to induce hepatotoxicity in mice.

When the results of serum malondialdehyde and glutathione peroxidase were compared between group A and group B, highly significant elevation in the level of serum malondialdehyde observed in group B as compared to those in group A. While, highly significant decline in the level of glutathione peroxidase was observed in group B as compared to that in group A. Highly significant elevation of malondialdehyde indicates lipid peroxidation, as malondialdehyde is one of the secondary metabolites of lipid peroxidation. Hence, it indicates the induction of oxidative stress by chloroquine. The large number of free radicals, generated in lipid peroxidation process, were scavenged by glutathione peroxidase. Hence, due to excessive utilization of glutathione peroxidase for scavenging purpose, its serum level declined. These results are consistent with those determined by Pari, (2005). They had used chloroquine to induce hepatotoxicity in female wister rats. Single oral dose of 970mg/kg of chloroquine was used. They observed significant elevation of hydroperoxides and thiobarbituric acid reactive substances. On the other hand, reduced serum level of glutathione peroxidase indicated its utilization in scavenging the free radicals which were generated in lipid peroxidation process.

The ethanolic extract of mentha arvensis was used in the current study because the previous studies had revealed that ethanolic extract exhibited most significant hepatoprotective and antioxidant effects due to the greatest concentration of antioxidants, i.e., flavonoids and phenolic acids, present in the ethanolic extract. In the current study, when the results were compared between group C (mint and chloroquine) and group B (chloroquine only), significant reduction of AST (43.63±25.74) and highly significant reduction of ALP (104.57±20.34) occurred in group C (mint+chloroquine). Serum albumin levels were raised (2.65±0.39) significantly in group C. These findings suggest that ethanolic extract of mint (mentha) possess hepatoprotective effect. This hepatoprotective effect seems to be due to the antioxidant effects.

When the serum levels of malondialdehyde and glutathione peroxidase were compared between group C and group B, highly significant decline in malondialdehyde (0.18±0.05) and highly significant elevation of glutathione peroxidase (0.94±0.17) was observed in group C as compared to that in group B. Reduction of serum levels of malondialdehyde, which is a secondary metabolite of lipid peroxidation process, indicates decline in lipid peroxidation process by the ethanolic extract of mint. While the increased serum level of glutathione peroxidase, which had declined in group B due to its utilization in scavenging the increase number of free radicals, indicated that antioxidants in the ethanolic extract of mint had also increased their formation and activity. Hence, these findings indicate that mint (mentha) possessed antioxidant effects, which is responsible for its hepatoprotective effect.

These findings are comparable with the findings obtained by Patil *et al*, (2012). They studied the hepatoprotective effect of mint (mentha). For which, they induced hepatotoxicity by administering CCl4. ALT, AST and ALP levels were raised. They used three different extracts i.e. aqueous, methanolic and ethanolic extracts. Pretreatment with ethanolic extract showed most significant decrease in serum ALT, AST and ALP levels. They depicted that hepatoprotective effect was most likely due to the presence of antioxidants such as flavonoids.

Dar *et al*, (2014) revealed the antioxidant role of mentha arvensis. Their results showed that antioxidants, such as phenolic acids, possessed hydroxyl group, due to which they were able to scavenge free radicals. The antioxidants also inhibited non-enzymatic lipid peroxidation process by converting Fe^{+3} into $Fe^{+2.}$

Similar findings were obtained by Wani *et al*, (2018). Their results also showed that ethanolic extract of mentha arvensis possessed highest concentration of flavonoids and phenolic acids.

Polyphenols in mentha arvensis, have been found to possess various antioxidant roles. They inhibit lipid peroxidation by iron chelation. They inhibit enzymes, NADPH oxidase and xanthine oxidase, which are involved in generation of reactive oxygen species. They suppress formation of malondialdehyde by inhibiting cyclooxygenase and lipoxygenase. They also increase the formation of antioxidant enzymes.

CONCLUSION

Ethanolic extract of the mint has hepatoprotective effect due to its antioxidant potential against chloroquine induced hepatotoxicity in mice.

AUTHORS' CONTRIBUTION

SK: Literature search, conceptualization of study design, data collection, data analysis, data interpretation, write-up, proof reading. AF: Data collection, data analysis, dta interpretation. SK: Write-up

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Submitted: May 31, 2024	*Revised: November 15, 2024*	*Accepted: November 18, 2024*

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ORIGINAL ARTICLE

SIMPLE MICRONEEDLING VERSUS MICRONEEDLING WITH TOPICAL INSULIN IN THE TREATMENT OF POST ACNE ATROPHIC SCARS; A SPLIT FACE COMPARATIVE STUDY

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Background: Acne vulgaris is a common skin condition, involving upto 90% of the teenage population, being more common in women than in men. Post acne scars are the sequelae, leading to low esteem and self confidence in the affected individuals. **Methods:** Thirty patients participated in the study. On each patient, over the left side of the face, microneedling was done using topical insulin as a medium, while on the right side of the face, simple microneedling was done. Four such sessions, a month apart, were done in all the patients. They were called for follow up and the response was based on the "Acne scar assessment scale", in which Grade-0 referred to no improvement, Grade-1 referred to an improvement of less than 25%, Grade-2 was an improvement between 25–50%, Grade-3 meant an improvement between 50–75%, and, Grade-4 referred to an improvement of greater than 75%. **Results:** After completion of the sessions, over the left side of the face, where microneedling was done with insulin 11 (36.7%) patients showed Grade-2 improvement, while 19 (63.3%) patients showed Grade-3 improvement. On the right side of the face where simple microneedling was done, 10 (33.3%) patients showed an improvement of Grade-0, and 20 (66.6%) patients showed an improvement of Grade-1. **Conclusion:** After this study, we conclude that microneedling combined with topical insulin, shows better results in patients with scarring. It can be a breakthrough in the treatment of post acne scars, due to easier availability and lesser cost of insulin.

Keywords: Acne vulgaris; Post acne scars; Insulin; Microneedling; Adolescence

Citation: Ali M, Ahmed N, Khan S, Kiran A. Simple microneedling versus microneedling with topical insulin in the treatment of post acne atrophic scars; a split face comparative study. J Ayub Med Coll Abbottabad 2024;36(4):707–10.

DOI: 10.55519/JAMC-04-12893

INTRODUCTION

Acne vulgaris is a common skin condition of adolescence, involving almost 90% of the teenage population, globally[1,2], persisting into adulthood in 12–14% of the people affected[3]. It is more common among women than in men.[4] 50–60% of the women are aged between 20–25 years, and 12% are above 25 years of age.[5] It is caused by the inflammation, alteration of keratinization and bacterial invasion by the “Propionebacterium acne”, of the pilosebaceous glands, which is secondary to the increase in androgen production during the pubertal stage.[6,7]

There are multiple factors associated with the development of acne, like smoking, mental stress and dietary habits, including the intake of food which is high in calories and is spicy.[8,9] Avoidance of any of these factors has an important role in the improvement and prevention of the skin condition. Psychological impact of acne is a common phenomenon that has been reported worldwide, as the teenagers affected have a feeling of low esteem and confidence, as compared to their fellow students or colleagues.[10,11]

Post acne atrophic scars are a frequent and bothersome consequence, and can be present in around 20% of the population affected with acne.[12] Scarring that occurs after acne vulgaris, is usually a sequelae to the healing process. It is either caused by a loss of collagen, leading to "Atrophic scars", which is the cause in most of the patients, or by the gain of collagen, and reduced activity of the collagenases, producing "Hypertrophic" and "Keloidal scars".

Atrophic scars are the most common types, and are further divided into the following types: a. Ice pack scars; comprising 60–70% of the scars, are punctiform, with an opening of less than 2 mm and form a typical 'V' shaped infundibulum. b. Boxcar scars; are the second common type, occurring in 20–40% of the patients with scars, they are well, circumscribed, round to oval in shape with a size of 4mm. c. Rolling scars; are the least common type consisting 15–25% of the scars, they have the widest diameter of about 5mm. These scars have an undulating surface as they tie up the dermis to the subcutis. Hypertrophic scars appear as heaved up, solidified and raised scars within the boundary of the injury site and are pinkish in colour.

Keloidal scars are purplish to reddish in colour and extend beyond the borders of the site of the original injury, occurring more commonly over the back.

Most of the patients have all the types of scars concurring at the same time. Many treatment options are available to treat atrophic acne scars, including dermabrasions, fillers, lasers and microneedling.[13,14] Among all of these treatment modalities available, microneedling has given encouraging outcomes, and is usually combined with PRP for better results[15], but having said that, it makes the procedure, overpriced and less readily available. Insulin is known to have a role in wound healing as it has angiogenic, re epithelizing and collagen forming properties with directly producing VGEF and TGEF1 factors.[16] Insulin acts by migrating vascular endothelial cells and keratinocytes towards the wound site, thus, improving formation of new vessels and epithelialization. There are insulin receptor substrates that act as signalling molecules and direct insulin toward the wound. Insulin resistance is one factor, that produces hindrance in the healing process, but, even in such patients, topical application of insulin has shown its response. This factor does not exist in our study and will not be limiting for us, because we have excluded diabetic individuals from our criteria. Unfortunately, not much work has been done in this regard, and the role of insulin in wound healing remains to be an unfolded chapter in the field of medicine, and needs to be widely explored. This became the basis of our work, and we aimed to compare the treatment efficacy of simple microneedling, with that of microneedling done in combination with topical insulin as a medium.

MATERIAL AND METHODS

This split face, comparative study was conducted for a period of six months from April to September 2023, at the dermatology department of PNS Shifa hospital, Karachi, after approval from the local ethical review committee (ERC/2022/DERMA/13) given on 27th April 2023. A total number of thirty patients with post acne atrophic scars were included in this study.The sample size was calculated using OpenEpi, Version 3, open source calculator—SSCohort[1], with 95% confidence interval. The participants who were included in the study were aged more than 18 years and less than 60 years, having a Fitzpatrick skin type ranging from IV-VI. Patients with active nodular or pustular acne lesions, with diabetes mellitus, bleeding disorders, pregnant females and breastfeeding mothers were excluded from the study.

A comparative, split face study was conducted, in which the left side of the face was treated with micro needling done along with regular insulin, used topically as a medium, while the right side was treated with simple micro needling.

All the treatment was done after taking written informed consent from all the patients. Under all aseptic measures, the face was cleaned with gauze piece, which was made wet with sterile saline. Local anaesthesia was applied to numb the face and micro-needling were done using a derma pen tipped with 36 disposable needles (Dr Pen). The protrusion length of the needle was adjusted to 2 mm, till pinpoint bleeds appeared on the face. To prevent any blood crusting on the face, it was being wiped with sterile saline during the procedure. On the left side of the face topical insulin (Human actrapid 40IU/ml) was used as a medium, while on the right side no medium was used, during the procedure. The face was again cleaned after the procedure. Pre and post procedure blood sugar levels were checked in all the patients. Four such sessions were done in all the patients, with every session a month apart, and they were called for follow up one month after all four sessions. They were advised to take preventive measures against the sunlight, and fusidic acid was advised for local application twice daily for five days after the procedure. The minimum sample size (n=30) necessary to conduct a study was recruited in this research.[17]

The assessment of effectiveness was done according to the "Acne scars assessment scale", where Grade 0 showed no improvement, Grade 1 represented an improvement of less than 25%, Grade 2 referred to an improvement of 25–50%, Grade 3 was an improvement of 50–75%, and Grade 4 showed an improvement of greater than75%. Pictures were taken, before the commencement and after the completion of the sessions.

RESULTS

A total number of 30 patients participated in the study, 12 (40%) patients were males and 18 (60%) patients were females. The demographic details are given below. The scars present in our patients were of the atrophic type. Eighteen (60%) patients had icepack scars, 6 (20.0%) patients had boxcar scars, while 4 (13.4%) patients had rolling scars, and 2 (6.6%) patients had mixed type of scars. It is represented in the table below.

Mean duration of acne scars in all our patients was 2.03±2.02 years. At the end of treatment sessions, they were graded based on Acne Scars Assessment Scale. After four sessions of treatment, the left side of the face which was treated with microneedling combined with insulin as a topical medium, 11 (36.7%) patients reported Grade II improvement (25–50%), and the remaining 19 (63.3%) patients reported Grade III improvement (50-75%) (Figure-1). On the right side where simple microneedling was done, 20 (66.7%) patients reported no improvement (Grade 0) and 10 (33.3%) reported an improvement of less than 25% (Grade 1). The extent of improvement in acne scars was compared for microneedling combined with topical insulin on the left side of the face, to that with simple microneedling done on the right side of the face, as shown with detail in table 3.

Table-1: Demographic profile of study participants (n=30)

Demographic variables		Frequency (%)
Gender	Male	12 (40)
	Female	18 (60)
Marital status	Married	22 (73.3)
	Unmarried	8 (26.7)
Age (mean ± SD) in years		29.47±8.36

Table-2: Frequency of different scar types present in our patients.

Type of acne lesion	Frequency (%)
1. Ice pick scars	18 (60)
2.Boxcar scars	6 (20.0)
3.Rolling	4 (13.4)
4.Mixed	2 (6.6)

Table-3: Extent of improvement in acne scars with microneedling done alone vs microneedling done with topical regular insulin.

Graded improvement	Mirco-needling with insulin, n (%)	Simple microneedling, n (%)	*p*-value
Grade 0	0	10 (33.3)	0.000
Grade I	0	20 (66.7)	
Grade II	11 (36.7)		
Grade III	19 (63.3)		
Grade IV	0	0	

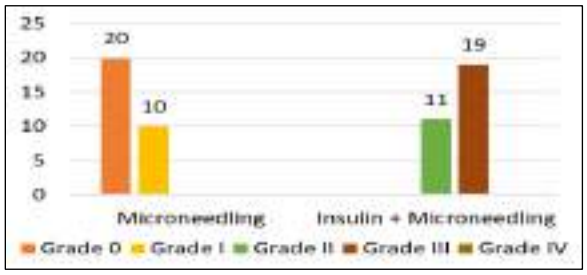

Figure I: Graded improvement in two study groups (microneedling alone vs microneedling done with topical insulin) after four sessions of treatment.

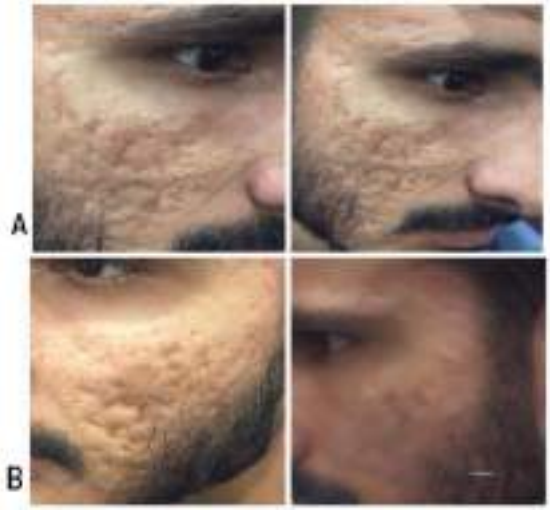

Figure-2. A: Before and after treatment with simple microneedling. B: Before and after treatment with microneedling along with topical insulin

DISCUSSION

Microneedling is a safe and an effective method of treatment in patients with scarring secondary to acne vulgaris. It promotes neo-collagenesis, leading to skin healing and repair, as stated by Farrukh *et al*[13], who conducted his study on 50 patients with acne scars, treated them with microneedling and did the same number of sessions as ours, after which he reported improvement by two grades in 36 (73%) patients. We have used topical insulin as a medium in our study on one side of the face. Insulin known to promote healing in wounds and scars by neo-vascularzation, endothelial proliferation and formation of granulation tissue, with faster epithelization rates, attributed to IGF-1. Among the 30 patients who participated in our study, out of which 18 (60%) they were females and 12 (40%) were males, with a mean duration of scars of 2 years. These patients had three types of atrophic scars, with icepick scars in 18 (60%),boxcar scars in 6 (20.0%), rolling scars in 4(13.4%) and mixed type of scars in 2 (6.6%) patients, also reported by Goodrazi *et al.*[19] According to our work, on the left side of the face , where topical insulin was used as an adjuvant, improvement of grade II was observed in 11 (36.7%) patients and an improvement of grade III in 18 (63.3%) patients, which is much higher than Pawar and Singh *et al*[20] who reported that 45% of their patients showed a positive response, which is quite less than our result and this difference, might be attributed to the fact that the above mentioned study had a smaller sample size and, short termed follow ups, moreover, abbas *et al*[21] reported significant improvement ranging from grade 2 to grade 4 in 16 (53.3%) patients which is closer to our result.

The right side of the face showed no improvement in 10 (33.3%) patients, and, grade I improvement in 20 (66.7%), this is much similar to Dogra *et al*[22], who stated that improvement was seen in 22 (73%) patients, quite similar to what we achieved after our study, also, Rasheed *et al*[23] stated that most of the patients in his study reported satisfactory results with microneedling, and this better efficacy might be because he compared microneedling with glycolic acid peels. About adverse effects, only one of our patients reported erythema, that remained for about a week, but settled after that, and the next session was done more gently, considering the sensitivity of the skin of the patient and, hence did not occur in the subsequent sessions. One of our patients reported pain, but that was mild, and was reduced after longer duration of application of the topical anaesthesia. These adverse effects were also reported by abbas *et al*, but the frequency in our study was much lesser. Our patients were asked about the level of satisfaction they

had and majority of them were joyous to see the results after four sessions.

CONCLUSION

After our study, it is clearly evident that microneedling when done with topical insulin as an adjunct, showed significant and superior results than simple microneedling, leading to better healing of the scars and satisfaction among the patients. Insulin, being cost-effective and easily available can bring a breakthrough in the treatment of these scars, as everyone will have an easy access, in contrast to other modalities that are expensive and not frequently available.

Much work is hereby needed in this regard to increase the authenticity of this treatment modality, especially in diabetic patients, as they might get more beneficial results, but their blood sugar levels, need to be taken into consideration and monitoring.

AUTHORS' CONTRIBUTION

MA: Literature search, conceptualization of study design, data collection, data analysis and interpretation, article writing. NA: Literature search, conceptualization of study design, data collection, data analysis and interpretation, proof reading. SK: Literature search, conceptualization of study design, data collection, data analysis and interpretation, proof reading.

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Submitted: January 27, 2024	*Revised: October 6, 2024*	*Accepted: October 15, 2024*

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ORIGINAL ARTICLE

EVALUATING THE ACCURACY OF THE NEUTROPHIL-TO-LYMPHOCYTE RATIO IN DIAGNOSING ACUTE APPENDICITIS

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Background: Acute Appendicitis, a surgical emergency, is one of the most common causes of acute abdomen. Its' immediate diagnosis and surgery are of immense significance for the disease itself and its surgery carries a potential risk of morbidity and mortality. The goal of this study was to find out the role of Neutrophils to Lymphocyte Ratio (NLR) in making a confident diagnosis of acute appendicitis in a facility limited setup. **Methods:** It is a cross-sectional validation study on 100 patients admitted to the surgical wards of Ayub Teaching Hospital Abbottabad, with suspicion of Acute Appendicitis (AA), who subsequently underwent open appendectomy. Data were collected regarding the demography (name, age, gender) of the patient, physical examination, clinical presentations, and investigations including the complete blood count, from which the NLR value was calculated. Data was also collected regarding the histopathology examination of the appendix. **Results:** The sensitivity was 70.65% while the specificity was 87.5% and accuracy was 72%. Positive Predictive Value (PPV) was 98.4% and NPV was 20.6%. **Conclusion:** There is a strong correlation between NLR value and Acute Appendicitis. According to the results of our study, NLR $\geq$ 2.5 seems to be a reliable parameter to obtain a more certain diagnosis of Acute Appendicitis.

Keywords: Neutrophils to lymphocytes ratio; Acute Appendicitis; Alvarado score; Validity parameters

Citation: Rashid MA, Javed H, Muhammad F, Asad F, Dawood D, Jadoon E, *et al.* Evaluating the accuracy of the neutrophil-to-lymphocyte ratio in diagnosing acute appendicitis. J Ayub Med Coll Abbottabad 2024;36(4):711–15.

DOI: 10.55519/JAMC-04-10763

INTRODUCTION

Acute appendicitis is the most common cause of acute abdomen and a surgical emergency. The diagnosis of Acute Appendicitis poses a significant challenge for surgeons due to the overlapping signs and symptoms with other causes of acute abdomen[1]. Delay in diagnosing and treating AA can result in complications, occurring in 28–29% of cases, such as abscess formation, appendiceal perforation, systemic septic complications, wound infections, adhesions, bowel obstruction, and pulmonary issues from general anaesthesia.[2] Appendectomy accounts for approximately 10% of all abdominal surgeries worldwide, with a mortality rate ranging from 0.1–5.1%.[1,3] Therefore, prompt diagnosis and surgery for AA are of critical importance.

Obstruction of the appendicular lumen, regardless of its cause, leads to polymorphous leukocyte infiltration of the muscularis mucosae, accompanied by oedema and separation of the muscle fibres in the muscularis externa. This is the widely accepted pathogenesis of acute appendicitis.[4] Inflammation of the surrounding peritoneum results in pain in the right lower quadrant of the abdomen.[5] The systemic inflammatory response triggers neutrophilia and lymphocytopenia, which in turn increases the neutrophil-to-lymphocyte ratio (NLR) — a known marker of inflammation in various acute inflammatory conditions.[5,6]

The diagnosis of acute appendicitis (AA) is primarily based on patient's history and clinical examination, supplemented by investigations such as complete blood count (CBC), abdominal ultrasound (USG), and computed tomography (CT) scans.[6–8] A study in the UK found that the diagnostic certainty using the Alvarado scoring system ranged from 70–80%, though the diagnosis of AA remained uncertain in approximately 30–40% of cases.[9] Conditions that are commonly misdiagnosed as acute appendicitis due to the overlap of signs and symptoms with other gastrointestinal and genitourinary disorders include mesenteric lymphadenitis, constipation, gastroenteritis, obstructive hernia, orchitis, urinary tract infections, and gynaecological conditions such as ovarian cysts and pelvic inflammatory disease.[10] Prospective studies suggest that the Alvarado scoring system alone is insufficient for an accurate diagnosis of acute appendicitis, as it may lead to both false positive and false negative results.[11]

A systematic review and meta-analysis examining the diagnostic accuracy of procalcitonin, C-reactive protein (CRP), and white blood cell (WBC) count for suspected acute appendicitis found that the

diagnostic value of these variables is limited.[12] Diagnostic tools such as CT scans and ultrasounds are both expensive and often unavailable in peripheral healthcare settings, where the diagnosis of acute appendicitis is primarily based on clinical evaluation in conjunction with baseline investigations.[6] Therefore, there is a strong need for the development of new biological markers to improve clinical decision-making. In a review of randomized trials, Maximos Frountzas *et al*. recommended the use of the Alvarado and RIPASA scoring systems, with supplementary tools necessary for confident diagnosis, particularly in hospitals in developing countries and rural areas.[13] This study aims to assess the diagnostic accuracy of the neutrophil-to-lymphocyte ratio (NLR) as a biological marker for acute appendicitis.

The results will help in adopting a proper and easy test in the diagnosis of the condition. It will be useful for future researchers as a catalyst. Further research in different setup may consolidate the validity of the test.

MATERIAL AND METHODS

This cross-sectional validation study was conducted on patients suspected of having Acute Appendicitis in surgical wards of Ayub Teaching Hospital Abbottabad from January to 15th April 2019. All consecutive patients during the period of data collection as per sample selection criteria were included. After informed consent, 100 patients were included while 9 patients were excluded (two pregnant ladies, 7 conservatively managed patients). Data were collected regarding the socio-demography of the patients and detailed history by interviewing them, and thorough clinical examination. Relevant investigations were performed as per ward protocols, including preoperative complete blood counts (CBC), Urine R/E, and Ultra sonography of abdomen and pelvis. Percentage Neutrophils count and percentage lymphocyte count were recorded from the CBC report and NLR value was then calculated from it. Postoperatively appendectomy specimens were taken for histopathology examination (the gold standard for diagnosis of AA). Clinical histopathologist of histopathology department of Ayub Medical College would examine the specimen after processing as per their protocols to make definitive diagnoses. Data was analyzed on SPSS version 25. A *p*-value of <0.05 was considered statistically significant.

RESULTS

A total of 100 patients were included in this study, with a mean age of 23.84±10.2992 years (ranging from 6–60 years). Of these, 92 out of 100 patients (92%) were confirmed positive for acute appendicitis (AA) based on histopathology, with a male-to-female ratio of 1.49:1. Among the confirmed cases, 55 (59.78%) were male and 37 (40.22%) were female. Regarding the geographical distribution, 51 (55.43%) patients were from urban areas, while 41 (44.56%) were from rural areas, yielding an urban-to-rural ratio of 1.24:1. The majority of patients were young, with 74% falling within the 2nd and 3rd decades of life, while only 4% of patients were over the age of 50. (Table 1)

The parameters of the Alvarado score were cross-tabulated with the gender and residence of patients. All patients reported abdominal pain in the right iliac quadrant (RIQ), and the other Alvarado scale parameters were present in varying percentages. Tenderness in the RIQ, the second most commonly observed parameter, was found in 55 out of 59 (93.2%) male patients and 53 out of 55 (96.36%) rural patients. In females, 37 out of 41 (90.2%) exhibited tenderness in the RIQ, while 39 out of 45 (86.66%) urban residents presented with this symptom, making it the second most commonly observed clinical feature. The least frequent Alvarado scale parameter was a shift in neutrophils, which was observed in only 27 out of 59 (45.7%) male patients and 29 out of 55 (52.72%) rural patients. In females, both the shift in neutrophils and temperature were the least observed Alvarado score parameters, each appearing in 22 out of 41 (53.6%) patients. Among urban residents, the shift in neutrophils was the least observed, present in only 20 out of 45 (44.44%) patients. (Table 2)

Preoperative complete blood count (CBC) reports were obtained, and data regarding the percentage of neutrophils and lymphocytes were recorded. These values were then used to calculate the Neutrophil-to-Lymphocyte Ratio (NLR). The NLR values ranged from 0.65–29.50, with a mean value of 5.76±5.23. (Table 3)

The Neutrophil-to-Lymphocyte Ratio (NLR) was correlated with the histopathological examination of the appendix. Out of the 100 patients, 92 (92%) had histopathological evidence of inflammation (positive appendectomy), while 8 (8%) had a normal appendix, resulting in a negative appendectomy rate of 8%. (Table 4)

At cut-off values of NLR ≥2.5 and NLR ≥3, the validity parameters were calculated and found to be significant with a *p*-value of 0.001 on the Chi-square test. The Pearson's correlation between an NLR value ≥2.5 and histopathologically confirmed cases of Acute Appendicitis was found to be significant at a *p*-value level of 0.01. (Table 5)

Table-1: Socio-demographic parameters of the participants.

Age Mean = 23.84 ± 10.2992 years Minimum 6 - Maximum 60 years	6 to 10 years	10/ 100 (10%)
	11 to 20 years	30/ 100 (30%)
	21 to 30 years	44/ 100 (44%)
	31 to 40 years	12/ 100 (12%)
	41 to 50 years	1/ 100 (1%)
	51 to 60 years	3/ 100 (3%)
Gender Ratio M:F = 1.49:1	Male	55 (59.78%)
	Female	37 (40.22%)
Residence Ratio U:R = 1.24:1	Urban	51 (55.43%)
	Rural	41 (44.56%)

Table-2: Cross-tabulation of Alvarado score parameters with gender and residence.

Alvarado Scale Parameters		**Pain RIQ**	**Anorexia**	**Nausea**	**Temp**	**Tenderness**	**Rebound Tenderness**	**Leucocytosis**	**Shift**
Gender	Male	59/59 (100%)	41/59 (69.5%)	40/59 (67.8%)	31/59 (52.5%)	55/59 (93.2%)	47/59 (79.6%)	41/59 (69.5%)	27/59 (45.7%)
	Female	41/41 (100%)	32/41 (78%)	32/41 (78%)	22/41 (53.6%)	37/41 (90.2%)	34/41 (82.9%)	27/41 (65.8%)	22/41 (53.6%)
Residence	Rural	55/55 (100%)	41/55 (74.5%)	43/55 (78.18%)	31/55 (56.4%)	53/55 (96.36%)	46/55 (83.63%)	35/55 (63.63%)	29/55 (52.72%)
	Urban	45/45 (100%)	32/45 (71.11%)	29/45 (64.44%)	22/45 (48.9%)	39/45 (86.66%)	35/45 (77.77%)	33/45 (73.33%)	20/45 (44.44%)
Total		100	73%	72%	53%	92%	81%	68%	49%

Table-3: Descriptive statistics of Neutrophils count, Lymphocytes count, and NLR.

	Minimum	**Maximum**	**Mean**	**Std. Deviation**
%age Neutrophils count on CBC	36.30	94.00	72.8360	12.91844
%age Lymphocytes count on CBC	3.10	55.40	20.8660	11.52422
Neutrophils to Lymphocytes Ratio	0.65	29.50	5.7566	5.22573

Table-4: Comparison of NLR with histopathology of the appendix.

	Histopathology confirmed cases.		**Total**
	Yes	No	
NLR ≥2.5 (indication of AA) Yes	(TP) 65	(FP) 1	66
No	(FN) 27	(TN) 7	34
Total	92	8	100

TP= True Positive, FP= False Positive, FN= False Negative, TN=True Negative

Table-5: Outcome value for NLR

Parameters	**NLR ≥ 2.5**	**NLR ≥ 3**
Sensitivity	70.65%	63.04%
Specificity	87.5%	100%
Positive predictive value (PPV)	98.49%	100%
Negative predictive value (NPV)	20.6%	19.04%
Accuracy	72%	64%.
Chi-Square Test	$p = 0.001$	P = 0.001

DISCUSSION

Appendectomy is more common in men than in women, with a male-to-female ratio of 1.5:1.[14,15] The lifetime risk of developing acute appendicitis is higher in males (about 8.6%) compared to females (6.7%).[16] Acute appendicitis (AA) has a peak incidence during the second and third decades of life, making it a disease predominantly affecting young adults.[17] In our study group, the majority of patients were young, with 74% in their second and third decades of life. The mean age of patients was 23.84±10.2992 years, which aligns well with the mean age reported in the literature.[18] Of the 92 confirmed cases on histopathology, 55 (59.78%) were male and 37 (40.22%) were female, yielding a male-to-female ratio of 1.49:1. Kukuk E studied changes in the neutrophil-to-lymphocyte ratio (NLR) in 241 patients with AA and observed a male-to-female ratio of 1.5:1 for Acute Appendicitis.[14]

The mean negative appendectomy rate reported in various studies varies, ranging from as low as 8.2% to 15–30%.[4,6] The rate of negative appendectomy in our study was 8%. The lower rate in our study can be attributed to the heightened awareness among surgical residents when data collection began. They became more concerned about negative appendectomies and took extra precautions

by ordering all necessary investigations and seeking senior consultations before proceeding with surgery. This can be considered a classic example of Hawthorne Bias.[19] However, since the objectives of our study are not related to the quality of diagnosis in a tertiary care setting and we did not include any subjective parameters that could have been influenced by clinicians, this observation is not significant to our study.

The literature includes studies on various laboratory markers such as CRP, MPV, TLC, red blood cell distribution width, interleukin-6, and procalcitonin for diagnosing acute appendicitis (AA). However, the neutrophil-to-lymphocyte ratio (NLR) has demonstrated greater diagnostic accuracy than any other laboratory marker when used alone.[1,20] Rabindra K.C. and colleagues investigated the relationship between NLR and the severity of Acute Appendicitis. They found that a preoperative NLR value greater than 5.60 is a valuable predictor of gangrenous appendicitis.[17]

Faraj F.H. *et al*. concluded that the neutrophil-to-lymphocyte ratio (NLR) has high diagnostic accuracy in diagnosing acute appendicitis, especially when used in conjunction with clinical examination.[5] Prasetya D. *et al*. also demonstrated that NLR is highly accurate in diagnosing acute appendicitis and distinguishing between uncomplicated and complicated cases.[21] The NLR increases, and the lymphocyte percentage decreases in acute appendicitis, making it a useful diagnostic marker[22]. However, the literature suggests that individual differences in inflammation response among patients may cause NLR to vary from person to person in response to inflammatory stimuli.[14]

Kostakis ID *et al*. reported that an NLR ≥3 showed [sensitivity: 90%, specificity: 88%, accuracy: 89%], while an NLR ≥3.5 demonstrated [sensitivity: 90%, specificity: 90%, accuracy: 90%] in diagnosing acute appendicitis.[23] Chirag Pereira *et al*. correlated NLR values with histopathology and found a significant relationship between acute appendicitis and NLR at a cutoff value of >2.4 (p=0.0001), with sensitivity of 70.1% and specificity of 43.2%. An NLR >4.3 was associated with complicated appendicitis cases, showing a sensitivity of 72.25% and specificity of 54.09%.[18]

In our study, the cutoff value for NLR was set at ≥2.5. Of the 92 confirmed cases on histopathology, 65 cases were true positives based on NLR, resulting in a sensitivity of 70.65% for NLR, while 27 cases were false negatives. Of the 8 confirmed negative cases on histopathology, 7 were true negatives based on NLR, yielding a specificity of 87.5% for NLR. Among the 66 positive cases on NLR, 65 were true positives, providing a positive predictive value (PPV) of 98.49% for NLR in diagnosing acute appendicitis. Out of the 34 negative cases on NLR, 7 were true negatives, resulting in a negative predictive value (NPV) of 20.6%. The overall accuracy of NLR in diagnosing acute appendicitis was 72%. When the cutoff value for NLR was set at ≥3, we found a sensitivity of 63.04%, specificity of 100%, PPV of 100%, NPV of 19.04%, and accuracy of 64%. The Pearson's correlation between NLR value ≥2.5 and histopathology confirmed cases of Acute Appendicitis was found significant at the p-value levels of 0.01.

The strengths of the study are that procedural rigor was applied to enhance the internal validity. However, a small size sample makes the external validity difficult to employ.

CONCLUSION

In conclusion, an NLR ≥2.5 appears to be a reliable parameter for enhancing the accuracy of acute appendicitis diagnosis. However, a normal NLR value does not exclude the diagnosis.[21] To determine the optimal NLR cutoff and assess its accuracy, prospective randomized studies are required. A primary limitation of our study is that it only included patients who underwent appendectomy, and we lack data from patients with suspicious abdominal findings who did not have surgery. The diagnosis of acute appendicitis can be made with confidence through a thorough history, proper examination, and correlation with CBC, abdominal USG, and urine analysis.[24] The NLR can be particularly useful in diagnosing doubtful cases of right lower quadrant pain.[12,25] Additionally, in peripheral healthcare settings, where acute appendicitis is diagnosed clinically in conjunction with baseline investigations due to the unavailability of advanced tools, this simple, cost-effective, and easily interpretable marker can be a valuable diagnostic aid.

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Submitted: March 8, 2022	*Revised: May 9, 2024*	*Accepted: October 25, 2024*

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ORIGINAL ARTICLE

EFFECTIVENESS OF YOUTUBE AS AN EDUCATIONAL TOOL FOR TEACHING ORTHODONTICS TO UNDERGRADUATE DENTAL STUDENTS

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Background: The advent of modern technology has dramatically influenced the availability of resources for students to learn and gain knowledge as well as improve their skills. **Methods:** Over six months, a randomized control trial (pretest-post-test design) was conducted at Khyber College of Dentistry, Peshawar. The aim was to compare the traditional method with YouTube learning to enhance students' diagnostic skills in lateral cephalometry and benefit the local dental community. **Results:** Seventy-four participants took part, with an average age of approximately 23 years having 35.1% male and 64.9% female participants. The control group's pre-test mean score was 5.54, significantly increasing to 13.62 in the post-test. The experimental group's pre-test mean score was 4.08, significantly rising to 15.29 in the post-test. The experimental group outperformed the control group in the post-test, with mean scores of 15.29 and 13.62, respectively. Participants showed overall satisfaction with course content, materials, instructor knowledge, and YouTube learning, though opinions on class location and equipment varied, with some expressing less satisfaction in this aspect. **Conclusions:** This current study signifies the use of YouTube as a teaching tool. YouTube based learning had a superior efficacy to traditional based learning for instruction of cephalometric landmarks identification.

Keywords: Teaching tool; Orthodontics; Medical Education; E-Learning; YouTube.

Citation: Shah SS, Jameel B, Ijaz W, Iqbal N, Adeeb H, Ahmad S. Effectiveness of YouTube as an educational tool for teaching orthodontics to undergraduate dental students. J Ayub Med Coll Abbottabad 2024;36(4):716–20.

DOI: 10.55519/JAMC-04-12740

INTRODUCTION

Effective education is vital for academic success, with recent technological advances transforming learning globally, including dental education.[1] E-learning, especially through platforms like YouTube, has become a significant alternative to traditional methods.[2,3]

The COVID-19 pandemic has accelerated the adoption of e-learning in dentistry.[4] YouTube has emerged as a practical resource for dental students, offering insights into clinical practices and surgical techniques.[5,6]

Lateral cephalometric imaging plays a crucial role in orthodontics and orthognathic surgery, aiding in the identification of dental abnormalities.[7,8] However, interpreting cephalograms poses challenges that advanced technologies, such as 3D visuals and videos, could address.[9]

Dental students face difficulties in mastering cephalometric interpretation through conventional lectures.[1] The study explores the potential of YouTube-based learning to enhance instruction for cephalometric landmarks tracing, addressing a gap in current research.[10]

This study aims to compare the effectiveness of traditional learning and YouTube-based learning in cephalometric landmark identification and related analyses. The goal is to contribute to improved lateral cephalometry diagnosis, benefiting local dental education.

MATERIAL AND METHODS

The research was conducted at the Orthodontic Department of Khyber College of Dentistry in Peshawar and spanned six months from approval. It utilized a Randomized Controlled Trial with a pretest-posttest design, sanctioned during the 134th meeting of the KMU AS&RB on May 25, 2023 (Ref No: DIR/KMU-AS&RB/EY/002028). By using openepi, the total sample size was 74 (37 in each group) by using the mean of Point (Or) of the Traditional learning group 6.65±6.24 and 3.67±1.64 in the Smartphone-based mobile learning by keeping a 95% confidence interval with 80% power of the test.[1]

One hundred final-year students were divided into two groups using systematic random sampling based on performance in their third professional examination. The 3rd Professional BDS examination marks for the entire batch were graded from highest to

lowest, and a comprehensive list was created. To evenly distribute students of similar abilities into two groups, all even serial numbers were assigned to Group I, and all odd serial numbers were assigned to Group II.

Data collection commenced post-approvals, with validated pre/post-tests and YouTube videos link. Participants were ensured confidentiality, provided informed written consent, and randomly assigned to two groups, each exposed to specific teaching methods. Both groups were exposed to a pretest of 20 MCQs. Group 1 was taught cephalometric tracing topics by the traditional method with direct observation and practice in the demonstration room, while Group 2 used a YouTube video for the same topics of 10–15 minutes for learning and practice, supervised by the same Trainee Medical Officer. Both groups had a three-day session of one and a half hours, followed by a post-test (20 MCQ's) on the fourth day. Students feedback evaluation was conducted on a five-point Likert scale. (Figure 1)

Data analysis was performed using SPSS version 24, presenting results through tables and graphs Numeric data like age and score of the participant in each group were computed as a mean and standard deviation. Categorical data like gender was described as frequency and percentages. Paired sample T-test was applied to compare each group's pre and post-intervention scores. An Independent Sample T-test was used to compare post-intervention scores between both groups. Data was stratified for age and gender to see effect modification using a paired sample T-test. The level of significance was $p \leq 0.05$.

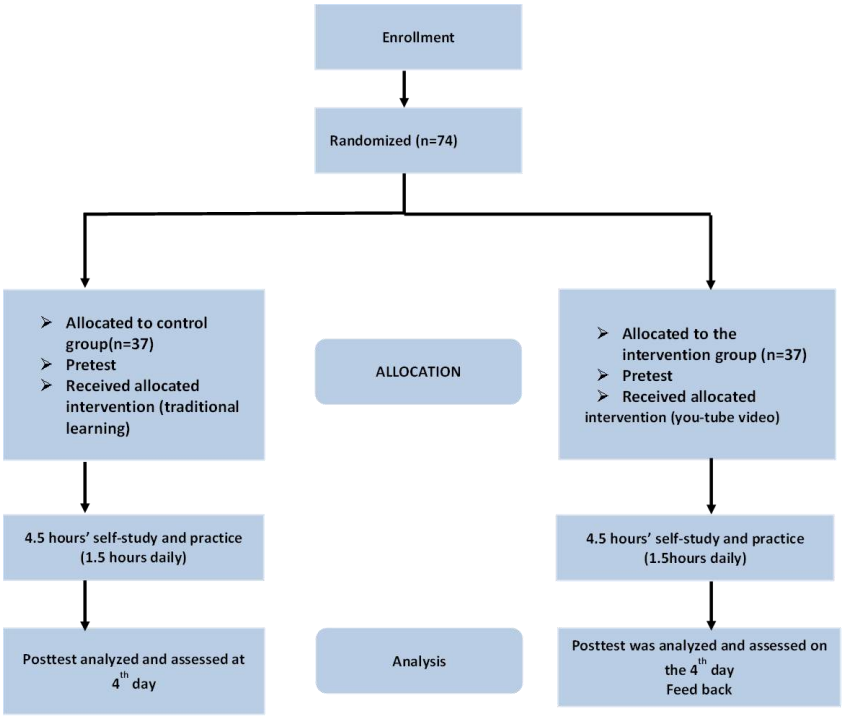

Figure-1: Consort flowchart

RESULTS

Among 74 participants, the average age was approximately 23 years, showing little variation (figure 2). Gender distribution indicated n = 26 (35.1%) male and n=48 (64.9%) female participants (figure 3).

In the control group, the mean pre-test score of 5.54 increased significantly to 13.62 post-intervention through traditional teaching, with a highly significant t-value of -11.43 (p=0.001). A weak negative correlation (r = -0.124) suggested that higher pre-test scores were associated with slightly lower post-test scores. Cohen's d-effect size of 2.79 indicated a substantial impact.

For the experimental group, the mean pre-test score of 4.08 rose significantly to 15.29 post-intervention, with a highly significant t-value of -25.27 (p=0.001). A very weak negative correlation (r = -0.049) suggested a slight tendency for higher pre-test scores to be associated with slightly lower post-test scores. The large Cohen's d effect size of 6.03 highlighted a significant impact, with the intervention

having a greater influence on the experimental group than the control group.

Both groups showed significant post-test score improvements post-intervention, with the experimental group demonstrating a larger effect size, indicating a greater impact of the intervention on their results. (Table 1)

Generally positive feedback on course content, materials, instructor, communication, and YouTube learning.

Varied opinions on class location and equipment, with some participants expressed less satisfaction. (Table 3)

The experimental Group outperformed the Control Group on post-test (mean scores: Control = 13.62, Experimental = 15.29) (Table-2). Lower standard deviation in the Experimental Group suggests higher consistency in post-test scores. A significant difference between groups was confirmed by t-value (-2.45) and *p*-value (0.017), with a moderate effect size (Cohen's d = 0.56). (Table-2)

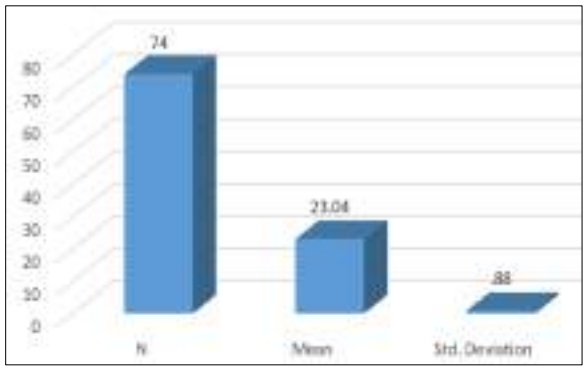

Figure-2: Age of Participants

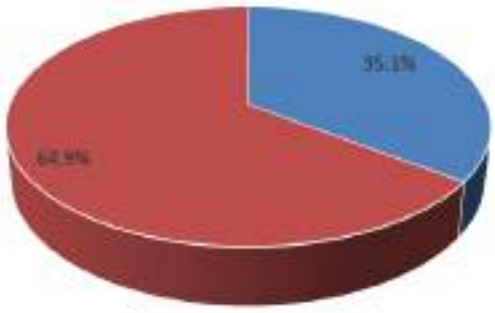

Figure-3: Gender distribution

Table-1: Mean comparison of pre-test and post-test on control group and experimental group

	Pre-test		Post-test					
Variables	**M**	**SD**	**M**	**SD**	**T**	**p**	**r**	**Cohen's d**
Control Group	5.54	1.96	13.62	3.58	-11.43	.000	-.124	2.79
Experimental Group	4.08	1.58	15.29	2.10	-25.27	.000	-.049	6.03

Table-2: Mean comparison of control and experimental groups on post-test score

	Control Group		Experimental Group				
Variables	**M**	**SD**	**M**	**SD**	**t**	***p***	**Cohen's d**
Post-test Score	13.62	3.58	15.29	2.10	-2.45	.017	.56

Table-1: Item means of feedback evaluation

	N	Mean & SD
Course content met your needs	34	4.23±.43
Course material and educational resources	34	4.26±.44
Class location and equipment	34	2.32±1.12
Knowledge of the subject matter	34	4.50±.50
Communicated the course material effectively	34	4.52±.50
YouTube learning is interesting and engages our attention throughout	34	4.47±.50
The YouTube video duration was just right	34	4.52±.50

DISCUSSION

The study aimed to assess the effectiveness of teaching cognitive skills using traditional and YouTube learning methods for orthodontic students. Results indicated a positive impact of YouTube teaching compared to the control group, confirming the effectiveness of YouTube as a complementary teaching tool. The study's inclusion of participants with a mean age of 23 years adds demographic diversity, enhancing the study's generalizability. In contrast to the current study, Abdelaziz et al used blended learning and investigated the effect of blended learning on new nursing students' outcomes in nursing subjects at Ain Shams University. The study recruited younger students (second-year nursing students), and the average age of students in the study group using traditional lectures was 18.27, while the mean age of students in the control group using e-learning was 18.4.[11]

In comparison to previous research Reime et al. emphasized that in the e-learning group, younger students outperformed older students across the age range of 22–57 years.[12] The current study's inclusion of participants with a mean age of 23 years highlights a specific age group, allowing for focused insights into e-learning approaches for young adults. This focus contrasts with studies that did not discuss age as a factor influencing learning gain. Although the age range was narrow, the emphasis on this specific demographic provides valuable understanding of e-learning strategies tailored to young adults

The study found no significant gender differences in learning gain, differing from other studies revealing gender-based variations. In contrast to this study, Reime et al. conducted research where students were provided with learning objectives and divided into two groups: one using an e-learning program and the other attending 48 three-hour-long

lectures. Their study also revealed a gender-based distribution, with women scoring higher than men.[12] Elham Soltanmehr *et al*. conducted a similar study, comparing the effect of virtual and traditional education on the theoretical knowledge and reporting skills of dental students in the radiographic interpretation of bony lesions of the jaw by evaluating 39 dental students who had not received any instruction in the radiographic interpretation of bony lesions of the jaw. There were 7 males (35%) and 13 females (65%) in the virtual learning group, and 5 males (26.3%) and 14 females (73.7%) in the traditional learning group. In terms of sex, the difference between the two groups was insignificant ($p>0.05$).[13]

As the current study aimed to assess the effectiveness of an intervention by comparing pre- and post-test performances in control and experimental groups. Traditional teaching significantly improved control group outcomes while the YouTube video intervention led to a rise in experimental group. Baseline knowledge showed no significant difference between groups, and overall, the intervention had a marginal impact on learning gain, with no statistical difference between groups.

Comparisons with similar studies, such as O'Leary & Janson (2010), highlighted the unique focus on e-learning in their study. The intervention had a meaningful impact on post-test scores, emphasizing its practical importance and significant positive changes, supported by a moderate effect size (Cohen's d).[14]

Additional literature, including Mitchell *et al*. and Basoglu & Akdemir, corroborated the positive effects of continuous electronic access and educational applications on student performance, aligning with the current findings. Smartphone applications were found to be optimally effective for learning enhancement, as reported by Fernandez-Lao *et al*., Fozdar & Kumar, and Hartnell-Young & Heym. Leasure et al. indicated that electronic learning is 19% more effective than traditional learning.[15]

Strength and limitations:

The study's strengths include using a randomized control group design to reduce bias and enhance validity, pretest and posttest assessments for robust measurement, focus on undergraduate dental students for real-world applicability, standardized YouTube content to control confounding variables, quantitative data for clear analysis, and evaluation of video quality to ensure information reliability.

The study's limitations include a small sample size (74), which may limit statistical power and generalizability; a short timeframe for pretest and post-test assessments, hindering understanding of long-term impacts; restriction to a single institution, limiting broader applicability; inability to confirm YouTube as the sole source of improvement due to potential confounding factors; and focus on short-term results without exploring long-term consequences of using YouTube as a learning aid.

Recommendations:

To strengthen the study's findings, expand the sample size to include more diverse students and incorporate follow-up assessments for long-term impact. Add qualitative analysis through focus groups and surveys to understand student perceptions. Use learning analytics to tailor content and conduct comparative analyses with other teaching methods. Include feedback from educators to refine and maximize YouTube's educational impact.

CONCLUSION

In conclusion, the experimental group showed a greater increase in post-test scores than the control group, highlighting the effectiveness of YouTube as a teaching tool. YouTube based learning had a superior efficacy to traditional based learning for instruction of cephalometric landmarks identification.

AUTHORS' CONTRIBUTION

SSS conceived and designed the study, analysed and interpreted the data, and wrote the manuscript. BJ helped in designing the study and writing the manuscript, did review and final approval of the manuscript. HA did statistical analysis & editing of the manuscript and is responsible for the integrity of the research. NI, WE & SA helped in data collection and manuscript writing.

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Submitted: December 16, 2023	*Revised: September 8, 2024*	*Accepted: September 24, 2024*

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ORIGINAL ARTICLE

EFFECT OF FAT GRAFTING ON IMPROVEMENT OF SCAR-AN INTERVENTIONAL STUDY

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Background: Scars are inevitable after effect of wound healing, a natural process that restores tissue integrity following injury, burns or surgery. They can be aesthetically displeasing and functionally impairing, depending on their location, size, and depth. Depending on the severity of the injury, scars can be hypertrophic, atrophic, or keloid. These variations can lead to pain, itching, contractures (limited movement), and psychological distress, impacting a patient's quality of life. Objective was to evaluate the efficacy of autologous fat grafting in improving the appearance and quality of scars, with a focus on patients presenting with facial scars due to burns, trauma, surgery or acne at a tertiary care hospital in Karachi, Pakistan. **Methods:** In this quasi-experimental study, 30 patients of age 18 years to 60 years, irrespective of gender having facial scar because of burn, trauma, surgery or acne were included in the study. A comprehensive scar assessment was performed using the Patient and Observer Scar Assessment Scale (POSAS) before treatment, and follow-up evaluations were conducted on the seventh day, at three months, and at six months post-fat grafting. Fat grafting was executed using a tumescent technique based on Klein's formula, with the aspirated fat injected into the subdermal plane of the scar. Data analysis was performed using SPSS version 23. **Results:** The patient cohort had a mean age of 26.77 years, with a predominance of female participants (73.3%). Trauma was the most common cause of scars (50%), with the forehead being the most frequent location (36.67%). Significant improvements in scar quality were observed, with both patient and observer POSAS scores showing notable reductions from baseline to 6 months (p<0.05). All patients (100%) demonstrated an improvement in scar appearance. **Conclusion:** Fat grafting presents a promising treatment for improving the appearance and quality of facial scars.

Keywords: Fat grafting; Scar improvement; Patient and Observer Scar Assessment Scale (POSAS); Regenerative medicine; Facial scars

Citation: Sattar SA, Akhlaq F, Sami W, Noor M, Zahid F, Sheikh U. Effect of fat grafting on improvement of scar-an interventional study. J Ayub Med Coll Abbottabad 2024;36(4):721–5.

DOI: 10.55519/JAMC-04-13211

INTRODUCTION

Scars are inevitable after effect of wound healing, a natural process that restores tissue integrity following injury, burns or surgery.[1] They can be aesthetically displeasing and functionally impairing, depending on their location, size, and depth.[2,3] Depending on the severity of the injury, scars can be hypertrophic, atrophic, or keloid. These variations can lead to pain, itching, contractures (limited movement), and psychological distress, impacting a patient's quality of life.[1,4]

The conventional management of scar include pressure therapy, silicone gel sheets, and topical/injectable corticosteroids.[5] While these methods can improve scar appearance to some extent, they often yield limited and inconsistent results, particularly for more severe scars.[5–7] In recent years, regenerative medicine has emerged as a promising approach for scar treatment, offering the potential to improve scar quality and function.[1] First introduced in the 1890s by Neuber and later popularized by Coleman in the 1990s, fat grafting utilizes adipose tissue, a rich source of mesenchymal stem cells (MSCs) and adipose-derived stromal vascular fraction (SVF).[3,8,9] These components possess regenerative properties, including the ability to promote tissue repair, angiogenesis, and immunomodulation.[1] Studies revealed that fat grafting has a favourable effect on scars via angiogenesis, immunological modulation, and lipofilling, among other things, making it a potential therapy.[10–13]

Klinger M *et al*. revealed that fat grafting is a successful treatment for burn scars, trauma scars, post-surgery scars, and post-radiation scars.[4] Recently, Ishaque et al. also found that fat grafting is a successful technique for the improvement of post burn scar of hands and face.[14] Moreover, it has become a common procedure in aesthetic and reconstructive surgeries due to its high biocompatibility and availability.[3,9]

Despite its promising outcomes, there remains a dearth of local data exploring the full potential of this treatment. Therefore, the aim of current study was to evaluate the efficacy of fat grafting for improvement of scar among patients presenting at a tertiary hospital of Karachi, Pakistan. This study would help plastic surgeons who are constantly seeking for techniques to improve scar quality.

MATERIAL AND METHODS

It was a quasi-experimental study conducted at the Plastic surgery department, Civil hospital Karachi, Pakistan from 03-04-2023 to 02-01-2024. Sample size was calculated using WHO sample size calculator by taking pre-treatment POSAS score as 35.83±4.08 (baseline) and post-treatment POSAS as 27.50±3.04 (at six months) among surgeons,[3] power of test as 80% and 99% confidence level. The estimated sample size was 10, but we included 30 patients in order to increase the generalizability of the results. Patients of age 18 years to 60 years of either gender having facial scar because of burn, trauma, surgery or acne were included in the study. Patients with keloids and contractures were excluded from the study. Non-random consecutive sampling technique was employed for sample selection.

The institute's ethical review committee approved the study (ERC#: IRB-2943/DUHS/Approval/2023/146). Before data collection begins, all eligible individuals were provided written informed consent. Data regarding age, gender, cause for the scar, and location of the scar was also obtained from patient. Before fat grafting, both the patient and a plastic surgeon examined the scar and scored it using the patient and observer scar evaluation scale (POSAS). A tumescent solution based on Klein's formula (lidocaine 800 mg/l and adrenaline 1:1000,000) was administered to the donor site. Fat was extracted 10 minutes after infiltration of tumescent solution using 3mm cannulas with side holes of 1-2 mm. Syringe of harvested fat was allowed to sit on end and sedimentation occurred that separate fat from oil and aqueous component.

Aspirated fat was transferred to 1 cc syringes with 1mm cannula for injection into the scar. Only the subdermal plane at the recipient location was injected with fat. The scar quality was re-scored on the POSAS scale by both the patient and the same surgeon on the seventh day, three months, and six months. The decrease in POSAS score at 6th month was deemed as improvement. Some of the cases are displayed in figure 1 to 3.

Figure-1: A 40-year-old female with history of fire burn 6 months back A. Pre-operative B. Post operative after 2 sessions of fat grafting

Figure-2: A 27-year-old female with history of road traffic accident in childhood having scar in left sided periorbital region A. Pre-operative B. Post operative after two sessions of fat grafting

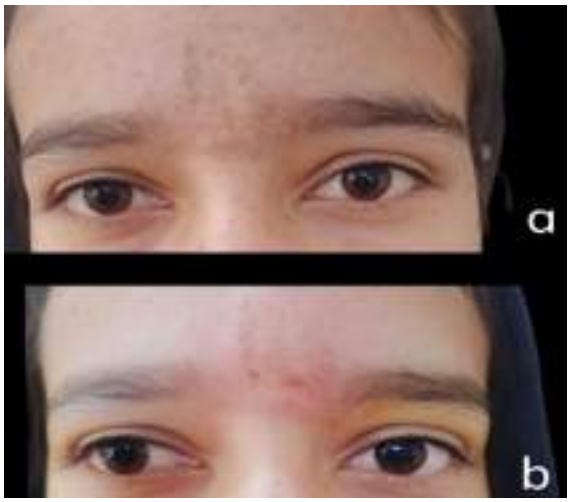

Figure-3: A 19-year-old female with history of trauma on glabellar region A. Pre-operative B. Post-operative after 1 session of fat grafting

Data was analyzed using SPSS version 23. Mean and standard deviation were reported for age, POSAS at baseline, at 7th day, at 3 months and at 6 months. Frequencies and proportions were reported for sex, reason of scar, location of scar and improvement. Pre- and post-operatively POSAS were compared using Repeated Measure ANOVA. Post-hoc analysis was performed to assess the pair-wise comparison. Level of significance was set at 1%.

RESULTS

The mean of the patients age was 26.77±6.60 years. Most of the patients were females (73.3%) and 26.7% were males. The most common cause is trauma (50.00%) and most frequent location is the forehead (36.67%) Table-1. The mean baseline POSAS scores were approximately 54 (patient) and 55 (observer), indicating the initial scar assessment scores. By the 6-month follow-up, the mean POSAS scores decreased to around 44 (patient) and 42 (observer). Repeated Measures ANOVA revealed significant changes in both patient and observer POSAS scores over time (Patient scores: $F(3,87) = 15.67$, $p<0.001$; Observer scores: $F(3,87) = 17.24$, $p<0.001$). Furthermore, all patients (100%) showed improvement in scar appearance Table-2.

The pair-wise comparisons using Tukey's Honest Significant Difference (HSD) test for both Patient and Observer Scar Assessment Scale (POSAS) scores are displayed in table 3. There is a significant reduction in the patient POSAS score by 7.33 points from baseline to 3 months, with a *p*-value of 0.001. While, observers noted a more pronounced reduction in POSAS score, with a difference of 9.73 points, also significant at $p=0.001$. The change in patient scores between 3 and 6 months is -3.07, with a *p*-value of 0.0785, which is not statistically significant. While, observers noted a significant mean difference of -3.13 points with a *p*-value of 0.0325. A significant improvement in patient scores by 5.43 points from the 7th day to 3 months ($p=0.0002$). While, observers reported a 6.67 points improvement, significant at $p=0.001$. A minor improvement of 1.9 points from baseline to the 7th day is noted, but this change is not statistically significant ($p=0.4404$. While, observers noticed a slightly more significant improvement of 3.07 points, with a *p*-value of 0.038. Both patients and observers reported significant improvements in scar quality from the 7th day to 6 months (8.5 and 9.8 points respectively, both $p=0.001$). However, the greatest improvements are seen from baseline to 6 months, with patients reporting a 10.4 points improvement and observers 12.87 points, both statistically significant ($p=0.001$).

Table-1: Baseline characteristics of study variables (n=30)

Characteristic	Statistics
Age	
Mean (SD)	26.77 (6.60) years
Gender	
Female	22 (73.33%)
Male	8 (26.67%)
Reason of Scar	
Trauma	15 (50.00%)
Post acne	11 (36.6%)
Burn	2 (6.7%)
Post-surgery	2 (6.7%)
Location of Scar	
Forehead	11 (36.67%)
Cheek	9 (30.00%)
Temple	4 (13.33%)
Chin	4 (13.33%)
Nose	2 (6.67%)

Table-2: Change in patient and observer POSAS scores over time (n=30)

Time Point	Patient Score Mean (SD)	*p*-value	Observer Score Mean (SD)	*p*-value
Baseline	53.97 (5.05)	0.001	54.77 (4.88)	0.001
7th Day	52.07 (4.75)		51.70 (4.07)	
3 Months	46.63 (5.19)		45.03 (4.50)	
6 Months	43.57 (4.61)		41.90 (4.01)	

Table-3: Post-hoc pair-wise comparisons for patients and observer POSAS scores (n=30)

Comparison	Patient Mean Difference	*p*-value	Observer Mean Difference	*p*-value
3 Months vs. Baseline	7.33	0.001	9.73	0.001
3 Months vs. 6 Months	-3.07	0.0785	-3.13	0.0325
3 Months vs. 7th Day	5.43	0.0002	6.67	0.001
7th Day vs. Baseline	1.9	0.4404	3.07	0.038
6 Months vs. 7th Day	8.5	0.001	9.8	0.001
6 Months vs. Baseline	10.4	0.001	12.87	0.001

DISCUSSION

Scarring, an inevitable outcome of the wound healing process, often presents both aesthetic and functional challenges that significantly impact individuals' lives.[15] Traditional treatments have yielded limited success in severe cases, prompting the exploration of more effective interventions.[16] Fat grafting, with its regenerative capabilities, has emerged as a promising technique, offering not just volumetric improvements but also biological changes in scar tissues that promote healing and improve scar appearance and functionality.[17,18] In the current study, we investigated the efficacy of fat grafting as a method for improving scar appearance, particularly in patients with facial scars due to various causes. The study was conducted

in Dr Ruth K.M Pfau Civil Hospital Karachi, Pakistan, and aimed to fill the gap in local data regarding fat grafting for scar improvement.

Our study revealed significant improvements in scar quality following fat grafting, as evidenced by the reduced POSAS scores. This suggests that fat grafting induces biological improvements in scar tissue, corroborating the hypothesis that the procedure extends beyond mere defect filling to stimulate biological healing and improve scar characteristics.

Our findings are similar with those in the literature, highlighting fat grafting's potential in scar management. The study by Bhooshan *et al*. on autologous emulsified fat injection for rejuvenation of scars further supports the regenerative potential of fat grafting. The study utilized the POSAS and showed significant improvements in scar symptoms (e.g., pain, itching, stiffness) and characteristics (e.g., vascularity, pigmentation, pliability) post treatment.[19] Similarly, Gargano *et al*. evaluates the outcomes of the SUFA technique, which combines subcision (a method used to break fibrous strands of scar tissue) and autologous fat grafting, in 9 patients with contracted burn scars. They found significant improvements in dermal thickness and a reduction in scar contracture ($p<0.05$), highlighting fat grafting's role in enhancing dermal properties and reducing scar severity.[20] Likewise, studies by Klinger *et al.* validate our findings, highlighting fat grafting's success across various scar types, including burns, trauma, and post-surgery scars.[4,21] The review by Alexandra Condé-Green *et al*. on the effect of fat grafting on scars also identified improvements in burn scar size, texture, and function, including enhanced angiogenesis and reduced inflammation.[22] While there's a consensus on fat grafting's beneficial effects, variations in outcomes may relate to differences in techniques, the severity of scars, and individual patient factors. The regenerative effects observed, possibly attributed to the stem cells within grafted fat as suggested by some studies, offer a pathway for enhanced healing beyond simple volumization. However, the variability in fat resorption rates and the occasional need for multiple sessions highlight areas where the technique could be further optimized.[2,12,23–25]

The strength of current study is its methodological rigor and comprehensive evaluation of fat grafting's effects on scars. Nevertheless, the limitations, such as the small sample size and lack of long-term follow-up data, highlight the need for further research. Future studies should delve into the mechanisms behind fat grafting's regenerative effects, optimal fat processing techniques, and patient selection criteria to refine this promising technique's efficacy.

CONCLUSION

Fat grafting presents a promising treatment for improving the appearance and quality of facial scars. This study substantiates the potential of fat grafting to induce positive biological changes in scar tissues, offering a significant advancement in scar management. Further research is warranted to optimize this technique and explore its full regenerative potential.

AUTHORS' CONTRIBUTION

SS, MN: Literature search. SS, WS: Conceptualization of study design. SS, FA, FZ, US: Data collection. SS, MN: Data analysis. SS, FZ: Data interpretation. SS: Write-up. FA, WS: Proof reading.

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Submitted: April 6, 2024	*Revised: June 3, 2024*	*Accepted: June 5, 2024*

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ORIGINAL ARTICLE

ASSOCIATION OF COMPLICATIONS OF DIABETES MELLITUS WITH SOCIODEMOGRAPHIC DETERMINANTS IN PATIENTS PRESENTING TO AYUB TEACHING HOSPITAL ABBOTTABAD

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Background: Diabetes mellitus is a disease with many possible complications like macrovascular, i.e., stroke, coronary artery disease, peripheral artery disease, and microvascular, i.e., retinopathy, neuropathy and nephropathy. Many studies have been done in past to find the frequencies of these complications and their association with sociodemographic determinants of diabetic patients, but there was limited data available in our setup. This study was carried out to determine the frequency of micro and macrovascular complications of diabetic patients and their association with socioeconomic determinants at Ayub Teaching Hospital, Abbottabad. **Methods**: This cross-sectional study was carried out at Ayub Teaching Hospital, Abbottabad, Pakistan, from July 2022 till December 2023 on 113 diabetic patients. The data was collected on micro and macrovascular complications of diabetes on a pre-designed structured proforma and analyzed by means of SPSS-23. **Results:** The most common macrovascular complication was coronary artery disease 10 (8.8%) while neuropathy 35 (31%) was the most common microvascular complication. Among macrovascular complications stroke was associated significantly with age (p=0.01) and duration of diabetes (p=0.032). Among microvascular complications neuropathy was associated with gender (p=0.047), nephropathy with smoking (p=0.02) and retinopathy with both gender (p=0.019) and smoking (p=0.017). **Conclusion:** In this study there was significant association between, gender with neuropathy and retinopathy, smoking with nephropathy and retinopathy, stroke with age and duration of diabetes.

Keywords: Diabetes mellitus; Microvascular complications; Macrovascular complications; Retinopathy; nephropathy; Neuropathy; Coronary artery disease; Stroke, Peripheral artery disease

Citation: Malik S, Naz F, Iqbal F. Association of complications of diabetes mellitus with sociodemographic determinants in patients presenting to Ayub Teaching Hospital Abbottabad. J Ayub Med Coll Abbottabad 2024;36(4):726–9.

DOI: 10.55519/JAMC-04-13758

INTRODUCTION

Diabetes mellitus is a group of metabolic abnormalities in which there is chronic hyperglycemia. The cause may be problem with insulin secretion or abnormality in insulin effect or usually both.[1] Diabetes mellitus (DM) can be classified mainly as Type I, in which there is absolute insulin deficiency because of destruction of Beta cells of pancreas, Type II where there is mainly insulin resistance, maturity onset diabetes of young (MODY), latent autoimmune diabetes in adults (LADA) and gestational diabtetes.[2] The most common type among all of them is Type II Diabetes mellitus (DM) and its prevalence has been increasing all over the world. Although this disease has many risk factors that can be modified like dietary control, exercise and control of obesity, many drugs has also been developed for this disease.[3] Diabetes has acute complication like Diabetic ketoacidosis (DKA), Hyperglycemic hyperosmolar state (HHS), microvascular complications like retinopathy, nephropathy and neuropathy, and can also have macrovascular complications like cardiovascular diseases, peripheral arteries, and cerebrovascular disease.[4]

In this study we intended to find the frequency of complications of diabetes mellitus and their association with socioeconomic determinants of patients presenting at Ayub Teaching Hospital, Abbottabad because there was limited data available in our setup. This study can benefit diabetic patients, by educating them about these socioeconomic determinants which were strongly associated with bad outcomes, in early stage of disease or as soon as patient is diagnosed with diabetes mellitus to prevent such disastrous possible outcomes later in life. Also, the hospital administration can initiate policies regarding screening of diabetic patients for common complications through proper setups inside the wards and outpatient departments where proper history, examinations and relevant investigations should be done, and patients must be counseled about the possibility of such bad outcomes in future, administration can also spread awareness in general population through media and pamphlets for prevention of common complications.

The sample size of 113 was calculated by using world health organization (WHO) software at 95% confidence interval, 3.4% absolute precision and 3.5%frequency of stroke among diabetic patients.[5]

MATERIAL AND METHODS

After approval from ethical committee of Ayub Teaching Hospital, Abbottabad, this study was conducted. Patients from both genders, >12 years of age and of both type I and II diabetes mellitus between July 2022 till December 2023 were enrolled. After taking informed consent from the patients, proforma were filled with patient's bio data, duration of diabetes, body mass index, and complications of diabetes mellitus. The sample size of 113 was calculated by using world health organization (WHO) software at 95% confidence interval, 3.4% absolute precision and 3.5%frequency of stroke among diabetic patients.[5]

Patients were diagnosed to have diabetes mellitus either if they had serum fasting blood glucose ≥126 mg/dl, or random blood sugar ≥200 mg/dl along with symptoms of, i.e., polyphagia, polydipsia, polyuria or HBA1c levels of ≥6.5% or history of intake of antidiabetic medication. Retinopathy in patients was diagnosed through fundoscopy in ophthalmology unit.Nephropathy in these patients was defined as the presence of albuminuria of >300 mg/24h. Neuropathy in these patients was diagnosed by history and clinical examination to check muscle strength, reflexes and sensitivity to position, vibration, temperature and light touch. All results were analyzed by means of SPSS-23. Shapiro-Wilk test was used to find the normality of data and variables like age and BMI were not normally distributed, they were expressed as median and IQR, frequencies and percentages were calculated for variables like gender, history of smoking, type of diabetes, duration of diabetes, presence of complications, retinopathy, nephropathy, neuropathy, coronary artery disease, stroke, peripheral artery disease. Chi-square test was applied to see the association of socioeconomic determinants with micro and macrovascular complications in diabetic patients. *p*-value of ≤0.05 was taken as significant.

RESULTS

Out of the total 113 patients enrolled, 41 (36.3%) were males and 72 (63.7%) were females. Median age of participants was 53(17.5) years and BMI was 23.8(4.85) Kg/m^2. About 50 (44.2%) patients were of age ≤50 years. Out of total, 57 (50.4%) patients developed complications of diabetes while 56(49.6%) had no complications. About 41 (36.3%) developed microvascular complications, of which 35 (31%), 17 (15%) and 16 (14.2%) developed neuropathy, nephropathy and retinopathy respectively. Macrovascular complications occurred in 3 (2.7%), of which 5 (4.4%), 10 (8.8%) and 3 (2.7%) developed stroke, coronary artery disease and peripheral vascular disease respectively as shown in table 1.

As illustrated in table-2, among the macrovascular complications, there was statistically significant association between stroke and age of patient (p=0.01) and duration of diabetes (p=0.03). It is evident that 50 (44.2%) patients were ≤50 years and all, i.e., 5(100%) had stroke. Similarly stroke developed in all patients 5 (100%) with >5years duration of diabetes.

Table-3 shows that among the microvascular complications, retinopathy was found to be significantly associated with gender (p=0.01) and smoking (p=0.01). Retinopathy was more common among male patients 10 (62.55%) and non- smokers 10 (62.5%). Neuropathy was also found to be significantly associated with gender (p=0.04) and was more common among females 27 (77.1%) while nephropathy was significantly associated with smoking (p=0.02).

Table-1: Sociodemographic characteristics and complications among diabetic patients (n=113)

Characteristics	Categories	Frequency (%age)
Gender	Males	41 (36.3%)
	Females	72 (63.7%)
Age category	≤50y	50(44.2%)
	>50y	63(55.8%)
Smoking	Smokers	19 (16.8%)
	Non-smokers	94 (83.2%)
Type of diabetes mellitus	Type I	6 (5.3%)
	Type II	107(94.7%)
Duration of DM	<5 years	53 (46.9%)
	≥ 5 years	60 (53.1%)
Complications	Present	57 (50.4%)
	Absent	56 (49.6%)
Macrovascular complications	Stroke	5 (4.4%)
	Coronary artery disease	10 (8.8%)
	Peripheral artery disease	3 (2.7%)
Microvascular complications	Retinopathy	16 (14.2%)
	Nephropathy	17 (15%)
	Neuropathy	35 (31%)

Table-2: Association of macrovascular complications with demographic determinants

Variables		Complication (Stroke)		*p*- value
		present	absent	
Age	≤50 years	5 (100%)	45 (41.7%)	0.01
	>50 years	0 (0%)	63 (58.3%)	
Duration of DM	<5years	0 (0%)	53 (49.1%)	0.03
	≥5years	5 (100%)	55 (50.9%)	

Table-3: Association of microvascular complications with demographic determinants

Variables		Complications		*p*-value
Gender		Retinopathy		0.01
		Present	Absent	
	Male	10 (62.5%)	31 (32.0%)	
	Female	6 (37.5%)	66 (68.0%)	
		Neuropathy		0.04
		Present	Absent	
	Male	8 (22.9%)	33 (42.3%)	
	Female	27 (7.1%)	45 (57.7%)	
Smoking		Retinopathy		0.01
		Present	Absent	
	Yes	6 (37.5%)	13 (13.4%)	
	No	10 (62.5%)	84 (86.6%)	
		Nephropathy		0.02
		Present	Absent	
	Yes	6 (35.3%)	13 (13.5%)	
	No	11 (64.7%)	83 (86.5%)	

DISCUSSION

Apart from poor drug compliance, complications in patients with diabetes mellitus have been associated with few important socioeconomic determinants.

The total number of patients in our study was 113, in which 50 (44.2%) were ≤50 years of age and 63 (55.8%) were above 50 years of age. There was significant association of age of patient with development of cerebrovascular accidents, with *p*-value 0.01. Among 113 patients only 5 developed stroke and they were ≤50 years of age, it was similar to one study conducted which reported that diabetic patients who developed stroke were 3.2 years younger patients who doesn't developed stroke.[6]

Gender of patients was also associated with some possible complications of diabetes mellitus such as retinopathy. In our study out of 113 patients, 16 developed retinopathies of which 10 (62.5%) were male and 6 (37.5%) were females with *p*-value 0.01. One study in past done on association of gender and retinopathy showed that frequency of retinopathy was higher in male than in female, i.e., 22.0% vs 19.3% respectively with p-value <0.0001.[7] Another study in past showed that frequency of retinopathy was higher in male than in female, i.e., 31.6% vs 25.7% respectively with *p*-value 0.04.[8] Another association was also observed between gender and development of neuropathy of patients, among 113 patients, total of 38 developed neuropathy, of which 27 (77.1%) were females and 8 (22.9%) were males with *p*-value 0.04. One study in past also supports our study, where A significantly large number of females (38%) than males (31%) had painful neuropathy symptoms with *p*-value <0.0001.[9] One more study also showed significant association of gender with diabetic neuropathy with *p*-value 0.04.[10]

Similar to the results about age and gender has been associated with complications in diabetic patients, duration of diabetes also has effect on possible complications of diabetes, and in this study, duration was found to be associated with development of stroke in diabetic patients. Out of total 113 patients 53 (46.9%) were those who had less than 5 years of diabetes, and 60 (53.1%) were those who had ≥5 years of diabetes. Among these 113 patients only 5 (100%) developed stroke and they all were having duration of diabetes of ≥5 years, which showed duration of the disease has effect on outcomes with strong association and with *p*-value of 0.03. Previously done, one study also concluded that more is the duration of diabetes, more is the risk of development of stroke in patients, their study also had strong association between duration of diabetes mellitus and stroke in diabetic patients with p-value of 0.02 for duration less than 5 years and p-value of <0.001 for duration ≥5 years.[10]

Out of 113 patients, 16 patients developed retinopathy and among these 16, 6 (37.5%) were smokers and 10 (62.5%) were non-smokers with p-value of 0.01. A study done previously showed some similar association between smoking and diabetic retinopathy, in that study, compared with non-smokers, the risk of

retinopathy was found to be significantly decreased in smokers with *p*-value 0.02.[11]

We were unable to conduct study on pregnant women. We did not have financial support from Hospital administration or any other source. Majority of Patients were unaware of their Exact history regarding diabetes and its complications

CONCLUSION

This study concluded that coronary artery disease was the most common macrovascular complication while neuropathy was the most common microvascular complication and there was significant association of age and duration of diabetes with stroke. Gender of patient was significantly associated with retinopathy and neuropathy, and smoking was associated with nephropathy and retinopathy.

RECOMMENDATIONS

This study is the first step in assessing complications of diabetes in terms of different risk factors however future studies with better study designs and sample sizes providing better insight into the natural history of diabetes in the local population is recommended. Based on the results of this study it is suggested that hospital administration should initiate policies regarding screening of diabetic patients for common complications like retinopathy by fundoscopy, peripheral neuropathy by proper history and neurological examination and nephropathy by tests for checking albuminuria among indoor and outpatient medical departments. Also, the general population should be educated about the possible disastrous complications, through media and pamphlets for prevention of common complications.

ACKNOWLEDGMENTS

We acknowledge the hospital administration for allowing us to conduct study, patients for participating, postgraduate residents in medical unit for help during collection of data. We also acknowledge Dr. Zainab Nazneen and Dr. Sobia Ali from community department for helping out in data analysis and interpretation and Dr. Fatima Iqbal PG medical C unit for literature review and report writing.

AUTHORS' CONTRIBUTION

SM: Conceptualization, interpretation, discussion. FN: Data analysis, discussion, literature review. FI: Data collection, Literature review.

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Submitted: August 24, 2024	*Revised: September 1, 2024*	*Accepted: October 16, 2024*

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ORIGINAL ARTICLE

ENHANCING THE QUALITY OF EMERGENCY ADMISSION CLERKING IN NEUROSURGERY: A COMPARATIVE STUDY OF TRADITIONAL METHODS VERSUS A SURGICAL CLERKING PROFORMA

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Background: Accurate and comprehensive documentation during emergency admissions is crucial for ensuring patient safety. This is especially important in high-risk environments such as neurosurgery. Traditional freehand clerking methods often result in incomplete or inconsistent records, potentially compromising patient care. This study aimed to evaluate the impact of introducing a structured surgical clerking proforma on the quality of emergency admission clerking in a tertiary care neurosurgery unit. **Methods:** A three-phase comparative audit was conducted, comprising an initial audit of traditional clerking methods (Cycle 1), the implementation of a surgical clerking proforma, and a subsequent re-audit using the proforma (Cycle 2). Data were collected retrospectively from 40 patient records in Cycle 1 and prospectively from 30 patient records in Cycle 2. The completeness of documentation was assessed across 31 key parameters, and statistical significance was determined using paired t-tests on simulated data. **Results:** The introduction of the surgical clerking proforma resulted in significant improvements in documentation completeness, particularly for parameters such as the Consultant Responsible and Reviewing Doctor, which saw increases of 30% and 32.5%, respectively ($p<0.05$). These improvements underscore the effectiveness of the proforma in standardizing and enhancing the reliability of clinical documentation. **Conclusion:** The structured surgical clerking proforma significantly improved the quality of emergency admission documentation in the neurosurgery unit. The findings support the broader adoption of such proformas across various medical specialties to enhance the accuracy, consistency, and reliability of clinical records, ultimately contributing to improved patient care and safety.

Keywords: Emergency Admission; Clerking Proforma; Medical Records; Neurosurgery; Clinical Documentation; Patient Safety; Quality Assurance; Health Care

Citation: Kazmi WAS, Durrani UK, Rathod Z, Elshalakany AA. Enhancing the quality of emergency admission clerking in neurosurgery: A comparative study of traditional methods versus a surgical clerking proforma. J Ayub Med Coll Abbottabad 2024;36(4):730–3.

DOI: 10.55519/JAMC-04-13720

INTRODUCTION

Accurate and comprehensive documentation is the cornerstone of effective patient care, particularly in high-risk medical environments such as neurosurgery. The admission clerking process serves as the primary record of a patient's initial assessment and clinical status upon entering the hospital. In neurosurgery, where clinical decisions often involve complex and high-stakes interventions, the quality of clerking notes can significantly impact patient outcomes. Traditional freehand clerking methods are frequently associated with incomplete or inconsistent records, leading to information gaps that can compromise patient safety and clinical decision-making.[1,2]

To address these limitations, structured proformas have been developed and implemented to standardize the documentation process, ensuring the completeness and accuracy of patient records.[3,4] However, despite the recognized importance of accurate documentation in neurosurgery, limited research has focused specifically on the impact of structured proformas in this specialty. Most existing studies have been conducted in general surgery or medical units, leaving a gap in understanding how these tools can benefit neurosurgical practice.[5,6]

This study aims to evaluate the effectiveness of a surgical clerking proforma in a tertiary care neurosurgery unit by comparing the completeness of emergency admission documentation before and after the proforma's introduction. This study contributes to the broader discourse on the role of structured documentation tools in enhancing patient safety and clinical efficiency.[7,8]

MATERIAL AND METHODS

This study was conducted as a comparative audit in a tertiary care neurosurgery unit, divided into three phases: an initial audit of traditional freehand clerking methods, the implementation of a structured surgical clerking proforma, and a subsequent re-audit of clerking practices post-implementation.

The study took place in the neurosurgery department of a tertiary care hospital where patients are admitted through emergency referrals. This unit manages a high volume of complex neurosurgical cases, making accurate and thorough documentation critical.

Retrospective data were gathered from the admission records of 40 emergency neurosurgical patients admitted before the introduction of the clerking proforma. These records were reviewed to assess the completeness of documentation. Prospective data were collected from the admission records of 30 emergency neurosurgical patients admitted after the implementation of the clerking proforma. The same parameters used in the initial audit were evaluated to allow for direct comparison. The completeness of each parameter was recorded and compared between the two cycles. Parameters included essential documentation elements such as "Consultant Responsible," "Reviewing Doctor," "Group & Screen," "Coagulation Profile," "White Cell Count," and "C-Reactive Protein (CRP)".[9,10]

A paired t-test was conducted to determine the significance of the differences observed between Cycle 1 and Cycle 2. The t-test compared the mean completeness scores of documentations before and after the introduction of the clerking proforma. Cohen's d was calculated to measure the effect size, and 95% confidence intervals were computed to estimate the true difference in completeness scores. Due to the summary nature of the data, simulated patient records were created for both cycles to apply paired t-tests and evaluate statistical significance.

The study was conducted in compliance with institutional ethical standards, ensuring the confidentiality of all patient data. As the research involved an audit of existing clinical practices, formal ethical approval was not required. However, all necessary institutional permissions were obtained. Patient records were anonymized, and no identifiable information was used in the analysis.

RESULTS

The completeness of emergency admission documentation was assessed across 31 key parameters before and after the implementation of the surgical clerking proforma. The mean completeness for Cycle 1 (pre-proforma) was 40.97% (SD=36.09%), whereas the mean completeness for Cycle 2 (post-proforma) significantly increased to 65.27% (SD = 22.99%).[11]

Significant improvements were observed in the documentation of the following parameters: Consultant Responsible improved from 12.5% in Cycle 1 to 42.5% in Cycle 2 (p=0.0034); Reviewing Doctor improved from 32.5% in Cycle 1 to 65.0% in Cycle 2 (p=0.0105); Group & Screen improved from 2.5% in Cycle 1 to 53.33% in Cycle 2; Coagulation Profile improved from 2.5% in Cycle 1 to 53.33% in Cycle 2; White Cell Count improved from 2.5% in Cycle 1 to 53.33% in Cycle 2; and C-Reactive Protein (CRP) improved from 2.5% in Cycle 1 to 53.33% in Cycle 2.[12] Paired t-tests performed on the simulated data for each parameter confirmed that the improvements observed between Cycle 1 and Cycle 2 were statistically significant for several parameters, indicating that the proforma had a substantial positive impact on the completeness of documentation in these areas.

Some parameters, such as Presenting Complaint (PC) and History of Presenting Complaint (HPC), did not show statistically significant differences, likely due to already high completeness in Cycle 1. These parameters had mean completeness scores of 97.5% in Cycle 1 and 100.0% in Cycle 2.

DISCUSSION

The introduction of the surgical clerking proforma in the neurosurgery unit led to significant improvements in the completeness of emergency admission documentation. Notably, the parameters Consultant Responsible and Reviewing Doctor showed statistically significant improvements, with documentation completeness increasing by 30% and 32.5%, respectively. These findings suggest that the proforma effectively standardizes the documentation process, ensuring that critical information is consistently recorded.[13]

This result is particularly important as the identity of the reviewing doctor is crucial for continuity of care and for ensuring that any follow-up actions are correctly attributed. Inaccurate or incomplete documentation in this area can lead to miscommunication among healthcare professionals and potential delays in patient care. The structured proforma minimizes these risks by ensuring that the reviewing doctor's details are clearly and consistently recorded, thereby improving the overall quality of patient management[14].

These findings align with previous studies that have demonstrated the benefits of structured proformas in various clinical settings. For instance, a study in BMJ Open Quality found that the use of a surgical clerking proforma significantly improved the completeness and clarity of patient records in a

surgical admissions unit.[15] Similarly, other studies have shown that structured documentation tools help reduce omissions and improve the quality of medical records, which are critical for patient safety and effective clinical decision-making.[16,17]

The results of this study support the broader body of evidence advocating for the use of structured proformas to enhance documentation accuracy and consistency. The significant improvements in documentation completeness observed in this study provide further evidence that proformas are valuable tools in high-stakes medical environments such as neurosurgery.

While the study's findings are encouraging, several limitations must be acknowledged. First, the use of simulated data for the paired t-tests, although necessary due to the summary nature of the original data, introduces certain assumptions about the data distribution. These assumptions may not fully reflect the real-world variability in documentation practices.[18] Second, the study was conducted in a single neurosurgery unit, which may limit the generalizability of the findings to other settings or specialties. Future studies could benefit from including multiple units or hospitals to validate these findings across different contexts.[19]

CONCLUSIONS

The implementation of the surgical clerking proforma in the neurosurgery unit led to significant enhancements in the completeness of emergency admission documentation. Notably, the parameters related to the Consultant Responsible and Reviewing Doctor demonstrated marked improvements, with documentation completeness increasing by 30% and 32.5%, respectively. These results highlight the proforma's effectiveness in standardizing documentation, ensuring that critical information is consistently and accurately recorded.

The improvement in documenting the reviewing doctor's identity is particularly crucial for ensuring continuity of care and correctly attributing follow-up actions, thereby minimizing the risks associated with miscommunication and delays in patient management. The structured proforma has proven to be an invaluable tool in enhancing the reliability of clinical records, which is essential for patient safety and effective clinical outcomes.

These findings strongly support the broader adoption of structured proformas in clinical settings, particularly in high-risk specialties like neurosurgery. By improving the accuracy and thoroughness of clinical documentation, such tools can significantly contribute to better patient care. It is recommended that healthcare institutions integrate these proformas into their documentation processes and ensure that clinicians receive adequate training on their use. Additionally, regular audits and feedback mechanisms should be implemented to maintain high documentation standards and foster continuous improvement in clinical practice.

Acknowledgements:

The authors would like to express their sincere gratitude to the surgical nursing and administrative staff of the Neurosurgery unit at Kings College Hospital NHS Foundation Trust for their invaluable support and cooperation throughout the study. We are also deeply appreciative of the assistance provided by the hospital's Medical Records Department in facilitating access to patient data and ensuring the smooth execution of the audit.

Special thanks to the Clinical Governance Department for their guidance and for registering the audit cycles, ensuring that the study adhered to all necessary institutional protocols.

Lastly, we extend our appreciation to our colleagues, Dr. Ushna Khan Durrani, Dr. Zara Rathod, and Aya Abdelhamid Elshalakany, whose contributions and collaboration were essential to the completion of this study.

AUTHORS' CONTRIBUTION

WASK: Conceptualization of the study design. UKD, ZR: ABE: Data collection, data analysis, data interpretation. WASK, UKD: Write-up, proof reading.

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Submitted: August 14, 2024	*Revised: October 8, 2024*	*Accepted: November 5, 2024*

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ORIGINAL ARTICLE

OUTCOME OF ARTHROSCOPIC NON-ANATOMIC REPAIR OF MASSIVE ROTATOR CUFF TEAR: A RETROSPECTIVE ANALYSIS

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Background: The aim was to assess the clinical outcome of non-anatomic rotator-cuff repair in large tears not amenable to anatomic repair and to assess the preoperative factors that affect the result of such repairs. A retrospective case-series at Ghurki Trust Teaching Hospital, Lahore. Twenty-seven cases that underwent non-anatomic rotator-cuff repair at GTTH over the last 5 years and met inclusion criteria were assessed over a three-month study period (from 01/10/2023 to 31/12/2023). **Methods:** Outcome was assessed in terms of improvement in pain as per visual-analog-scale (VAS), UCLA, as well as Constant score. Furthermore, patients' satisfaction was also assessed to measure subjective efficacy of the procedure. **Results:** Most commonly cases of rotator cuff tear present with pain, weakness, and restriction of shoulder range of motion. Pain improved significantly **(p<0.001)** from preoperative score of 3.68 to 1.45. Analysis of the objective assessment showed statistically significant **(p=001)** improvement in Constant score from a preoperative average score of 63.63 to a postoperative average of 77.27, with significant improvement **(p=0.05)** in each individual scoring criteria as well. The other scoring studied: UCLA also improved significantly **(p=0.001**) from 25.36 to 30.18. Despite this, on subjective assessment 40.9% of the sample was very satisfied and 27.3% were satisfied with the outcome. **Conclusion:** Non-anatomic repair is very effective at treating the presenting complaints of the rotator cuff tear patients. Thus, alongside good clinical outcome, patient satisfaction can be predicted after the procedure.

Keywords: Rotator cuff tear; Anatomic repair; Constant score; University of California at Los shoulder score

Citation: Usama M, Uddin B, Faheem MU, Amin A, Bajwa MA, Sohail A, Khan SA. Outcome of arthroscopic non-anatomic repair of massive rotator cuff tear: a retrospective analysis. J Ayub Med Coll Abbottabad 2024;36(4):734–7.

DOI: 10.55519/JAMC-04-13574

INTRODUCTION

One of the frequent complaints for which patients present to orthopedic OPD are shoulder issues.[1] Among elderly population rotator cuff tears affect up to 50% of patients [1] making it roughly up to 23% of the visits to a shoulder surgeon.[2] The rotator cuff consists of four muscle supraspinatus, infraspinatus, teres minor & subscapularis, their main function is to stabilize the humeral head inside the glenoid cavity and rotate the humerus in relation to the scapula. The s first 10° to 15° degree of elevation is initiated by supraspinatous muscle together with the infraspinatus, teres minor and subscapularis muscles. Injury to one of these muscle result in chronic pain, loss of functional capacity & weakness.[3]

Rotator cuff lesions are clinically challenging .[4] Rotator cuff injuries have incidence among female between age group 55-60 years are considered to be one of the commonest diseases of the shoulder.[1] The underlying pathology is either traumatic or degenerative origin.[5] The treatment plan may vary depending upon the age of patient & functional status, choice of procedure for young active patient is bit complex. As per literature in patients less than 65 years age surgical repair of rotator cuff injury with post operative rehabilitation provides better chance of tendon healing & functional status.[6] Patients with cuff deficiency suffer from severe functional disability resulting in loss of active elevation also known as pseudo-paralysis. Pseudo-paralysis is defined as inability to perform active elevation of arm above 90, with normal passive mobility of shoulder. This is generally the result of Cuff-tear arthropathy, which is an irreparable cuff rupture associated with osteoarthrosis of the shoulder .[7]This inability to perform active elevation secondary to rotator cuff injuries that are mainly large or extensive. Though the data suggest that the repair of these extensive injuries has good outcome [8] Active range of motion deficit is one of the alleged negative influencing factors of rotator cuff repair. Thus, with the recent popularity of reverse total shoulder arthroplasty (RTSA), there is a tendency toward performing RTSA in cases of nonarthritic large-to-massive tears with pseudo paralysis.[9]

Rotator cuff tears are of two types, complete or incomplete. Complete tears also referred as full thickness tear, tendon is completely separated from bone[13], complete repair of massive cuff tear is heralded by tendon retraction & poor quality of tissue .[10] On the other end, partial tears also referred as incomplete tears, the tendon

is not completely separated from bone. Incomplete tears are generally managed conservatively with physical therapy, NSAIDs and subacromial injections. In complete tears treatment of choice is anatomic or complete repair. For massive rotator cuff tears not amenable for total repair, partial repair with aim of creating biomechanically functional cuff without the need of full anatomic coverage is considered ideal treatment plan. Partial repair is also referred as non-anatomic repair is the one in which when tendon cannot be reduced to its anatomic origin, it is fixed at a non-anatomical site that is usually medial to its origin .[12] Where possible, complete anatomic repair should be performed.[14] In scenarios where tear is so massive that non-anatomic repair is also not possible, tendon transfer (pectoralis major or latissimus dorsi) is done if shoulder joint is not arthritis and RTSA is done if the joint is arthritic.[10,11] A research done by Shon MS *et al.* inferred that the good clinical improvement was noted in patients undergoing partial rotator cuff repair of massive rotator cuff repair.[13] Similar findings were presented in the publication of Malavolta EA.[2]

Thus, it was hypothesized that non-anatomic or partial repair has been shown to have promising results in terms of functional and radiologic improvement. Thus, aim of the study was to evaluate the clinical outcome of non-anatomic rotator cuff repair and to assess the preoperative factors that influence the outcome in such repairs.

MATERIAL AND METHODS

A retrospective cross-sectional analysis was performed at Ghurki trust teaching hospital Lahore, after getting ethical approval from Institutional Review Board of the hospital. All those that met sample inclusion criteria and had arthroscopic partial or non-anatomical repair of rotator cuff tear after 1st January 2017 were enrolled. Patients of both genders, aging greater than 18 years and having complete surgical and follow-up assessment record were included. The cases that had concomitant injury of the shoulder girdle as fracture of humerus, scapula or clavicle were excluded. Similarly, the cases in which the data was incomplete in any aspect were excluded, to avoid potential bias. Duration of the study was 3 months. Data collection was done using records present in hospital databases/HMIS and follow-up visits. It was done by using a pre-designed performa. The information collected included the patient's demographic details and other associated variables including pain, constant score and UCLA score. Constant score assesses function of the shoulder in terms of pain experienced, daily life function, power and range of motion (ROM) at the shoulder; where higher score represents better function. UCLA score assesses pain, ROM, strength, function and satisfaction: here too, higher score represents better function. The patients were reviewed at postoperative 3-week, 6-weeks, 12-week (3 months) and 6-month at the out-door unit; and thorough clinical and radiological assessment alongside physical rehabilitation (in collaboration with a fully equipped physiotherapy department) was done. Patient's satisfaction level with the results of non-anatomic repair was assessed on the last follow-up. All the data was processed through Statistical Package for the Social Sciences software (SPSS) version 23.0. Descriptive analysis was performed in terms of measures of central tendencies i-e mean and standard deviation (SD) and proportions. Pain and clinical scores were compared with pre-operatively recorded values via use of chi-square / fisher's exact test and student's t-test.

RESULTS

In this project, we examined the demographic as well as clinical data of 22 patients undergoing non-anatomic rotator cuff repair. The Demographic analysis showed a predominant presence of male participants 68.2% (15), with most sustaining injury of their right side 86.4% (19). A notable percentage 77.3% (17) reported the involvement of their dominant arm, while 54.5% (12) had diabetes, and 36.4% (8) had a history of smoking. Quantitative variables indicated that the mean age was 63.5 years, with a SD of 7.95, and the mean duration of symptoms was 43.68 months, with a SD of 9.06. The mean follow-up period was 14.27 months, with a SD of 3.43.

The inferential analysis showed significant improvements post-procedure in pain, constant score, and UCLA score (Table-1), all with *p*-values less than 0.001. Pain improved significantly ($p<0.001$) from preoperative values of 3.68 to 1.45. Results of objective assessment showed statistically significant ($p=001$) improvement in Constant score from a preop mean of 63.63 to a postop mean of 77.27. Furthermore, significant improvement ($p=0.05$) in each individual scoring criteria of Constant score was noted as well. This signified that the patients' pain was affectively reduced which led to significant improvement in mobility, strength and activities of daily life (ADL). The other studied score: UCLA, also improved significantly ($p=0.001$) from 25.36 to 30.18. On subjective assessment 40.9% of the sample was very satisfied and 27.3% were satisfied with the outcome. Patients' satisfaction levels are illustrated in Figure-1.

Table-1: Inferential analysis of clinical improvement following the procedure

Variable	Preoperative mean (SD)	Postoperative mean (SD)	t-value	*p*-value (at df of 21)
Pain (VAS)	3.68 (91.49)	1.45 (0.8)	5.72	**<0.001**
Constant score	63.63(11.35)	77.27 (11.31)	-3.79	**0.001**
UCLA score	25.36 (4.5)	30.18 (3.45)	-3.91	**0.001**

bold (*p*-values) stand for statistically significant results at confidence interval of 95%

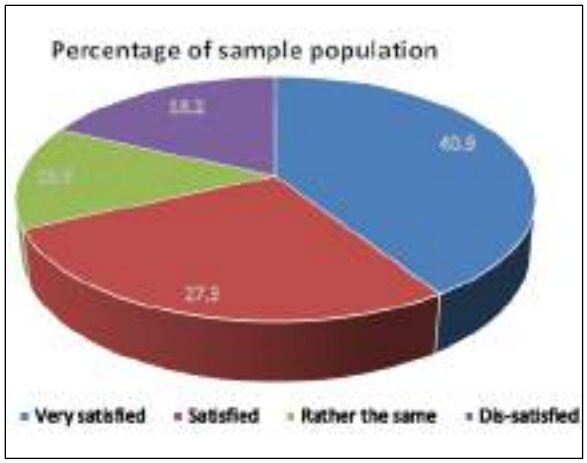

Figure 1: Patients' satisfaction level

Associations of gender, side affected, smoking, diabetes, and dominant arm involvement with patients' satisfaction were not statistically significant. Age showed a borderline statistically insignificant association (p=0.06), similarly duration of symptoms and follow-up period did not exhibit significant associations. These findings provide valuable insights into the clinical outcomes of the procedure and its impact on patient satisfaction. **(Table-2)**

Table-2: Association of studied variables with patients' satisfaction

Variable	*p*-value
Gender	0.35¥
Side affected	0.52¥
Smoking	0.19¥
Diabetes	1.00¥
Dominant arm involvement	1.00¥
Age	0.06
Duration of symptoms (months)	0.30
Follow-up period (months)	0.10

¥Fisher's Exact test applied

DISCUSSION

The current study favors arthroscopic partial repair, as it has shown better result in terms of pain improvement for patients with rotator cuff injuries. One of the studies published in The American Journal of sports medicine in which patients were followed for 1 year & 2 year minimum, when results serially compared it showed less satisfactory outcome, as one half of patients despite initial improvement reported symptoms deterioration over the time. On the contrary our study showed that 40.9% of the patients had significant improvement, with 27.3% being satisfied in general.[13] Presence of multiple factors such as involvement of dominant arm & comorbidity like diabetes mellitus influenced outcomes & patient satisfaction. Kim *et al*. had a mean follow up period of 41.3 month in their study ,reported that patients who did not have fatty degeneration in entire supraspinatous , infraspinatus ,or teres minor & that did not have severe atrophy in either of these three muscles , arthroscopic partial repair and margin convergence in irreparable large-to-massive tear were effective in reducing pain and improving functional outcomes .[15] However, in study exclusion criteria included patients with subscapularis tears requiring repair ,those with substantial fatty degeneration of the infraspinatus or supraspinatus muscles .

Mobilization of tissue to reduce the torned cuff tendon back to original anatomical point is challenging for surgeon in large massive tears. In cases where a torn tendon needs to be repositioned to anatomical point, stretch on fibers result in excessive tension, even if the fibers of the affected area have to be repositioned to the footprint's initial position, tension is often excessive. To overcome this tension, medicalization of insertion site of tendon of rotator cuff has been suggested. The repositioning of the anatomic insertion of the rotator cuff to the medial side of the cartilage of the humeral head, the medialization procedure allows the repair of the retracted tendons. However, this medialization alters shoulder range of motion & results in diminished moment arm, especially at the cuff tendon, and a smaller articular surface area of the humeral head.[16]

Results of our study are aligned with the literature. Lee *et al.* [17] conducted a similar study; the male-to-female ratio was 22:20 with a mean age of 61.2±9.1 years. The average follow-up duration was 35.4±7.3 months. At the final follow-up, significant improvement was observed in the average pain score of 1.9±1.2, UCLA score of 30.9 ± 2.3, and constant score of 88.8±7.9, i.e., p<.001, while the failure rate was 23.8% based on the radiological outcomes. In another study, 27 patients were included, and the constant score improved from 43.6±7.9 to 74.1±10.6 (P < .001). The pain level improved from preoperative 2.6±2.5 to postoperatively 9.6±2.4 (p<.001).[16] In a similar study with postoperative follow-up of 11.5±1.0 years, significant improvement in functional score was observed as 21.0±3.59 and 32.7±3.11, respectively.[18]

In our study all of the clinical parameters assessed showed significant improvement postoperatively. Literature suggests that it is the postoperative recovery of force couple mechanism of shoulder joint that offsets force and improves strength in a final common pathway. This indicates that in management of large massive rotator cuff injuries arthoscopic partial repair offers a better alternative treatment compared to complete repair even with high rate of retears. Thus, the implementation of non-anatomic repair is massive rotator cuff tears will help improve the clinical outcome in elderly patients sustaining these massive tears. Hence, this will abolish the need of major procedures including tendon transfers or RTSA in such cases.

One of the main strengths of our study is the comprehensive assessment of clinical outcomes using multiple validated scoring systems, including pain on VAS, Constant score, and UCLA score. This shows a effectiveness of partial repair in improving various aspect of shoulder function.

Study limitations: The study was performed in a single center with a limited number of cases. Thus, a multi-centric study with a larger sample size is required to present more generalized inferences. Furthermore, randomized control trials and systematic reviews are needed to formulate best practice guidelines for the management of massive rotator cuff tears with non-anatomic repair techniques.

Furthermore, future research should address the issue of the duration of efficacy and the sustainability of the obtained clinical changes and patients' satisfaction. Further research should also consider the conditions under which some characteristics, including tear size, muscle atrophy, and fatty degeneration, affect the results of partial repair.

CONCLUSION

On the basis of the inferential analysis stated above, it is obvious that incomplete or non-anatomic repair is very effective at treating the two most common presenting complaints of the patient. Thus, alongside good clinical outcome, patient satisfaction can be predicted after the procedure. Therefore, in massive rotator-cuff tears it should be considered as an effective repair technique.

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Submitted: July 10, 2024	*Revised: October 17, 2024*	*Accepted: November 21, 2024*

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ORIGINAL ARTICLE

COMPARISON BETWEEN EFFICACY OF TYMPANOPLASTY WITH AND WITHOUT CORTICAL MASTOIDECTOMY IN TUBO-TYMPANIC OTITIS MEDIA IN ADULTS

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Background: Chronic suppurative otitis media (CSOM) tubo-tympanic type is a common ear condition in underdeveloped nations. Cortical mastoidectomy in conjunction with tympanoplasty has long been regarded as the preferred surgical procedure for patients with chronic non-cholesteatomatous otitis media. Studies contrasting tympanoplasty with and without cortical mastoidectomy improved hearing, but the results were comparable. Both of these procedures are still debatable and mandate further research. This comparison has not been conducted in Pakistan before. Our objective is to evaluate whether tympanoplasty is effective in managing tubo-tympanic otitis media in patients with or without cortical mastoidectomy. **Methods:** Eighty-two patients (equally divided into two groups) were recruited from the Shaikh Zayed Hospital, Lahore. Group A (n=41) referred to tympanoplasty with mastoidectomy and group B (n=41) referred to tympanoplasty alone. Data was gathered using a pre-designed *Proforma*, and SPSS version 25.0 was used for analysis. Post-operative hearing improvement was calculated from the audiometric' air-bone gap before the operation minus the ABG of post-operative follow-up at 16 weeks. A hearing gain of at least 15dB was considered clinically relevant. **Results:** Hearing improvement was observed in 73.3% of participants in group A while 83.3% in group B, grafting status was 95.1% in group B and 90.2% in group A, and discharge presence was 7.3% and 17% in group A and group B respectively. **Conclusion:** In CSOM, mastoidectomy does not add significant benefit in terms of hearing & graft uptake, however, it is advantageous if the middle ear mucosa is unhealthy. Tympanoplasty alone is sufficient if the middle ear mucosa is healthy.

Keywords: Mastoid; Mastoidectomy; Otitis Media; Tympanoplasty

Citation: Shahzadi E, Qazi ZA, Latif S, Rehman A, Ullah I, Haroon T. Comparison between efficacy of tympanoplasty with and Without cortical mastoidectomy in tubo-tympanic otitis media in adults**.** J Ayub Med Coll Abbottabad 2024;36(4):738–43.

DOI: 10.55519/JAMC-04-13597

INTRODUCTION

Conductive hearing loss is caused by chronic suppurative otitis media (CSOM), a chronic inflammatory condition of the middle ear and mastoid that frequently culminates in partial or complete loss of the tympanic membrane (TM) and ossicles, can be as severeas 60–70 dB.[1] It is a widespread disorder affecting 0.5–30% of society. Therefore, a conservative estimate puts the number of CSOM patients at approximately 20 million worldwide.[2] Tubo-tympanic and atticoantral diseases are the two primary categories of CSOM.[3] An upper respiratory tract infection or water entry through a perforation may cause an intermittent, mostly mucoid or mucopurulent discharge, which is indicative of tubo-tympanic illness. The most typical signs of tubo-tympanic illness included discharge from the ear, recurring or chronic ear discharge (otorrhea), hearing loss, ear pain,and tinnitus throughout 2 to 6 weeks. There was a central hole and a lot of mucoid, odourless discharge. Infections in the oropharynx, nasopharynx, and oesophagus can spread to the middle ear via the eustachian tube and cause tubo-tympanic (mucosal) otitis. Poor living circumstances, lack of hygiene practices, and non-nutritious food contribute to a high prevalence of CSOM among children and young adults in the middle classes of developing nations.[4] Mastoiditis is only one of several variables that might hinderthe healing of a torn tympanic membrane. The mucoperiosteal lining of the middle ear cleft is inflamed, causing this illness.

Surgery is the mainstay of CSOM treatment, with the main objectives being the elimination of the illness, preventing recurrence, and maintaining or improving hearing. Tympanoplasty is a procedure intended to repair the middle ear hearing mechanism, whereas "mastoidectomy" is intended to eliminate the illness in the mastoid and middle ear.[5] Timing of surgery and patient selection are also important factors in the success of tympanoplasty and mastoidectomy (except for patients who need emergency surgery for

extracranial or intracranial complications of CSOM). Tympanoplasty is more challenging and has less consistently favourable results in children with CSOM than in adults, thus this is very important. However, there is a lack of conclusive proof.[6] Graft-take rates were shown to increase exclusively with increasing age, according to a meta-analysis of 30 trials on paediatric tympanoplasties. Successful recovery may or may not be predicted by factors such as surgical approach, history of adenoidectomy, presence of current infection, perforation size, contralateral ear health, or eustachian tube function. In mild cases of a disease, being young may not even increase your chances of getting sick. Results were similar in ears operated on between 2.5and 7 years of age and 8 to 14 years of age in 116 children with non-cholesteatomatous CSOM who were followed for 16–27 years. During the study, only 14% of ears were modified.[7]

There is still much uncertainty about whether or not mastoidectomy helps people who don't have active infectious illness. However, mastoidectomy has been demonstrated to have much better results in instances with current infections. In antibiotic-resistant instances of CSOM, a cortical mastoidectomy may be necessary to eliminate the infection.[8] The major function of mastoidectomy is to enhance ventilation and drainage of the temporal bone/mastoid air cell system, which benefits the middle ear and mastoid milieu interie mastoid air cell system (MACS). Tympanoplasty, with or without mastoidectomy, has a success rate in treating chronic paediatric otitis media. An estimated 0.5–30% of people worldwide suffer from chronic suppurative otitis media (CSOM), especially the tubo-tympanic type. The state of living, lack of hygiene, and inadequate nutrition in Pakistan continue to make the condition a serious public health concern. Children and young adults are especially prone to tubo-tympanic otitis media, which frequently results in recurrent infections and calls for surgical intervention. Reconstruction of the tympanic membrane using graft materials and techniques has been detailed in great detail since the inception of tympanoplasty by Zoellner and Wullstein in 1952.[9] Tympanoplasty and mastoidectomy are common surgical procedures used to permanently treat CSOM. Tertiary care centres in all industrialized nations often include an otologic section where such treatments can be performed. Through the use of bone drills and microsurgical tools, the mastoid air cells, granulations, and debris are removed during a mastoidectomy.[10]

Closing the tympanic membrane perforation with a soft tissue graft, with or without ossicular restoration, is what tympanoplasty is all about. Tympanoplasty procedures vary according to how severely the ossicular chain has been damaged;[11] for example, if the malleus, incus, and stapes have all been destroyed in rapid succession, the tympanic grafts will need to be gradually farther positioned medially. In cases when cholesteatoma is absent, a mastoidectomy and tympanoplasty may be done separately or concurrently to remove CSOM. In both, the middle ear is examined, and the ossicles and mucosa may be removed to ensure the infection is gone.[12]

It is also possible to remove the bony wall of the posterior canal that divides the middle ear and mastoid chambers by drilling, with the removal interrupted only to protect the facial nerve at its base. For comparison, when the posterior canal wall is kept and a hole is created through it to get access to the middle ear, this procedure is known as an intact canal-wall mastoidectomy (ICW).[13] The latter helps make tympanoplasty, which restores hearing by reshaping the eardrum, a more viable option by preserving the middle ear's natural architecture. However, because of the restricted surgical access to the middle ear, ICW mastoidectomy is more technically challenging and frequently results in recurring or persistent illness.[14] So, it's important to keep an eye on patients after surgery and have them informed about additional procedures if they need to checkfor complications or remove any lingering cholesteatoma. The Canal Wall Down (CWD) mastoidectomy may be less complicated to carry out, and it certainly provides excellent access to the middle ear,which is very helpful when dealing with large cholesteatomas. Recent investigations showed satisfactory postoperative hearing gain; nevertheless, the absence of graft support supplied by the posterior canal wall may be a threat to successful surgical restoration of hearing.[15] Compared to pre-CWD patients, those who have undergone CWD have a reduced risk of ear disease recurrence and require fewer further surgeries like tympanoplasty or mastoidectomy. Choosing the right operation frequently has less to do with research findings and more to do with individual patient characteristics and the surgeon's level of experience. When the air cells in the mastoid are constricted, for instance, an ICW mastoidectomy is impossible to perform.[16]

Successful graft (97%) take has been reported by Dave and the hearing outcomes were quite positive.[17] Eighty-seven percent of the type I tympanoplasties, seventy-three percent of the type III partial ossicular replacement prosthesis (PORP), and seventy percent of the type III total ossicular replacement prosthesis (TORP) tympanoplasties in their series were successful in closing the ABG to within 10 dB. In a broad series of cartilage tympanoplasties, Baz found that 92% of patients experienced successful drum closure and had average ABGs of less than 30 dB.[18] The percentage of type I

cartilage tympanoplasty among the 52 patients described by Dispenza *et al*. was 18%. In all cases, the TM closed, and the average ABG was 4 dB. Adkins documented 55 instances of tympanoplasties performed on cartilage to correct retractions. Successful graft take was seen in 18 patients, and the average conductive loss was less than 10 dB. Comparison of graft uptake, hearing improvement, and disease clearance noticed after tympanoplasty alone versus cortical mastoidectomy.[19]

Repair of a perforated tympanic membrane by tympanoplasty is well-established. Many recent studies have examined whether or not cortical mastoidectomy can enhance the effectiveness of tympanoplasty.[20,21]

In the study of 40 patients, Shew *et al*. found a 94% success rate when tympanoplasty was performed in conjunction with cortical mastoidectomy and a 93% success rate when tympanoplasty was performed alone, demonstrating that mastoidectomy is always necessary.[22] Zhu *et al*. found that Myringo plasty was successful in closing tympanic membrane perforations in 76.1% of 46 patients and in 78.3% (n=36) of 46 patients who also underwent mastoidectomy.[23] There was no discernable statistically significant change. Krishnan *et al*. found that postoperative hearing gain was 75% across the board for their study's two groups. Similarly, Huang *et al*. observed no statically significant difference in graft failure rates or hearing outcomes between tympanoplasty with and without mastoidectomy in a trial including 48 patients with CSOM. Poor eustachian tube function, a history of numerous bouts of acute otitis media, and living in crowded surroundings all raise the risk of CSOM.[12] In most cases, the disease manifests itself in young children. Acute otitis media (AOM) is an acute infection of the middle ear that can cause a tympanic perforation (eardrum rupture) in around 11 percent of the world's population every year. Approximately 4.4% of the population is affected by COM. There is a striking disparity in the global prevalence of COM, with rates being only one-third as high in high-income countries as they are in low-income ones. Around 21,000 individuals worldwide perish every year as a direct result of COM problems.[9]

Persistent mucosal inflammation causes permanent deformities in the middle ear and mastoid cavity in tubotympanic CSOM. In addition to a medialized uncinate process and middle turbinate hypertrophy, DNS is the most often seen etiopathological component in the development of CSOM.[11] The use of computed tomography (CT) scan documentation to validate DNS was crucial for the treatment of patients with active, no-risk CSOM who had sinus or nasal disease. It was determined that the average age was 32.45±12.36 years. Sixty-one percent of patients were between the ages of 31 and 50, and the male to female ratio was 1.20. Sixty-two percent of patients with benign CSOM had DNS, making it the most prevalent associated sinonasal pathology (*p* 0.003). The least prevalent reason was a hypertrophied middle turbinate (25% of cases). Significantly, CT scans confirmed DNS in62% of patients.[10] The goal of surgical procedures like mastoidectomy and tympanoplasty is to remove middle ear disorders and restore hearing. The need for cortical mastoidectomy in addition to tympanoplasty, however, is a topic of much discussion, especially when the middle ear mucosa seems to be in good condition. The purpose of this study is to compare the effectiveness of cortical mastoidectomy and tympanoplasty in treating adult patients with tubotympanic otitis media in 82 patients from Shaikh Zayed Hospital in Lahore. The study closes a gap in the literature and offers information on the best surgical treatments for Pakistani patients with CSOM.

MATERIAL AND METHODS

We conducted a randomized controlled trial involving adult patients of tubotympanic otitis media of both genders, who were admitted through OPD in Shaikh Zayed Hospital, Lahore. The sample size was estimated by using a 7% margin of error with a confidence level of 95%. The total sample size is 82 divided into two groups (41 in each group) using a lottery technique. The sample selection criteria included age 18–50 years of both genders, type I tympanoplasty (myringoplasty), while exclusion were extreme age patients, recurrent surgery, active infection of the nose and paranasal sinuses, comorbid DM, HTN, and other immunocompromised states.

A written informed consent was taken from each patient after explaining the risk, purpose, and benefits of this research. Detailed history including age, gender, and medical number were noted in data collection *Proforma*. The types of tympanic membrane perforations included in the study were categorized into central, anterior, and posterior perforations. Only stable and dry middle ears were included in the study, with perforations confirmed to be dry for a minimum of 4 weeks before surgery. Patients with unstable, wet, or discharging ears were excluded. The presence or absence of aural polyps was assessed, and patients with polyps were excluded from the study to minimize variability in post-operative healing. A pre-operative tonal audiogram was conducted for all patients, describing both air and bone conduction thresholds as a baseline for later comparison of hearing improvement. We performed a detailed ear examination with an otoscope, examination under a microscope, and CT scan in a few

cases to rule out cholesteatoma, aural polyp, and granulations. The fate of granulation tissue and aural polyp was assessed intra-operatively and during follow-up to evaluate the effectiveness of tympanoplasty with or without cortical mastoidectomy. First, 41 patients included in group A were referred to tympanoplasty with cortical mastoidectomy in tubo-tympanic otitis media. The second 41 patients of group B were referred to tympanoplasty alone in tubo-tympanic otitis media. Post-operative hearing improvement was calculated from ABG before the operation minus the ABG of post-operative follow-up at 16 weeks. Grade of assessment was assessed as full take rate, partial take, or reperforation 4 months after surgery while post-operative hearing of the patient was also assessed.

Data was entered and analyzed through SPSS version 25.0. Quantitative variables like age, hearing, gender, lateral side, cause of perforation, graft uptake, reperforation, recurrence of discharge, and frequencies and percentages were presented. Comparison between groups was made by applying an independent sample t-test and Whitney U-test. Both groups were compared for efficacy and findings between with and without cortical mastoidectomy.

RESULTS

This study included 82 patients, divided into two categories: tympanoplasty with cortical mastoidectomy and tympanoplasty without cortical mastoidectomy. Descriptive statistics of sex, duration of symptoms, course of perforation, eustachian tube dysfunction, deviated nasal septum, traumatic, grafting status, discharge and re-perforation status, and hearing outcome were performed. The mean age of both groups was 35.4±12.7. The PTA test was done preoperatively and postoperatively, with a mean preoperative value of 39.4±9.7 and postoperatively 27.9±8.4. Bifurcation of demographic and clinical features in Group A, tympanoplasty with cortical mastoidectomy and Group B, and the bifurcation in hearing outcome (pure tone audiometry test) were performed. In this study, acute otitis media (AOM) perforation was present in 27 (65.9%) in group I and 38 (92.7%) in group II, with a statistical significance (*p*-value 0.04). The grafting rate was 80.4% in group A and 85.6% in group B, with no statistically significant difference. Ear discharge was observed in 3 cases in group A and 7 cases in group B, showing marginal significance (*p*=0.08). Re-perforation occurred in 4.9% of patients in group A and 12.2% in group B, with marginal statistical significance (*p*=0.07). Hearing outcome, measured by the pure tone audiometry test, showed significant improvement in group A compared to group B.

Table-1: Bifurcation of grafting status, discharge, and re-perforation status in Group A; tympanoplasty with cortical mastoidectomy and Group B; tympanoplasty alone after surgery postoperatively.

Variable Categories	Group A 41 (50%)	Group B 41 (50%)	*p*-value
Grafting status			0.17
No	4 (9.8)	2 (4.9)	
Yes	37 (90.2)	39 (95.1)	
Discharge			0.08
No	38 (92.7)	34 (82.9)	
Yes	3 (7.3)	7 (17.1)	
Re-perforation status after surgery			0.07
No	39 (95.1)	36 (87.8)	
Yes	2 (4.9)	5 (12.2)	

DISCUSSION

Tymangioplasty with or without mastoidectomy is performed to eliminate middle ear disease and reconstruct the conductive hearing issue. In the current study, the patients selected were between 18 and 50 years old. Mastoid factors include the extent of mastoid pneumatization and the presence of inflammatory disease. A study conducted by Lasisi and Afolabi[5] reported that the commonest perforation size was medium but, in this study, the most common perforation size was central 37 (45.1%) followed by peripheral 28 (34.2%).

A study by Biswas *et al*. reported that the majority of patients had duration of symptoms within 1 year (62%) and had a right lateral side 51 (62.2%). Research has been carried out[24] which showed that the majority of the patients had a duration of symptoms within 1 year (62%) which was comparable with the present study as in this study majority of patients had a duration of symptoms up to 1 year (57.5%). Also, in this present study majority of patients had a right lateral side 51 (62.2%).

This investigation found that acute otitis media (AOM) lead to perforation was present in 27 (65.9%) in group I and 24 (58.5%) in group II with a statistically insignificant (*p*-value 0.04). Eustachian tube dysfunction was seen in 7 (17.1%) and 9 (22.0%) in groups I and II, respectively. The overall grafting rate was 76 (92.7%), with 37 (90.2%) grafting with cortical mastoidectomy and 39 (95.1%) grafting without. Ear discharge was reported only in 3 (7.3%) cases in group I, and recurrent perforation status after surgery was in 2 (4.9%) and 5 (12.2%) cases. These results were also comparable with the published data.[25] Hearing outcome (pure tone audiometry test) before and after surgery was 38.5±10.6 and 39.2±9.7. These results were comparable with published data.[26] The results may vary among institutions due to varying sterilization processes, the expertise of the surgeons, and the surgical facilities available at each hospital.

Almost all of the patients included in this

study were presented in Shaikh Zayed Hospital Lahore. This study's primary limitations include its single-center design and rather small sample size, which may restrict how broadly the findings may be applied. Furthermore, we are unable to evaluate the long-term sustainability of the surgical outcomes due to the absence of long-term follow-up. Future research should assess long-term safety and efficacy using longer follow-up periods and a larger, multi-center sample to get beyond these limitations. Furthermore, a more varied patient base might offer a clearer picture of the outcomes for various demographic categories.

CONCLUSION

We concluded that tympanoplasty provides a similar outcome to mastoidectomy in the tubo-tympanic type of CSOM, in terms of graft success rate and hearing gain. In our study, the p-value for both hearing outcome and grafting status was significant. However, if the middle ear mucosa is healthy, tympanoplasty alone is sufficient. For cases where there is persistent ear discharge or granulation tissue in the middle ear mucosa at a pre-operative examination under magnification, mastoidectomy may be more beneficial. Our research adds new insight by suggesting that mastoidectomy may be preferred in such cases, though its overall effect on postoperative hearing gain was not significantly positive.

ACKNOWLEDGEMENT

First and foremost, I would like to convey my profound thanks to my supervisors Prof. Dr. Naveed Aslam, Associate professor Dr Sarfraz for his support of my MS studies and research, as well as for his patience, inspiration, excitement, and vast knowledge. Throughout the whole period of my research and article writing, Assistant professor Dr Zia Qazi guidance was really helpful. I could not have imagined having a greater mentor and advisor for my doctoral studies. I'd like to thank the rest of my article co writers as well as my advisor.

Financial Disclosure:
No financial disclosure.

Disclaimer:
No disclaimer.

IRB Approval number:
SZMC/IRB/Internal/0091/2021

AUTHORS' CONTRIBUTION

ES, ZUS: Literature search. SL: Conceptualization of the study. IUR, IU: Data analysis, data collection. TH: Data interpretation. ES: Proof reading.

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Submitted: July 15, 2024	*Revised: September 26, 2024*	*Accepted: September 27, 2024*

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ORIGINAL ARTICLE

COMPARISON OF DOPPLER INDICES BETWEEN OBSTRUCTED AND NON-OBSTRUCTED KIDNEY

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Background: Acute renal colic is a common acute urologic conditions often caused by urolithiasis. However, diagnosis of obstruction due to urolithiasis sometimes becomes difficult especially when there is an insufficient dilation of urinary tract proximal to obstruction. In these situations, intrarenal artery doppler assessment may be utilized as a diagnostic modality.The aim of this study to evaluate intra-renal arterial Doppler parameters in patients presenting with unilateral acute renal colic, comparing obstructed and non-obstructed kidneys. **Methods:**This case controled study was done at Azeem Ultrasound and Xray Center and was completed in 6 months from 12-12-2023 to 11-06-2024. Sixty individuals were included in the study. Pelvicalyceal system dilatation was examined in each kidney using USG images. For the evaluation of inter-lobar arteries, a minimum of 3 doppler spectra were taken, and their mean was calculated. Resistiv index (RI) was measured using the standard formula, and the mean RI value was determined for each kidney. **Results:** The resistive index was elevated in the obstructed group (0.72±0.10) versus the unobstructed group (0.63±0.07; p<0.001). The predictive accuracy showed a sensitivity of 70.0%, a specificity of 86.67%, a postive pridictive value (PPV) of 78.97%, and an negatieve predictiev value (NPV) of 80.15%. **Conclusion:**The comparison of Doppler indices between obstructed and unobstructed kidneys in patients with urolithiasis reveals significant differences. Elevated RI and PI values, along with increased PSV, highlight that hemodynamics is altered in the presence of renal obstruction. These findings support the use of Doppler ultrasound as a valuable diagnostic tool, helping in the timely identification and management of obstructive uropathy.

Keywords: Urolithiasis; Acute renal colic; Obstructive uropathy; Doppler ultrasound; Resistive index; Pulsatility index

Citation: Ilyas S, Waseem F, Tariq AB, Shaukat S, Mehmood A. Comparison of doppler indices between obstructed and non-obstructed kidney. J Ayub Med Coll Abbottabad 2024;36(4):744–8.

DOI: 10.55519/JAMC-04-14004

INTRODUCTION

Urolithiasis is a common urologic condition in the general population with a global incidence of 115 million cases in 2019.[1] It may result in obstructive uropathy, any structural obstruction to flow of urine out of the urinary tract. As a result of this hindrance, pelvicalyceal dilatation occurs that, if left untreated, can causekidney damage.[2] The frequent symptoms of urolithiasis include acute renal colic, dysuria, hematuria, and difficulty passing urine.[3] Among these, renal colic is the most common presentation of renal obstruction with a prevalence of 18% in Pakistan.[4]

Prompt and correctidentification is important to prevent irreversible damage to the kidneys and guaranteeright management. However, diagnosing urinary obstruction due tostones becomes challenging sometimes, especially when there is insufficient dilation of the urinary tract proximal to obstruction.[5] The initial evaluation includes blood and urineanalysis, and imaging studies. It is challenging to diagnose early obstructive uropathy. When the urinary tract is obstructed, the pressure in the kidney rises, decreasing renal parenchymal compliance. It has a more significanteffect on intraparenchymal venous blood flow than arterial flow.[6–8]

Doppler ultrasonography has emerged as a potential diagnostic tool for evaluating renal blood flow and assessing the presence of obstruction. It is used to evaluate hemodynamics, and the resistivity (RI) and pulsatility (PI) offerdata about resistance to flow within blood vessel.[9] Viyannan *et al*., 2021 reported that RI in the arteries of the patients with obstructed kidneys was higher (0.75) than in those with unobstructed kidneys (0.56), with a p-value < 0.001, a sensitivity of 85% and a specificity of 93%.[5] Nadzri *et al*., 2015 also reported that RI was substantially varied between obstructed and non-obstructedkidney. Obstructed kidney had higher RI value (0.78) than non-obstructed kidney (0.70), with a p-value <0.05. For Doppler ultrasound the sensitivity was found as 100% and the sepecificty was 53%.[10]

However, there remains a gap in understanding how these Doppler parameters perform in patients presenting with acute renal colic, particularly within the first 24 hours of symptom onset. So, this study aimed to

evaluate intra-renal arterial Doppler parameters in patients presenting with unilateral acute renal colic, comparing obstructed and non-obstructed kidneys. By investigating these parameters, the study seeks to determine the use of Doppler ultrasonography in enhancing diagnostic accuracy and facilitating timely intervention, ultimately improving patient outcomes in cases of acute ureteric colic.

MATERIAL AND METHODS

This was a case controled study (cases were considered if they have Obstructed kidenies and controls were taken as non-Obstructed kidenies). The study was conducted at Azeem Ultrasound and Xray Center and was completed in 6 months from 12-12-2023 to 11-06-2024. The study included 60 patients (30 patients with Obstructed and 30 patients with non-Obstructed kidenies). The calculated sample size was very small in both groups, so we took 30 in each group. The sample size was calucalted uing mean RI as 0.75±0.08[5] in Obstructed kidnies and 0.56±0.09[5] in non Obstructed kidnies, using 80% power of test, 95% confidence level and 5% margin of error. We used convenient sampling technique to collect the data.

Patients aged 18–75 years presenting to or referred by a urologist with complaints of unilateral lumbar pain within 24 hours of onset were included in the study. Pateint with history of surgery, known renal malignancy, known chronic kidney disease, renal artery stenosis,and post-renal transplant were excluded.

After obtaining approval from ethical committee of the institute and informed consent from participants, 60 individuals were included in the study. Demographic variables such as age, gender, weight, and height were noted on pre-designed proforma. Clinical records were also monitored to assess serum urea and creatinine. We used Gray-scale ultrasonography in all patients ahving Philips iU-22 with C 1-5 transducer. Likewise, doppler evaluation of intra-renal arterieswas carried out using Siemens Acuson S-3000 with 6C1-HD transducer.Pelvicalyceal system dilatation was examined in each kidney using USG images. For the evaluation of inter-lobar arteries, a minimum of 3 doppler spectra were taken, and their mean was calculated.

The Doppler waveforms were generated using the lowest possible pulse repetition frequency to avoid aliasing, which maximized the Doppler spectrum size and minimized measurement error. Additionally, the lowest wall filter settings appropriate for each ultrasound scanner were employed. The Doppler sample width was adjusted to 2–3 mm. RI was measured using the standard formula, and the mean RI value was determined for each kidney.Normal RI ranges between 0.50–0.70 and value more than 0.70 denotes renal obstruction.[5]

SPSS version 26 was used for statistical analysis. Frequency and percentage were calculated for qualitative variable such as age groups, gender. Independent t-test was carried out for the continuous variables. While, chi-square statistics was used to determine the association between categorical variables. The supposed significance level was $p \leq 0.05$.The ROC(Receiver operating characteristic) curve was made and the AUC (area under the curve) was then estimated to compare the overall predictive accuracy of RI.

RESULTS

Table 1 shows the demographic parameters of patients. The mean age of patients was 44.70±15.93 years, indicating a middle-aged group with moderate variability. Males comprised 56.7% of the sample, while females accounted for 43.3%, showing a slight male predominance. The mean height was 165.82±7.00 cm, whereas the mean weight was 73.30±14.60 kg. Table-2 demonstrates clinical parameters of patients. The mean serum creatinine level was 1.33±0.77 mg/dl. The mean serum urea was 21.55±10.62 mg/dl. The mean PI was 0.89±0.29. The RI was 0.68±0.10, indicating normal to slightly elevated renal resistance. The PSV averaged 78.74±41.62 cm/s, while the EDV averaged 23.20±10.35 cm/s.

Table-3 compared various parameters between obstructed and unobstructed groups. The analysis shows no significant difference in age (obstructed: 44.50±15.41; unobstructed: 44.90±16.70; p=0.924) or gender distribution (p = 0.297) between the groups. Weight also does not differ significantly (obstructed: 72.90±12.83; unobstructed: 73.70±16.40; p=0.834), nor does height (obstructed: 166.90±7.69; unobstructed: 164.73±6.18; p=0.234). Significant differences were observed in serum creatinine levels, with the obstructed group showing higher levels (1.68±0.87) compared to the unobstructed group (0.98±0.45; p<0.001), indicating renal impairment. Serum urea levels were also higher in the obstructed group (25.70±11.84) versus the unobstructed group (17.40±7.32; p=0.002).

The pulsatility index was higher in the obstructed group (1.04±0.35) compared to the unobstructed group (0.75±0.10; p<0.001), indicating increased resistance to blood flow. Similarly, the resistive index was elevated in the obstructed group (0.72±0.10) versus the unobstructed group (0.63±0.07; p<0.001). Peak systolic velocity was also higher in the obstructed group (100.17±43.61) compared to the unobstructed group (57.32±25.93; p<0.001). However, no significant difference was found in end diastolic velocity (obstructed: 25.33±10.02; unobstructed: 21.07±10.39; p=0.112).

Table-4 shows predictive accuracy of RI. The analysis RI revealed that in the obstructed kidney group, 21 patients had an RI >0.70, while 9 had an RI ≤0.70. In the unobstructed group, 4 patients had an RI >0.70, and 26 had an RI ≤0.70. The predictive accuracy showed a

sensitivity of 70.0%, indicating that the test correctly identified 70% of obstructed kidneys, and a specificity of 86.67%, meaning it accurately identified 86.67% of unobstructed kidneys. PPV was 78.97%, suggesting a high likelihood that a positive test indicated obstruction, while NPV was 80.15%, indicating a strong chance that a negative result meant no obstruction. Overall, the diagnostic accuracy was 78.33%, reflecting the test's effectiveness in diagnosing obstructed kidneys.

Figure-1 showed ROC curve demostrating sensitivity and specificity of RI. The area under ROC curve was 0.77, indicating good diagnostic performance in distinguishing between obstructed and unobstructed kidneys.

Table-1: Demographic parameters of patients

Parametes		Mean±SD
Age (years)		44.70±15.93
Gender n (%)	Male	34 (56.7%)
	Female	26 (43.3%)
Height (cm)		165.82±7.00
Weight (kg)		73.30±14.60

Table-2: Clinical parameters of patients

Parameters	Mean±SD
Serum Creatinine (mg/dl)	1.33±0.77
Serum Urea (mg/dl)	21.55±10.62
Pulsatility index	0.89±0.29
Resistive index	0.68±0.10
Peak systolic velocity (cm/s)	78.74±41.62
End diastolic velocity (cm/s)	23.20±10.35

Table-3: Comparison of parameter between obstructed and unobstructed groups

Parameters		Mean±SD		*p*-value
		Obstructed Kidney Group	Unobstructed Kidney Group	
Age (years)		44.50±15.41	44.90±16.70	0.924[a]
Gender	Male	15 (44.1%)	19 (55.9%)	0.297[b]
	Female	15 (57.7%)	11 (42.3%)	
Weight (kg)		72.90±12.83	73.70±16.40	0.834[a]
Height (cm)		166.90±7.69	164.73±6.18	0.234[a]
Serum Creatinine (mg/dl)		1.68±0.87	0.98±0.45	<0.001[a]
Serum Urea (mg/dl)		25.70±11.84	17.40±7.32	0.002[a]
Pulsatility Index		1.04±0.35	0.75±0.10	<0.001[a]
Resistive Index		0.72±0.10	0.63±0.07	<0.001[a]
Peak systolic velocity (cm/s)		100.17±43.61	57.32±25.93	<0.001[a]
End diastolic velocity (cm/s)		25.33±10.02	21.07±10.39	0.112[a]

SD = Standard deviation; cm = centimetre; kg = kilogram; mg/dl = milligram per decilitre; cm/s = centimetre per second; [a] = independent sample t-test was used; [b] = chi-square test was used; p≤0.05 was significant.

Table-4: Predictive Accuracy of Resistive Index

Parameters		Obstructed Kidney	Unobstructed Kidney
RI	>0.70	21	4
	≤ 0.70	9	26
Predictive Accuracy	Sensitivity	70.0%	
	Specificity	86.67%	
	PPV	78.97%	
	NPV	80.15%	
	Diagnostic Accuracy	78.33%	

RI = Resistive index; PPV = positive predictive value; NPV = negative predictive value

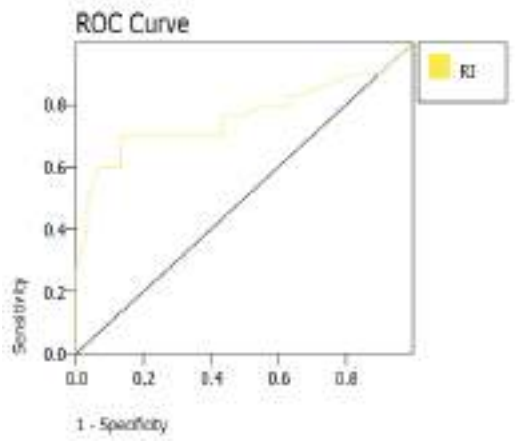

Figure-1: ROC curve demostrating sensitivity and specificity of RI

DISCUSSION

Urolithiasis, characterized by the formation of stones in the urinary tract, is a common urologic condition that can lead to significant complications, including renal obstruction.[11,12] Timely diagnosis and management are critical to preventing irreversible kidney damage.[13] Doppler ultrasound has emerged as a valuable non-invasive tool for assessing renal hemodynamics, particularly in differentiating between obstructed and non-obstructed kidneys.[10,13–15] So this research was conducted to explore the comparison of Doppler indices, including RI, PI, PSV, and EDV, in patients with urolithiasis.

RI is a measure derived from Doppler ultrasound that assesses intra renal artery resistance.[15,16] An RI greater than 0.70 is often

indicative of renal obstruction.[17] The current study showed that there was a significant variation in RI between obstructed and unobstructed kidneys.Obstructed kidneys had a higher RI (0.72±0.10), compared to unobstructed kidneys (0.63±0.07). This finding aligns with previous researches indicating that elevated RI values are associated with increased resistance to blood flow, reflecting compromised renal perfusion due to urolithiasis.[5,18]

A study by Katal *et al*. showed that mean RI was higher in obstruced kidneys (0.70±0.04) than in unobstructed kidneys (0.59±0.04).[17] Another study perfomed by Viyannan *et al*. revealed that RI was substantially higher in obstructed kidneys (0.75), compared to 0.56 in the unobstructed kidneys.[5] These findings are comparable to the present study. The present study also showed that the obstructed group had a significantly higher PI (1.04±0.35) than the unobstructed group (0.75±0.10). A higher PI suggests increased vascular resistance and reduced renal blood flow.[19] These findingshighlight that it is valuable to assess both RI and PI to find out any renal vascular resistance and predict the presence of obstructive uropathy.

Peak systolic velocity is a measure of the maximum speed of blood flow during systole.[20] The current results demonstrate that the obstructed group had a significantly higher peak systolic velocity (100.17±43.61 cm/s) than the unobstructed group (57.32±25.93 cm/s). Elevated peak systolic velocity in obstructed kidneys is caused by compensatory mechanisms where increased flow velocity occurs due to resistance. This observation is particularly common in acute renal colic, where a sudden obstruction leads to increased intrarenal pressure and the resultant hemodynamic changes.

On the other hand, the end diastolic velocity did not show a substantial variation between the two groups (25.33±10.02 cm/s in obstructed vs. 21.07±10.39 cm/s in unobstructed). This lack of significant variation indicate that diastolic flow remains relatively stable due to compensatory renal perfusion mechanisms or collateral circulation.

Elevated RI and PI values in patients with obstructed kidneys suggest that Doppler ultrasound can be used as a reliable diagnostic tool for identifying renal obstruction in urolithiasis. Thesensitivity and specificity was reported as 70.0% and 86.67%, respectively, for RI. It supports its use in clinical practice mainly because it offers a balance between correctly identifying obstructed kidneys and reducing the chances of false positive results.

Furthermore, PPV of 78.97% indicated that when the test indicates obstruction, there's a strong likelihood that the patient truly has an obstructed kidney and NPV of 80.15% also suggested that if the test suggests no obstruction, there is a strong chance the patient does not have significant obstruction. Our findings are consistent with previous researches that have emphasized on the use of Doppler indices to assess renal obstruction. Katal *et al*. reported that the sensitivity and specificity of RI to diagnose acute renal obstruction were 86.54% and 100%, respectively [17]. Similarly, another study reported the sensitivity and specificity of RI to be 85% and 93%, respectively [5]. One more study documented that sensitivity, specificity, PPV, and NPV of RI were 97.7%, 100%, 100% and 86.67%, respectively.[15]

In the present study, AUROC of 0.77 alsosupports the effectiveness of Doppler indices in diagnosing kidney obstruction. Additionally, a significant *p*-value (<0.001) and a 95% confidence interval (0.66–0.87) indicated that Doppler ultrasound is a strong tool to differentiate between obstructed and unobstructed kidneys.

However, several limitations also limit the implications of these results. The sample size is small and could be expanded to enhance the strength of the findings. Additionally, variations in operator experience and ultrasound equipmentimpact Doppler measurements. It highlights the needs for standardized protocols in the clinical practice.

CONCLUSION

The comparison of Doppler indices between obstructed and unobstructed kidneys in patients with urolithiasis reveals significant differences. Elevated RI and PI values, along with increased PSV, highlight that hemodynamics are altered in the presence of renal obstruction. These findings support the use of Doppler ultrasound as a valuable diagnostic tool, helping in the timely identification and management of obstructive uropathy.

AUTHORS' CONTRIBUTION

SI, FW: Conceptualization of the study, proof reading, write-up. ABT, SS, AM: Data collection, data analysis, data interpretation.

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Submitted: July 4, 2024	*Revised: November 5, 2024*	*Accepted: November 15, 2024*

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ORIGINAL ARTICLE

EVALUATING THE EFFICACY OF COGNITIVE BEHAVIOURAL THERAPY FOR AMPHETAMINE USE DISORDER: IMPACT OF SOCIO-DEMOGRAPHIC AND BEHAVIOURAL FACTORS IN PAKISTAN

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Background: Amphetamine use disorder (AUD) is a public health concern on a global scale and is a rising epidemic in Pakistan. Cognitive Behavioural Therapy (CBT) is a well-established treatment for substance use disorders, but its efficacy may be dependent on what is known as socio demographic and behavioural variables. The aims of this study are to provide evaluation of efficacy of CBT for AUD in Pakistani population and to find whether the presence of factors like education, job, duration of addiction, residence, age, family support, smoking and alcohol intake may affect treatment outcomes. **Methods:** A quasi-experimental design was applied with 100 participants recruited from outpatient treatment centers and rehabilitation centers in Pakistan. A culturally adapted CBT program was delivered to 50 participants along with treatment as usual and standard treatment as usual (TAU) was given to control group with 50 participants. Addiction Severity, anxiety, depression, psychological wellbeing, quality of life, as well as relapse rates were measured using pre-test and post-test assessments. Descriptive statistics, paired t-tests, ANOVA, multiple regression and survival analysis were completed to analyze the data. **Results**: The frequency of amphetamine use from pre to post change from 5.8 to 2.3 days per week (p<0.001) and ASI, addiction severity index scores from pre to post change from 30.2 to 18.7 (p<0.001) was significant in the CBT group. On the behavioural as well as on the psychological measures, improvements were observed, as evidenced by a decrease in the BDI from 22.4 to 14.1 (p<0.001) and a decrease in the GAD-7 from 18.5 to 11.3 (p<0.001). Significantly higher Quality of Life (WHOQOL-BREF) scores improved from 45.3 to 62.0 (p<0.001). But the TAU group also got better, just not as much as the CBT group. Positive associations were found with socio-demographic factors (such as higher education, stable employment and strong family support) and negative associations with unemployment, longer duration of addiction and regular alcohol intake. **Conclusion:** Both the effectiveness of CBT and its suitability to reduce amphetamine use, enhance psychological wellbeing, and improve quality of life among individuals with AUD in Pakistan were demonstrated. The significance of incorporating social demographic factors, and behavioural factors in the development of CBT interventions to ensure maximal treatment effect is underscored.

Keywords: Amphetamine Use Disorder; Cognitive Behavioural Therapy; Behavioural Factors; Socio Demographic Factors; Pakistan; Substance Use Treatment

Citation: Azad AH, Ali I, Nazir F, Anjum MU, Raza MA, Dar AA, *et al*. Evaluating the efficacy of cognitive behavioural therapy for amphetamine use disorder: Impact of socio-demographic and behavioural factors in Pakistan. J Ayub Med Coll Abbottabad 2024;36(4):749–54.

DOI: 10.55519/JAMC-04-14131

INTRODUCTION

Worldwide there is a growing recognition of amphetamine use disorder (AUD) as a significant public health problem. There is high prevalence in Pakistan. In the category of most potent central nervous system stimulants, amphetamines carry the high risk of severe dependence and multiple adverse health consequences. An assessment of the rising trend of amphetamine misuse in Pakistan seeks an urgent demand for accurate treatment and strategies. Although the effectiveness of Cognitive Behavioural Therapy (CBT) has been shown to be contingent upon a number of socio-demographic and behavioural factors, CBT is an emerging intervention for substance use disorders. This study, aims at assessing the efficacy of CBT in Pakistan for AUD with an aim that it could examine the factors like education level, profession, duration of addiction, rural vs. urban residence, age, family support, smoking and a use of alcohol as factors that could affect the treatment efficacy. Stimulant drugs amphetamines work by increasing the levels of neurotransmitters (dopamine and norepinephrine) released causing a feeling of alertness, euphoria, and energy.[1] Although chronic use can make one psychologically and physiologically dependent. Research studies[2] have proven that the misuse of amphetamines has direct effects on multiple systems in human body such as heart and arterial system, mental health, brain function etc. Amphetamine

use in Pakistan, particularly among the youth and the people of the urban centers is a matter of great concern, and needs effective treatment interventions.[3] The use of CBT as psychological intervention for substance use disorders is well established.[4] This is a structured series of sessions where people learn to find and refute hazardous cognitive distortions, to create coping systems, and adapt behaviour changes to lessen substance use and forthcoming relapse.[5] Many Studies have shown the effectiveness of CBT in at least some forms of substance use disorders including alcohol and cocaine dependence.[6] Forty studies of CBT for amphetamine use disorder have demonstrated reduced drug use and improved psychological functioning overall, although the treatment outcome was moderate.[7] The effectiveness of CBT depends on socio-demographic and behavioural factors. Previous studies showed that education level plays a role in treatment outcomes, with higher education level often accompanied by better engagement and adherence to therapy.[8] Treatment access and efficacy may also be affected by profession and socio-economic status; one example is that people with jobs and higher income may be better resourced to support their recovery.[9] Among the many factors that influence treatment success, time duration of addiction is important since research shows that longer history of substance use contribute to more entrenched behaviours and more severe addiction.[10] On the other hand, treatment outcomes are affected by geographical residence; rural areas frequently lack access to specialized treatment services and social support, which are available in urban settings[11] Due to striking differences between urban and rural areas, there are other problems, including higher grades of exposure to substance use triggers and stressors[12] Another important factor is age, as for instance, younger people might not deal with treatment challenges in the same way as older adults do. This is because developmental stages and experiences in life vary.[13] A major component of successful treatment is family support again a major component of therapy.[14] Measures to reduce drinking and smoking during addiction treatment can prove to be crucial for the utility of CBT in the management of amphetamine dependence and, ultimately, the success of treatment.[15] In this study we aim to contribute to the understanding of CBT's effectiveness for AUD in Pakistan by investigating how socio-demographic and behavioural factors influence treatment outcomes. The aim of the research is to increase our understanding of how to adapt CBT to better suit the particular needs of individuals with AUD to eventually improve treatment and outcome.

MATERIAL AND METHODS

A quasi-experimental design was used to evaluate the effectiveness of Cognitive Behavioural Therapy (CBT) for Amphetamine Use Disorder (AUD) and to explore the determinants for this outcome, using a number of socio demographic and behavioural factors. AUD symptoms and related outcomes were assessed before and after the intervention with pre-test and post-test assessments. The participants were recruited from two outpatient treatment facilities and two other rehabilitation centers in Pakistan. The sample size was 100. a Purposive sampling method technique was applied, to select as the participants.

Adults with amphetamine use disorder, 18-65 years of age, based upon DSM-5 criteria for amphetamine use disorder, willing to participate in the study and complete CBT, without severe co-occurring psychiatric disorders (e.g., psychosis, severe bipolar disorder)

Persons with severe medical conditions of such nature and interfering to the extent that they could not participate or get involved in specialist mental treatment procedure. Participants were involved in a culturally adapted CBT program that had been structured especially for the treatment of substance use disorders. Standard treatment as usual (TAU) consisted of general counselling plus routine medical care such as detoxification. The control group of 50 participants received TAU, while experimental arm of 50 participants received CBT intervention along with TAU. This made it possible to compare the results of the CBT group with the control group to figure out the potential added benefit of CBT. Independent variables included education level (classified into groups such as unemployed, skilled labour, professional, and others), duration of addiction (measured in years of amphetamine use), residence (rural or urban, measured according to participants living areas), age (expressed in age brackets, e.g., 18–30, 31–45, 46–65), family support as measured by a validated scale of perceived family support, smoking status (non-smoker, current smoker, former). Dependent variable like Severity of amphetamine use was measured using Addiction Severity Index (ASI) and validated self-report measures of amphetamine use frequency and quantity, psychological wellbeing was measured by Beck Depression Inventory (BDI) and General Anxiety Disorder 7 (GAD 7 scale), quality of life was measured by World Health Organization Quality of Life- Brief Form (WHOQOL-Bref) questionnaire and relapse rates were computed based on self-reports and clinical ratings at follow up visits. Assessments were done before the commencement of CBT intervention. Structured interviews were conducted to confirm AUD diagnosis and get socio demographic and behavioural information. Questionnaires (ASI, BDI, GAD-7 and WHOQLOLBREF) and behavioural assessments of smoking and alcohol intake patterns were applied. The post treatment assessments were conducted 1 week after the CBT program and again at 6 months follow up. Substance use monitoring was by urine toxicology screens for substances, self-reported frequency of amphetamine use, psychological and quality of life evaluations using the same measures

used in the pre-treatment assessments. Relapse tracking was done using self-reports and clinical interviews. Descriptive statistics, conditional descriptive statistics and comparisons of pre versus post treatment between and within the CBT and control groups were achieved through quantitative analysis using SPSS; multiple regression analysis to determine the effect of socio-demographic and behavioural factors on treatment outcome, controlling for potential confounders. Survival analysis of relapse rates and time to relapse between the CBT and control groups was studied. The qualitative analysis addressed participants that were interviewed to obtain feedback on CBT experience, and this was followed by thematic analysis identifying the themes and patterns of treatment experiences and perceived effectiveness.

RESULTS

The purpose of this research was twofold: to assess CBT for Amphetamine Use Disorder (AUD) and to investigate the moderating factors that may influence treatment outcomes. The study targeted 100 patients, out of whom, 50 patients received CBT and TAU and the other 50 patients received TAU only. Measurements were made prior to receiving active treatment and after completion of the active treatment phase, and at 6 months after active treatment completion.

Table-1: Participant Demographics

Variable	CBT Group (n=50)	TAU Group (n=50)	Total (n=100)
Age (years)			
18–30	15	14	29
31–45	22	23	45
46–65	13	13	26
Gender			
Male	35	36	71
Female	15	14	29
Education Level			
No Formal Education	5	6	11
Primary Education	12	15	27
Secondary Education	18	19	37
Higher Education	15	10	25
Profession			
Unemployed	10	11	21
Skilled Labor	18	20	38
Professional	17	15	32
Other	5	4	9
Residence			
Urban	30	29	59
Rural	20	21	41
Family Support			
Low	10	12	22
Moderate	25	23	48
High	15	15	30

Table-2: Pre- and Post-Treatment Comparison for CBT and TAU Groups

Measure	CBT Group Pre-Treatment	CBT Group Post-Treatment	TAU Group Pre-Treatment	TAU Group Post-Treatment
Frequency of Use (days/week)	5.8±1.2	2.3±1.1	5.9±1.3	4.8±1.4
Addiction Severity Index (ASI)	30.2±6.5	18.7±5.2	29.8±6.7	24.3±7.0
Beck Depression Inventory (BDI)	22.4±4.8	14.1±4.2	23.1±5.0	20.5±4.9
General Anxiety Disorder-7 (GAD-7)	18.5±5.1	11.3±4.7	19.0±5.3	16.0±5.2
Quality of Life (WHOQOL-BREF)	45.3±7.1	62.0±8.3	44.7±7.5	50.2±8.1

Table-3: Regression Analysis of Factors Influencing CBT Effectiveness

Variable	Coefficient (β)	Standard Error	t-Value	p-Value
Education Level				
No Formal Education	-3.4	1.2	-2.83	0.005
Primary Education	-2.2	1.0	-2.20	0.028
Secondary Education	-1.5	0.9	-1.67	0.097
Higher Education	0.5	1.1	0.45	0.654
Profession				
Unemployed	-2.8	1.3	-2.15	0.033
Skilled Labor	-1.8	1.1	-1.64	0.102
Professional	-1.2	1.0	-1.20	0.232
Duration of Addiction	-0.7	0.3	-2.33	0.021
Residence				
Urban	2.1	1.2	1.75	0.082
Rural	-2.1	1.3	-1.62	0.105
Family Support				
Low	-3.2	1.2	-2.67	0.008
Moderate	-1.5	1.0	-1.50	0.135
High	0.5	1.1	0.45	0.652
Smoking Status				
Current Smoker	-2.0	1.2	-1.67	0.097
Former Smoker	-0.8	1.1	-0.73	0.464
Alcohol Intake				
Occasional Drinker	-1.5	1.0	-1.50	0.135
Regular Drinker	-2.5	1.2	-2.08	0.039

Mean frequency of amphetamine use was decreased significantly from 5.8 days per week (SD=2.1 days per week) to 2.3 days per week (SD=1.5 days per week) in the CBT group (p<0.001). Addiction severity was decreased from 30.2 to 18.7 (p<0.001) as measured by the Addiction Severity Index (ASI) scores. Significant improvement was observed for psychological measures (e.g., decreases in Beck Depression Inventory [BDI] and General Anxiety Disorder 7 [GAD 7] scores; p<0.001 for both). Quality of Life (WHOQOL-BREF) scores increased significantly from 45.3 to 62.0 (p<0.001) and the TAU group also showed improvements, but the changes were less important than in the CBT group. Amphetamine use frequency decreased from 5.9 to 4.8 days per week (p≤0.01) and ASI scores from 29.8 to 24.3 (p<0.01). The CBT group showed superior improvement on psychological and quality of life measures, however the differences were generally smaller relative to the control group. Education Level: Better treatment outcomes were associated with higher education, while this effect was significant only among those with neither formal education (p=0.005) or only primary education (p=0.028). Profession: Results indicate that unemployment decreased treatment outcomes, with significant decrease in effectiveness (p=0.033). Less impact was placed on the status of professional and skilled labour.

Duration of Addiction: Treatment effectiveness was also negatively affected by a longer duration of addiction (p=0.021), which poses a challenge for people involved in a lengthy history of substance use. Residence: However, there was not a statistically significant difference between ASI improvement among rural and urban residents (p=0.082). Family Support: Finding among treatment outcomes – high family support was significantly associated with better (p=0.008) treatment outcomes, underscoring the importance of family involvement in treatment process. Smoking and Alcohol Intake: More significant effects of regular alcohol intake (p=0.039) were found.

DISCUSSION

This study gives a comprehensive detail of the treatment effectiveness of Cognitive Behavioural Therapy (CBT) for Amphetamine Use Disorder (AUD) and the significant influence of different socio-demographic and behavioural factors on treatment outcomes. The results provide important insights on how CBT could be optimized for the treatment of AUD in the context of Pakistan and show that a tailored approach is necessary to suit the needs of the diverse population in Pakistan. This matches with former research that shows CBT leads to reductions in substance use and better functioning.[16,17] Additional confirmation of the effectiveness of CBT for alleviating the seriousness of addiction comes in the form of a significant decrease in Addiction Severity Index (ASI) scores in CBT participants (from 30.2 to 18.7). It was also shown that CBT resulting in significant reductions in Beck Depression Inventory and General Anxiety Disorder-7 scores. Consistent with the literature, we find these findings in line with the notion that cognitive distortions can be addressed and improving healthy coping mechanisms can help reduce co-morbid psychiatric symptoms.[18-20] In addition, the CBT groups had better Quality of Life scores (WHOQOL-BREF) than the control groups[21], demonstrating that life satisfaction benefits are facilitated by CBT. Quality of life is an important variable for AUD patients. It turns out that those with more education tend to get more out of CBT, but only for those at the extreme ends — with no formal education and primary education — did statistically significant improvements. Educational attainment related to ability to engage and adhere to CBT principles. Other studies in the past have also shown that the more education you have the better the outcomes of treatment.[22,23] Nevertheless, the lack of much of an effect observed among people who are educated could be because education by itself does not mean the presence of supportive resources or stable living. Unemployment is a massive negative factor affecting CBT outcomes with those who are unemployed showing less improvement than those who are employed or working in professional jobs. The finding highlights the problems that people with unstable jobs face financial stress and a lack of social support that can interfere with treatment progress. There is some correlation between socio economic stability and employment status, and both affect treatment and therapeutic activities.[24] Consistent with the premise that longer histories of substance use can result in more entrenched behavioural patterns and greater severity of addiction[25], reduced treatment effectiveness was found in these analyses associated with longer histories of amphetamine use. This supports research that addictive behaviours and cognitive distortions are deep seated and have histories of extended substance use complicating the effort to treat.[26] Urban residents, however, displayed a trend for improvement of ASI scores better than rural residents, but no statistically significant difference was found. As in the developed countries, it has been suggested that the urban areas usually provide better access to specialized treatment services and support networks leading to more favourable treatment outcomes.[27] The lack of a significant difference suggests, however, that improved substance use treatment infrastructure and support are urgently needed in rural areas, where access to care can be more limited.[28] Overall,

significantly better treatment outcomes were linked to greater family support. All this substantiates the importance of family in recovery. Family support increase motivation and compliance with treatment. These findings are consistent with literature reviewing the role played by the family in client's success with the treatment of the substance use disorder.[29] Less improvement was seen among current smokers and regular drinkers than non-smokers and occasional drinkers. The finding is in agreement with research suggesting that comorbid substance use may intensify AUD treatments and hinder therapeutic progress.[30] This underscores the importance of integrating different approaches of treatment for substance use disorders at the same time

CONCLUSION

CBT showed pronounced efficacy compared to standard treatment as usual (TAU): for reduction of amphetamine use, better psychological well-being and better quality of life. Higher education levels, stronger family support, or being a non-smoker, were associated with greater treatment outcomes. Unemployment, longer periods of drug addiction duration and everyday drinking of alcohol were negatively associated with treatment effectiveness. In light of these findings, emphasis is made on the need of the targeted CBT interventions and focusing on socio demographic and behavioural factors to treat Amphetamine Use Disorder in Pakistan. To confirm these findings and refine treatment for AUD, future research with larger, more genetically and phenotypically diverse samples is needed.

AUTHORS' CONTRIBUTION

Authors have the following contributions in the present article: AHA, IA, SAU and PW prepared data collection instruments. AAD and MAR collected data for the study. FN and MUA wrote Introduction and Methods sections for respective manuscript. AHA finally prepared the results, reported and discussed. IA reviewed the manuscript. All authors approved the final manuscript.

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Submitted: June 6, 2024	*Revised: October 2, 2024*	*Accepted: November 9, 2024*

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ORIGINAL ARTICLE

OUTCOMES OF TRANSFORAMINAL LUMBAR INTERBODY FUSION AND POSTERIOR LUMBAR INTERBODY FUSION IN MANAGING SINGLE-LEVEL LUMBAR SPONDYLOLISTHESIS

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Background There is significant discussion over the most effective surgical approach for treating lumbar spondylolisthesis, despite the recommendation of a number of surgical approaches. The aim of this study was to explore the Outcomes of transforaminal lumbar interbody fusion and posterior lumbar interbody fusion in managing single-level lumbar spondylolisthesis. M**ethods;** the current study was conducted at the department of orthopaedic and neurosurgery at Hayatabad Medical Complex, Peshawar from January 2022 to February 2023 after taking approval from the ethical committee of the institute. Those individuals who had experienced a single-level condition with a low-grade categorization (grades I or II) in the Meyerding grading system were included in the study. A total of 52 patients were enrolled in this study and were divided in to group A and B. 26 received PLIF, and were placed in group A while 26 had done TLIF and were placed in group B. The two groups' mean operating times, blood loss, VAS scores for back and leg discomfort, and complications were compared. **Results:** A total of 52 individuals were enrolled in this investigation, distributed evenly into two groups. The mean age of the participants was 35.14±7.76 years. Out of 52 patients male were 30(57.6% and 22(42.30) were females. Patients in group B underwent TLIF while patients in group A got PLIF. With respect to the results for the two groups, individuals in the group A had mean operative time 126.44±12.03 minutes and Group B had a considerably shorter duration of 113.32±8.48 minutes (p<0.05). In group A, the average blood loss was 440±76.33 cm^3 but Group B experienced a much lower value of 371.40±39.2 cm^3 (p<0.05). Concerning postoperative VAS leg pain, there was no difference between the two groups (p>0.05) while group B experienced considerably less postoperative pain in the back on the VAS than group A did (p<0.05)**.** Dural tear was noted in 4 participants in group A, while 2 in group B. 3 patients in group A experienced a neurologic impairment, but in group b there was no neurologic deficit noted. 3 individuals in group A experienced wound infections, whereas none of the patients in group B did. **Conclusion:** Based on our research, TLIF is better than PLIF in terms of functional result and rate of complications in patients with grade I/II single-level lumbar spondylolisthesis.

Keywords: Posterior lumbar interbody fusion (PLIF); Transforaminal lumbar interbody fusion (TLIF); spondylolisthesis

Citation: Khattak HA, Gul N, Khaliq A, Haq MI, Nawaz S, Khan SA. Outcomes of transforaminal lumbar interbody fusion and posterior lumbar interbody fusion in managing single-level lumbar spondylolisthesis. J Ayub Med Coll Abbottabad 2024;36(4):755–8.

DOI: 10.55519/JAMC-04-13192

INTRODUCTION

The forward sliding of one vertebra on another is known as spondylolisthesis.[1] Among its five kinds, the most prevalent in adulthood are isthmic and degenerative spondylolisthesis.[2] Both have a chance to cause compression and instability that can cause low back and radicular pain.[3] In individuals with persistent low back pain, surgical fusion is an essential technique for fixing the spine in instances of lumbar spondylolisthesis and for relieving pain.[4] There are now several surgical fusion methods accessible, such as posterolateral fusion, anterior interbody fusion, posterior interbody fusion, and pars interarticularis repair.[5] Posterior lumbar interbody fusion (PLIF) and Transforaminal lumbar interbody fusion (TLIF) can apply a single posterior technique for placing pedicle screws and an interbody spacer to achieve circumferential spinal stabilization.[6] As an alternative to conventional PLIF, (TLIF) is a minimally invasive surgical method. It involves employing a unilateral posterolateral technique to access the diseased spinal region, usually from the patient's symptomatic or affected side.[7] PLIF instead, is a more traditional surgical technique that entails removing the posterior part of the vertebral lamina through a midline incision.[8] The current study was conducted to

determine the Outcomes of transforaminal lumbar interbody fusion and posterior lumbar interbody fusion in managing single-level lumbar spondylolisthesis.

MATERIAL AND METHOD

The current study was conducted at the department of orthopaedic and neurosurgery at Hayatabad Medical Complex, Peshawar from January 2022 to February 2023 after taking approval from the ethical committee of the institute. Participants diagnosed with adult lumbar spondylolisthesis were subjected to lumbar interbody fusion and pedicle screw fixation treatment. Those individuals who had experienced a single-level condition with a low-grade categorization (grades I or II) in the Meyerding grading system and had major pain in their legs and back, which had not improved with conservative therapy approaches were included in the study while those individuals who had spondylolisthesis grades III and IV and had a previous history of lumbar spine fusion surgery and the coexistence of spine deformities were excluded. The body mass index, or BMI, was calculated for each participant before to the surgical operation and those having a BMI of 40 or more, indicating severe obesity, were not included in the study. A total of 52 patients were enrolled in this study and were divided in to group A and B. Twenty-six received PLIF by applying two cages and pedicle fixation, and were placed in group A while 26 had done TLIF through single cage and pedicle fixation and were placed in group B. A single, highly experienced consultant neurosurgeon with over five years of expertise carried out each surgery. Everyone who participated gave their informed consent, and the specific lumbar fusieechnique selected was determined by a number of factors, such as the patient's clinical needs, the surgeon's preferences, and the patient's informed consent after a thorough explanation of the various surgical procedures. The two groups' mean operating times, blood loss, VAS scores for back and leg discomfort, and complications were compared.

SPSS 24 was used for data analysis. While frequency and percentages were used to analyze categorical data, mean and standard deviation were used for analyzing numerical statistics. To compare numerical values between the two groups, the Independent Samples T-test was used, with the *p*-value significant at <0.05.

RESULTS

A total of 52 individuals were enrolled in this investigation, distributed evenly into two groups. The mean age of the participants was 35.14±7.76 years. Out of 52 patient's males were 30 (57.6% and 22 (42.30) were females. Patients in group B underwent TLIF while patients in group A got PLIF. With respect to the results for the two groups, individuals in the group A had mean operative time 126.44±12.03 minutes and Group B had a considerably shorter duration of 113.32±8.48 minutes ($p<0.05$). In group A, the average blood loss was 440±76.33 cm^3 but Group B experienced a much lower value of 371.40±39.2 cm^3 ($p<0.05$). Concerning postoperative VAS leg pain, there was no difference between the two groups ($p>0.05$) while group B experienced considerably less postoperative pain in the back on the VAS than group A did ($p<0.05$). (Table 1). Dural tear was noted in 4 participants in group A, while 2 in group B. 3 patients in group A experienced a neurologic impairment, but in group b there was no neurologic deficit noted. 3 individuals in group A experienced wound infections, whereas none of the patients in group B did as display in table 2.

Table-1: Evaluation of outcomes between both groups

Outcomes	Groups	N	Mean	Standard deviation	*p*- value
Operative time in minutes	A	26	126.43	12.02	0.0001
	B	26	113.31	8.47	
Loss of blood in cm3	A	26	441	76.34	0.0001
	B	26	371.42	39.3	
VAS leg pain Postoperative	A	26	2.15	1.01	0.112
	B	26	1.71	.890	
VAS back pain Postoperative	A	26	3.15	.897	0.001
	B	26	2.31	.801	

Table-2: Major Complications in both groups

Complications	Group A		Group B
	N (%)		N (%)
Dural tear	Yes	4(15.3)	2(7.6)
	No	22(84.6)	24(92.3)
Neurologic deficit	Yes	3(11.5)	0
	No	23(88.46)	26(100)
Wound infection	Yes	3(11.5)	0
	No	23(88.6)	26(100)

DISCUSSION

In recent years, there has been an increase in the occurrence of degenerative lumbar disease, which is characterized by lower back stiffness and possible issues with the limb nerves mostly linked to the ageing population. This illness presents serious difficulties for those who are affected. A well-recognized treatment strategy for treating degenerative spine conditions such disc degeneration, spondylosis, and spondylolisthesis is lumbar decompression and fusion surgery. The effectiveness of this therapy has revealed distinguished improvements during its advancement, chiefly recognized to the advancements in operating practices, predominantly interbody fusion techniques.[9] The TLIF and PLIF lumbar fusion techniques are two widely used techniques. In the past, PLIF has been seen to be the best option.[10] However, this surgical technique's substantial decompression may reduce the amount of viable surface area for successful bone fusion, hence limiting its effectiveness. Treatment for lumbar spondylolisthesis with TLIF is now more common than posterior lumbar fusion (PLF) due to the use of interbody techniques, which increase the area available for fusion.[11] Patients with degenerative spondylolisthesis treated with TLIF experienced a significant increase in frequency, rising from 13.6 percent in 1999 to 32 percent in 2011. A major factor in this transformation was the observed rise in fusion rates using TLIF compared to PLF, which in some cases reached up to 90%.

Many benefits come with using an interbody spacer, including as load distribution, indirect compression relief, biomechanical support for the anterior column, and reinforcement of the posterior pedicle screw and rod arrangement.[12] Spondylolisthesis often presents with symptoms such as nerve-related issues and back pain, which can be attributed to instability and compression, regardless of its aetiology—degenerative or isthmic.[13] Nevertheless, surgical treatment for spondylolisthesis includes not only relieving pressure on neural tissue and stabilizing the affected spinal segment, but it also priorities restoring disc space height and realigning the spine in terms of translation and rotation in the sagittal plane.[14] According to our research, the TLIF group had a significantly shorter mean operating time and blood loss than the PLIF group ($p<0.05$). Another study that found that the mean operational time and blood loss with TLIF were considerably lower than in PLIF ($p<0.05$) noticed a similar findings.[15]

We found that the TLIF group's back pain score on the VAS was significantly lower than the PLIP groups' ($p<0.05$); however, we did not find a significant difference in the leg pain score between the two groups ($p>0.05$), which is consistent with the findings of the previously mentioned study.[16] We found that the TLIF group had fewer post-operative complications.

CONCLUSION

Based on our research, TLIF is better than PLIF in terms of functional result and rate of complications in patients with grade I/II single-level lumbar spondylolisthesis.

AUTHORS' CONTRIBUTION

HAK, NG: Conceptualization of the study design. AK, MIUH: Data collection, data analysis, data interpretation. SN, SAK: Review, write-up.

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Submitted: April 3, 2024	*Revised: September 13, 2024*	*Accepted: October 28, 2024*

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ORIGINAL ARTICLE

ASSOCIATION OF POST-TRAUMATIC GROWTH WITH THE USE OF RELIGION AND SPIRITUALITY AS A COPING STRATEGY AMONG REFUGEES OF AZAD JAMMU AND KASHMIR

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Background: Migration under hostile circumstances and taking refuge in another country is a process which can have a great toll on mental health of the affected individuals. Religious beliefs and closeness to God could be instrumental in bringing post-traumatic growth and positive changes in one's life after any traumatic event. This study was carried out to evaluate the association of post-traumatic growth with use of religion and spirituality as a coping strategy among refugees residing in Azad Jammu and Kashmir. **Methods:** In this cross-sectional study, individuals who migrated from Indian Kashmir and got settled in the Thotha refugee camp at AJK were recruited during February to April 2024 for the study. Post-traumatic growth (PTG) was assessed via post-traumatic growth inventory. Religiosity as coping strategy was measured on brief religious coping scale (Brief RCOPE). Relationship of religious coping and other socio-demographic factors was correlated with PTG among the study participants. **Results:** A total of three hundred and thirty participants were included in this study with mean age of 44.89±14.81. Majority of participants were male (n=237 (71.8%), married (n=260 (78.8%) and Unemployed (n=103 (31.2%). Participants who were ≤45 years old, single, employed, did not use illicit drugs and had more income had high PTG mean scores (p-value<0.05). The PTG scores of the study participants and Positive Religious coping score had positive correlation while PTG scores had negative correlation with Nnegative religious coping (r=-0.238, p-value <0.001). **Conclusion:** Post-traumatic growth was observed in individuals who were lining as refugees in camps at AJK. Individuals who were young, single, well paid and did not used illicit drugs had more chances of having PTG. Positive religious coping also increased the chances of having post-traumatic growth in individuals after migration and taking refuge in another country.

Keywords: Coping; Post-traumatic growth; Refugee; Religiosity

Citation: Jehangir Z, Zubair U, Kazmi SAA, Haider A, Burki A, Butt AJ. Association of post-traumatic growth with the use of religion and spirituality as a coping strategy among refugees of Azad Jammu and Kashmir.J Ayub Med Coll Abbottabad 2024;36(4):759–63.

DOI: 10.55519/JAMC-04-13407

INTRODUCTION

Migration under hostile circumstances and taking refuge in another country is a process which can have a great toll on mental health of the affected individuals.[1,2] Multiple natural disasters or wars may force the individuals to leave their home land and move to a new place; temporarily or permanently.[3] Trauma of this migration and refuge may predispose the individuals towards stress but it may also enhance their resilience and help them achieve post-traumatic growth.[4,5]

Growth in different capacities and positive impact on one's life after various traumatic events has been an area of interest for mental health professionals and researchers. Role of various socio-demographic factors in achieving post-traumatic growth has also been an interesting phenomenon. Lodhi *et al*. in 2022 published a local study which revolved around post-traumatic growth in trauma victims and revealed that religious beliefs and closeness to God could be instrumental in bringing post-traumatic growth and positive changes in one's life after any traumatic event.[6] A study was published from Netherlands which targeted refugees living in asylum centers. The results revealed that both post traumatic growth (PTG) and PTSD existed in their study participants and PTG was associated with satisfaction with life.[7]

A network meta-analysis was done to look for PG and PTSD in refuges of Iraq and Syria. It was observed that support after the trauma can help the individuals to have post-traumatic growth along with stress symptoms due to trauma.[8] Veterans from Iraq and Afghanistan were studied and it was found out that positive religious and spiritual coping was associated with PTG while negative religious coping was associated with PTSD.[9]

After the creation of Pakistan, huge number of refugees came and settled in different areas of the Azad Kashmir. This process didn't even stop after years of partition especially due to Kashmir issue. Even till early 90's number of refugees were entering into Azad Jammu Kashmir from Pakistan and setting into refugee camps especially designed to accommodate incoming refuges and not letting them intermingle with local population. Due to limited number of mental health professionals; attention could not be paid on mental health related aspects of these immigrants residing in refugee camps for years now. Azeem *et al*. in 2022 studied individuals who went through trauma of War on Terror in FATA and concluded that it was not PTSD which was the only outcome of trauma but significant number of participants had post-traumatic growth.[10] Limited local data on refugees residing in various refugee camps of AJK compelled us to design this study with the rationale to evaluate the association of post-traumatic growth with use of religion and spirituality as a coping strategy among refugees of Azad Jammu and Kashmir.

MATERIAL AND METHODS

This cross-sectional study was conducted during the period of February to April 2024. Individuals living in Thotha refugee camp near Muzaffarabad AJK were enrolled in this study. Sample size was calculated to be 330. The sample size was calculated using WHO sample size calculator taking confidence interval 95%, margin of error 5%, the level of PTG across studies ranged from 10–77.3%.[11] Non probability convenience sampling technique was used to recruit the required sample size for this study.

Individuals of both genders between the age of 18 and 70 years who migrated from Indian Kashmir and were residing in Thotha refugee camp were recruited in this study.

Individuals who did not migrate and were born in this camp or who were brought here before the age of 12 years were not recruited. Those who were diagnosed already with any mental health disorder and were under treatment were also not recruited. Individuals with any recent serious physical illness, accident or bereavement (death of a close relative, divorce etc.) were excluded from this study. Individuals who did not understand English or those who refused to participate in study or were not comfortable in sharing their religious or spiritual beliefs were excluded as well.

Ethical approval was granted by the Poonch Medical College/CMH Rawalakot ethical committee. All the study participants signed the informed consent form before getting enrolled into the study. Research team had visits to Thotha refugee camp near Muzaffarabad to interview the study participants.

Post-traumatic growth was assessed by Post Traumatic Growth Inventory (PTGI). PTGI is a validated tool used for this purpose. It has five domains (Personal Strength, New Possibilities, Improved Relationships, Spiritual Growth, Appreciation for Life) covered in total 21 items. Each item is scored on a scale of 0–5 (ranging from "did not experience" to "experience to very great degree".[12]

Religious coping was assessed with the help of The Brief RCOPE: Positive and Negative Coping Subscale.[13] The positive religious coping subscale (PRC) of the Brief RCOPE taps into a sense of connectedness with a transcendent force, a secure relationship with a caring God, and a belief that life has a greater benevolent meaning. The negative religious coping subscale (NRC) of the Brief RCOPE is characterized by signs of spiritual tension, conflict and struggle with God and others, as manifested by negative reappraisals of God's powers (e.g., feeling abandoned or punished by God), demonic reappraisals (i.e., feeling the devil is involved in the stressor), spiritual questioning and doubting, and interpersonal religious discontent. Both sub scales have seven items. When a 1-to-4 four-point Likert scale is used, mean scores for PRC and NRC can range from a minimum of 7 to a maximum of 28.[14]

All the questionnaires and sociodemographic proforma were administered to the study participants by the team at Thota camp with complete assurance of confidentiality.

Data was analyzed by using Statistical Package for the social sciences (SPSS) version 23.00 and MS Excel 2016 software. Mean±SD was calculated for continuous variable. Frequency and percentage were calculated for categorical variables. ANOVA and correlation were used for mean comparison and relationship of variables. The *p*-value ≤0.05 was considered significant.

RESULTS

A total of three hundred and thirty (n=330) participants were included in this study. Their mean age was 44.89±14.81, ranging from 18 to 78 years. Majority of participants were male (n= 237: 71.8%), married (n=260: 78.8%) and Unemployed (n=103: 31.2%). Most participants had monthly income between 25000–50000 rupees. Furthermore, 80 (24.2%) participant used Tobacco, 10 (3.0%) used amphetamines and 240 (72.7%) did no use any substances. The detail of demographic profile of the study participants is shown in Table-1. Table-2 showed the comparison of PGT among participants in different groups of categorical variables. Participants who were ≤45 years old had high PTG mean score (63.56±13.68) as compared to >45 years old participants (*p*-value

0.001). There was no difference of PTG scores among the two genders (*p*-value =0.051). Single participants had higher mean score of PTG as compared to others (*p*-value <0.001). Ssimilarly, employed participants and those who had more income higher score of PTG than others (*p*-value<0.05). Moreover, individuals who did not use any illicit substance had more PTG scores as compared to those who had used Tobacco or Amphetamines (*p*-value <0.001).

Table-1: Demographic characteristics of study participants

Parameters		Values
Age in Years	Mean±SD	44.89±14.81
	Range	18 - 78
Gender	Male	237 (71.8%)
	Female	93 (28.2%)
Marital status	Single	58 (17.6%)
	Married	260 (78.8%)
	Divorced/Separated	4 (1.2%)
	Widow/Widower	8 (2.4%)
Occupation	Employed for wages	56 (17.0%)
	Self Employed	51 (15.5%)
	Unemployed	103 (31.2%)
	Retired	25 (7.6%)
	Student	23 (7.0%)
	House Wife	72 (21.8%)
Income (PKR)	10000-25000	103 (31.2%)
	25000-50000	213 (64.5%)
	50000-150000	14 (4.2%)
Substance Use	Tobacco	80 (24.2%)
	Amphetamines	10 (3.0%)
	None	240 (72.7%)

Table-2: Comparison in PTG scores among participants in in different groups of categorical variables

Parameters		PTGI scoring Mean±SD	*p*-value
Age in Years	≤ 45 Years	63.56±13.68	<0.001#
	> 45 Years	56.18±17.49	
Gender	Male	59.29±18.09	<0.051#
	Female	62.15±8.30	
Marital status	Single	68.00±8.84	<0.001^
	Married	58.43±16.91	
	Divorced/Separated	63.0±0.02	
	Widow/Widower	55.50±12.19	
Occupation	Employed for wages	64.08±13.96	<0.001^
	Self Employed	57.45±16.22	
	Unemployed	55.18±21.30	
	Retired	61.88±11.30	
	Student	66.17±9.36	
	House Wife	63.33±7.11	
Income (PKR)	10000-25000	66.77±7.60	<0.001^
	25000-50000	56.09±7.78	
	50000-150000	71.85±9.94	
Substance Use	Tobacco	53.96±8.45	<0.001
	Amphetamines	57.00±2.34	
	None	61.60±14.61	

independent t test, ^ Anova Test

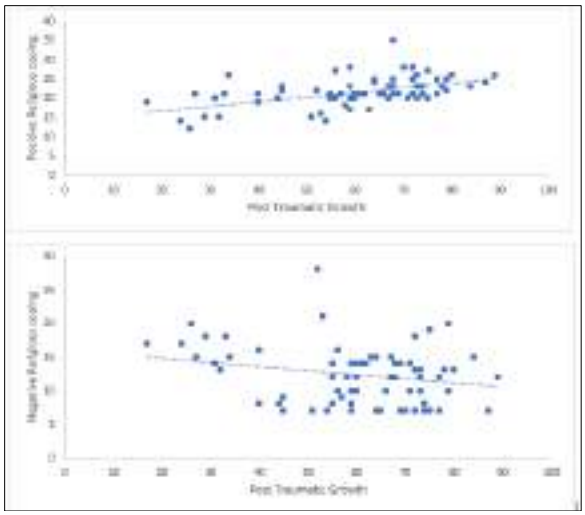

Figure-1: Correlation Analysis of PTG with Positive and negative religious coping

The PTG scores of the study participant and Positive Religious coping score had positive correlation coefficient (r=0.428, *p*-value<0.001) and had negative correlation with negative religious coping (r=-0.238, *p*-value <0.001).

Table-3: Correlation of PGT factors (n=330)

	New Possibilities	Improved Relationship	Spiritual Growth	Appreciation for life
Personal Strength	0.568**	0.725**	0.612**	0.642**
New Possibilities	-	0.688**	0.407**	0.500**
Improved Relationship	-	-	0.568**	0.635**
Spiritual Growth	-	-	-	0.567**

**Correlation is significant at the 0.01 level (2-tailed)

In addition, we calculated correlation analysis of PTG factors. They showed positive significant correlation with each other (Table-3).

DISCUSSION

Dynamics of South Asian region had been an area of interest for historians, political analysts, defense analysts, health professionals and professionals from other genres as well. Partition in 1947 has been a big event in history of subcontinent which displaced millions of people and that too with the bloodshed. Disputed areas like Kashmir posed problems for people living in these areas even after 1947 and process of migration did not stop. People were being displaced from Indian Kashmir to Azad Jammu Kashmir even till late 1990s. This coercive displacement though brought a lot of positive changes in lives of individuals but still they had to move to a new land where they were kept in refugee camps specially designed and dedicated to keep them. A lot

of work has been published regarding post-traumatic stress in individuals undergoing migration and seeking refuge. We tried to explore the positive side of trauma and tried to evaluate the post traumatic growth in these individuals and relationship of this growth with religious coping.

Hirad *et al*. studied refugees from different countries and tried to look for post-traumatic growth after facing war or forced migration. They discussed about complex interaction of trauma, adaptation process and then post traumatic growth and resilience.[15] We took our study sample from one refugee camp of AJK and found out that post-traumatic growth was a consistent finding among the study participants and no of social, demographic and religious/ spiritual coping related factors affected this phenomenon.

Hamadedh *et al*. published a meta-analysis in 2024 regarding experiences of Arab people during war and conflict in middle east region. It was revealed that both post-traumatic stress and growth were noted in this group of population and coping strategies determined the pathway after they faced the trauma.[16] Positive religious coping had significant positive correlation with post traumatic growth in our study participants while negative religious coping was inversely correlated with post-traumatic growth scores.

Forcibly displaced muslins were studied for relationship of religious coping, perceived discrimination, and posttraumatic growth. It was revealed that religious coping predicted more post-traumatic growth in muslins that faced discrimination.[17] We did not study level of discrimination in our study participants but found out that post-traumatic growth was observed in individuals who seek refuge in camps at AJK. Individuals who were young, single, well paid and did not used illicit drugs had more chances of having PTG. Positive religious coping also increased the chances of having post-traumatic growth in individuals after migration and taking refuge in another country.

A study conducted in Germany evaluated refugees and immigrants for spiritual Needs, religious coping and mental wellbeing. It was concluded that negative religious coping was inversely related to well-being. Authors on the basis of their findings suggested strengthening of religious and spiritual integration in-order to increase the wellbeing of refugee and immigrant population.[18] Positive religious coping was positively correlated with post-traumatic growth in refuges recruited in our study as well. On the other hand, individuals with negative religious coping had significantly low post traumatic growth inventory scores.

CONCLUSION

Post-traumatic growth was observed in individuals who were living as refugees in camps at AJK. Individuals who were young, single, well paid and did not used illicit drugs had more chances of having PTG. Positive religious coping also increased the chances of having post-traumatic growth in individuals after migration and taking refuge in another country.

LIMITATIONS

There were certain limitations in their study. Refugees from one camp were recruited and that too via non probability convenience sampling. This may have created a bias and sample may not have been actual representatives of refugees living in the area. Moreover, study participants may under or over rate experiences at self-reported questioners especially regarding sensitive issues of religion and spirituality.

AUTHORS' CONTRIBUTION

ZJ: Conceptualization, data collection, data analysis, interpretation, proof reading, write-up. UBZ: Conceptualization, data collection, write-up. SAAK: Conceptualization, data collection, data interpretation. AH: Data analysis, data interpretation. AB: Data collection write-up, proof reading. AJB: Data analysis, data interpretation, proof reading.

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Submitted: May 21,2024	*Revised: November 10,2024*	*Accepted: November 18,2024*

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ORIGINAL ARTICLE

ALLERGIES DOCUMENTATION IN HMIS HISTORY OF PATIENTS ADMITTED IN GASTROENTEROLOGY AND PULMONOLOGY WARD AT LADY READING HOSPITAL, MEDICAL TEACHING INSTITUTE – PESHAWAR

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Background: This clinical audit aimed to assess the accuracy of allergy documentation within the Hospital Management Information System (HMIS) of the Gastroenterology and Pulmonology Wards at Lady Reading Hospital, MTI Peshawar. Proper documentation of allergies, including food, drugs, and other types, is crucial for patient safety to prevent adverse reactions. **Methods:** The clinical audit was conducted using the "HOPE" Hospital Management Information System (HMIS), donated by the Shaukat Khanum Memorial Trust. It involved a retrospective review of medical records for 20 patients from each ward across two audit cycles. In the first cycle, 10 patients were randomly selected from each ward, making a total of 20 patients. After identifying gaps in allergy documentation, interventions were implemented. A second cycle was then conducted to reassess documentation, selecting another set of 10 patients from each ward. Data collection involved checking if allergies were documented, and the results were recorded in an Excel sheet, marked as 'Yes' or 'No' for allergies. Data analysis was done using Microsoft Excel 2023 and the graphical representations were created in Microsoft Office Word 2023 and Microsoft Excel 2023 (Microsoft® Corp., Redmond, WA). The audit aimed for a 100% documentation standard as per the HMIS reading manual. **Results:** In the first cycle, 70% (n=7) of patients in the Gastroenterology Ward and 60% (n=6) in the Pulmonology Ward had no documented allergies. After implementing the recommended interventions, the second cycle showed a remarkable improvement, with a 100% documentation rate achieved in both wards. **Conclusion:** After implementing the recommendations, allergy documentation in the HMIS of Lady Reading Hospital MTI Peshawar significantly improved, which helped in preventing allergic reactions in patients admitted to the Gastroenterology and Pulmonology Wards.

Keywords: Allergy and immunology; Documentation; Medical Records; Hospital Information System; Electronic Health Record; Clinical Audit

Citation: Khan MH, Shah MK, Mehmood A, Muhammad UF, Khawaja AM, Tauqir J, *et al.* Allergies documentation in HMIS history of patients admitted in gastroenterology and pulmonology ward at lady reading hospital, medical teaching institute – Peshawar. J Ayub Med Coll Abbottabad 2024;36(4):764–7.

DOI: 10.55519/JAMC-04-13441

INTRODUCTION

Allergy is defined as an immune-mediated inflammatory response to common environmental allergens that are otherwise not harmful. Allergies included food, drug and unlisted allergies respectively.[1] Hypersensitivity is an exaggerated immune response to antigens, manifesting from minor (atopic dermatitis and rhinitis) to dangerous manifestations such as anaphylaxis which can be life-threatening.[2] The clinical audit aimed to confirm the proper documentation of allergies in the medical history section of the hospital management information system (HMIS) of patients admitted to the Gastroenterology and Pulmonology Ward of Lady Reading Hospital Medical Teaching Institute – Peshawar. Accurate documentation of allergies is important for patient safety and helps clinicians avoid potential allergic reactions during treatment.[3] A few years ago, Shaukat Khanum Memorial Trust called "HOPE" entered into a Support Services Agreement with four medical teaching institutes in Khyber Pakhtunkhwa, including Lady Reading Hospital in Peshawar, to introduce its advanced Hospital Management Information System (HMIS).[4] This software application is developed by Trust (HOPE) with ORACLE, a computer company in the United States of America and plays an important role in delivering quality patient care by providing an effective HMIS. This hospital management information system is made up of different components that cover everything from the clinical to administrative and financial needs of healthcare organizations. It provides fast and dependable access to patient diagnosis and treatment information, ensuring efficient healthcare services.[5]

This clinical audit aimed to assess the allergy documentation in the Hospital Management Information

System (HMIS) for patients in the Gastroenterology and Pulmonology Ward at Lady Reading Hospital and recommend improvements for proper documentation.

MATERIAL AND METHODS

This clinical audit was conducted at Lady Reading Hospital Medical Teaching Institute (MTI), Peshawar, with a focus on the Pulmonology and Gastroenterology wards. Data collection involved reviewing patient records within the hospital's management software to determine whether allergies were properly documented. Patients were identified using medical record numbers obtained from the admission register. In the first audit cycle, 10 patients were randomly selected from each ward, making a total of 20 patients. Following the initial review, a second cycle was conducted to reassess the documentation of allergies, again selecting 10 patients from each ward, totalling another 20 patients. The findings were recorded in an Excel spreadsheet, with allergy documentation marked as either "Yes" or "No." Data analysis was performed using Microsoft Excel 2023 (Microsoft® Corp., Redmond, WA), and the graphical representations were created in Microsoft Office Word 2023 and Microsoft Excel 2023 (Microsoft® Corp., Redmond, WA). Grammar and language checks were completed using the Grammarly software application.

The audit standard was based on the allergy documentation section within the Hospital Management Information System (HMIS) software, to achieve 100% compliance.

RESULTS

In the first cycle of the audit, the Gastroenterology Ward showed that out of 10 audited patients, 7 had no documented history of allergies, resulting in a 70% (n=7) rate of undocumented allergies and only 30% (n=3) documented allergies as shown in Figure A. Similarly, in the Pulmonology Ward, 10 patients were audited, and it was found that 6 had no documented history of allergies, leading to 60% (n=6) being undocumented and 40% (n=4) having their allergies properly documented.

In the second cycle of the audit, there was a remarkable improvement in allergy documentation within both wards. In the Gastroenterology Ward, all patients (100%) had their allergies (food and drug allergies) documented (Figures B and C), showing a complete adherence to the recommended documentation practices. Similarly, in the Pulmonology Ward, the audit revealed that all patients (100%) also had their allergies documented. (Figure D)

Recommendations

To achieve our target, several key recommendations were effectively implemented. First, we improved the documentation of allergies by providing healthcare professionals with clear guidance on accurately recording drug and food allergies in patient histories in HMIS (Figure E, F). New doctors and nursing staff received orientation from the HMIS/IT Department to ensure they understood this documentation process. This initiative was regularly reviewed and updated to maintain best practices. Second, we enhanced allergy prevention and management by educating healthcare professionals on the importance of verifying patient allergies before prescribing medications. Informative pamphlets were distributed in both wards to increase awareness (Figure G). Additionally, a system to flag potential drug-allergy interactions was implemented, providing alerts during the medication ordering process (Figure B, C). Collaboration with the dermatology department was also established to ensure comprehensive assessment, diagnosis, and treatment of allergic conditions. To further raise awareness, an Allergy Day was celebrated with the dermatology department, which included a hospital-wide walk to promote knowledge about allergies and their management.

Ward name	Total patients	Allergy documented	Allergy Not documented
Gastroenterology	10	n=3 (30%)	n=7 (70%)
Pulmonology	10	n=4 (40%)	n=6 (60%)

Figure-A: Undocumented Allergies in HMIS shown by Red Question marks

Ward name	Total patients	Allergy documented	Allergy Not documented
Gastroenterology	10	n=10(100%)	0(0%)
Pulmonology	10	n=10(100%)	0(0%)

Figure-B: Documented Food Allergies in HMIS shown by Red Checkmark.

Figure-C: Documented Food Allergies in HMIS shown by Red Checkmark.

Figure-D: Allergy Documentation percentage of Gastroenterology and Pulmonology wards in both cycles

Figure (E, F): Food and Drug Allergy selection lists in HMIS

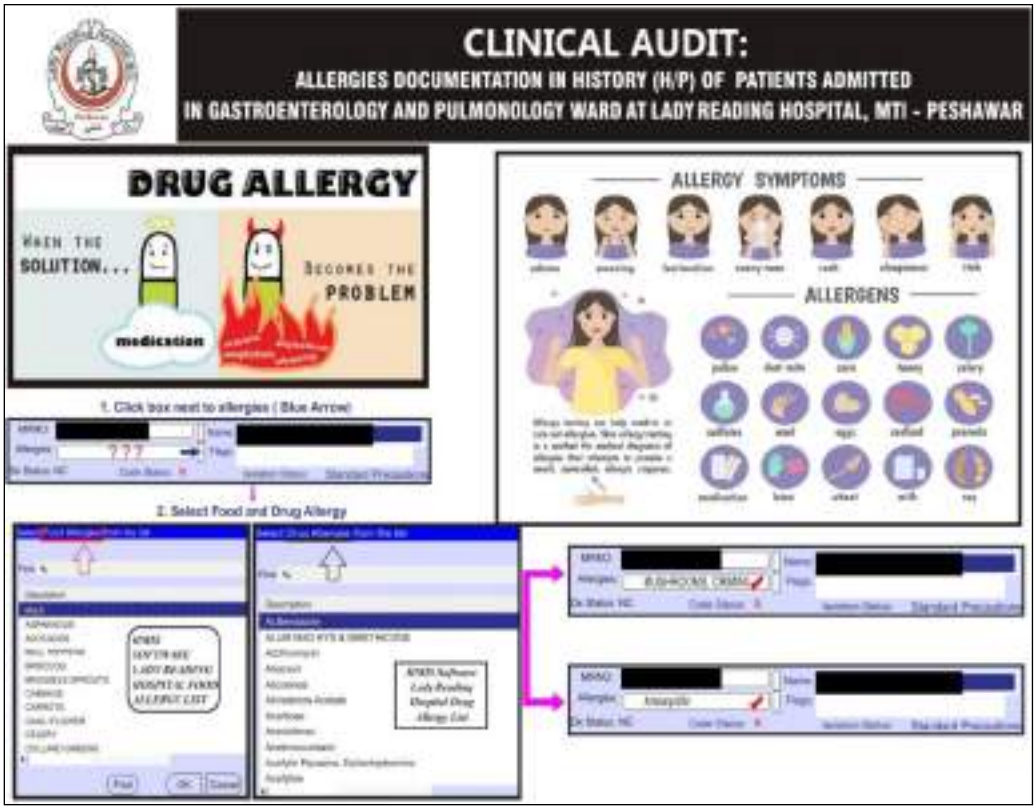

Figure G: Informative Pamphlets for Increasing Allergy Awareness in Wards

DISCUSSION

Drug hypersensitivity reactions, including allergic responses to medications, result from heightened immune or inflammatory responses. [6] These reactions are mediated by basophils and mast cells, leading to symptoms such as rash, hives, itching, swelling, wheezing, breathing difficulties, low blood pressure, and potentially life-threatening anaphylaxis.

In our initial audit, the documentation of allergies in the HMIS was recorded as 30% in the Gastroenterology ward and 40% in the Pulmonology ward. However, after implementing interventions, the second audit cycle demonstrated a significant improvement, with 100% compliance in documenting allergy status, as depicted in Figure D. Similar findings were reported by Graham-Clarke *et al.* (2010), where lower documentation rates were observed in the first cycle of their audit due to various

factors.[7] In their study, medications were the primary cause of allergies, with antibiotics such as penicillin being the most frequently reported (n=22), along with other medications like aspirin, cyclizine, metoclopramide, co-codamol, barium meal, and paracetamol.[7] Like Graham-Clarke *et al*., we utilized a computerized system—HMIS for our audit—while they used electronic patient records (EPR). Our first cycle findings also aligned with Khalil *et al*. (2011), who found that in a rural Australian hospital, 48% of patient records reported some form of allergy, but only 0.6% had accurately documented details.[8] Khalil *et al*. emphasized the need for healthcare professionals to actively identify and accurately record drug allergies to enhance patient safety[8]. Similarly, Farooq *et al*. (2008) found that 30% of preoperative drug charts in a surgical department lacked documented allergy information, and recommended strategies like computerized systems and staff education.[9] Rehman *et al*. (2022) also conducted a clinical audit on drug allergy documentation in a cardiology unit. Initially, 93% of clinical notes recorded allergies, which improved to 100% after interventions.[10] Our audit mirrored this process, as we conducted two cycles, achieving 100% documentation in the final cycle. The primary difference was that we used an HMIS, whereas Rehman *et al*. documented allergies in patient charts. One limitation of our study is the small sample size, as this was a clinical audit rather than a comprehensive research project. This restricted the focus to a specific patient subset within the Gastroenterology and Pulmonology wards. In future, we plan to conduct a broader study assessing allergy documentation across all wards at Lady Reading Hospital MTI Peshawar. Another limitation was the lack of distinction between different types of allergies, such as food versus drug allergies, an area we aim to explore in future research. Additionally, we plan to use a sample size calculator to ensure an appropriate sample size for our expanded study. Finally, our audit only covered two departments, so the findings may not be representative of the entire hospital. A more comprehensive study including all departments will provide a clearer understanding of the overall state of allergy documentation at the hospital.

CONCLUSION

Following the implementation of recommendations, the documentation of allergies in the HMIS at Lady Reading Hospital MTI Peshawar significantly improved, contributing to the prevention of allergic reactions in patients admitted to the Gastroenterology and Pulmonology wards

AUTHORS' CONTRIBUTION

MHK: Conceptualization. MHK, UFM, MKS: Supervision & Project Administration. AM, MND, MHK, BA, AMK: Manuscript Writing. JT, MKS, AMK, MHK, UFM, MND, AJ: Data Collection. MKS, UFM, AJ, MND, AM: Results Analysis & Interpretation. MHK, UFM, MKS, AJ, MND: Recommendations Development. AM: Manuscript Review & Editing. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Submitted: May 31, 2024	*Revised: September 24, 2024*	*Accepted: September 24, 2024*

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ORIGINAL ARTICLE

COMPARATIVE EVALUATION OF DENTAL CARIES AMONG PATIENTS OF 6-15 YEARS AGE PRESENTING TO THE OUTPATIENT DEPARTMENT OF AYUB COLLEGE OF DENTISTRY, ABBOTTABAD

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Background: Dental caries in the mixed dentition stage is a common problem leading to tooth decay and extractions. This study aimed to evaluate the pattern of caries among children of 6-15 years age presenting to Ayub College of Dentistry and its association with different factors such as age, dietary habits, snacking habits, and previous dental visits. **Methods:** It was cross-sectional research on 250 participants of 6–15 years presenting to Ayub College of Dentistry from November 2023 to April 2024. Dental caries was examined and DMFT index calculated with the help of questionnaires. DMFT was correlated with age, tooth brushing habits, gender, snacking habits, and previous dental visits. Data was analyzed using SPSS software version 22. Statistical correlation tests were applied to find the association between different variables such as age group, brushing habits, snacking habits and prevalence and severity of caries. **Results:** Dental caries was prevalent among 79.7 percent whereas the mean DMFT of sample was 5.82±4.48. There was a trend of higher DMFT scores among male population than females. A greater DMFT score of 4.2±1.8 was seen among children of 13–15 years followed by 10–12 years (3.8±1.7) and 6–9 years (2.7±1.5). **Conclusion:** This study highlights the high prevalence of dental caries among children and adolescents and its association with brushing habits, snacking habits, age, gender, and previous dental visits. Regular dental check-ups, proper oral hygiene practices, and a healthy diet low in sugar are key factors in preventing dental caries in elementary school students.

Keywords: Dental caries; DMFT index; Mixed dentition

Citation: Rehman A, Ashraf H, Munir N, Syed R, Nayyar K. Comparative Evaluation of dental caries among patients of 6-15 years age presenting to the Outpatient Department of Ayub College of Dentistry, Abbottabad. J Ayub Med Coll Abbottabad 2024;36(4):768–72.

DOI: 10.55519/JAMC-04-13381

INTRODUCTION

Dental caries, commonly known as tooth decay or cavities, is a prevalent oral health concern among school going children aged six to fifteen years.[1] It is a bacterial infection that causes demineralization of tooth enamel, leading to the formation of cavities. If left untreated, caries can progress and affect the deeper layers of the tooth, resulting in pain, infection, and potential tooth loss. It can also have a significant impact on a child's overall well-being, including eating habits, speech development, and self-esteem.[2]

The mixed dentition stage typically occurs between the ages of 6–12 years old, where a child has a combination of primary (baby) teeth and permanent teeth. This stage is crucial for monitoring dental health as it sets the foundation for a lifetime of good oral hygiene habits. Dental caries can have a significant impact during the mixed dentition stage, affecting both primary and permanent teeth if left untreated. It is essential to educate children and their caregivers about the importance of maintaining healthy oral practices during this developmental period.[3]

Studies have shown that one of the most widespread diseases of oral cavity is dental caries that affects individuals of every age particularly children, affecting their overall health and well-being.[4] According to recent statistics, the prevalence of dental caries in this age group varies from country to country, with some regions reporting higher rates than others. Several factors contribute to the high prevalence of dental caries among school-going children aged six to fifteen years. These factors include poor oral hygiene practices, high consumption of sugary and acidic foods and beverages, lack of access to dental care services, and limited awareness about the importance of oral health.[4]

Other contributing factors may include socioeconomic status, parental education level, and environmental factors such as water fluoridation and availability of dental health programs in schools. Addressing these factors is trivial in reducing the prevalence of dental caries and promoting good oral health habits among children.[5]

The decayed, missing and filled teeth (DMFT) index is a widely used method for evaluating

dental caries. It is used to quantify the prevalence of caries in a population. The sum of these three components (DMFT) gives an overall score that reflects the dental caries experience in an individual or a group. Using the DMFT index, researchers or dentists can evaluate the severity of caries, track changes over time, and assess the effectiveness of interventions such as oral health education programs or fluoridation initiatives.[3,6]

By emphasizing the importance of regular dental check-ups, proper brushing and flossing techniques, and a healthy diet low in sugar, we can help reduce the prevalence of dental caries and improve the overall oral health of children in the six to fifteen years age group.[7] Teaching children the importance of proper oral hygiene, including brushing twice a day and flossing, can significantly reduce the risk of dental caries. Using fluoride toothpaste and mouthwash can also help strengthen the teeth and prevent decay. Encouraging children to follow a balanced diet rich in fruits, vegetables, and dairy products can promote good oral health. Limiting sugary and acidic foods and drinks can minimize the risk of dental caries.[8,9]

Many schools going children daily report to the dental outpatient department (OPD) of Ayub College of Dentistry with the complaint of carious lesions in their teeth. This study aimed to evaluate the prevalence of dental caries with the help of DMFT scores, and its association with brushing habits, snacking habits, age, gender, and previous dental visits. Scarce data is available on caries prevalence in Abbottabad district. This research was aimed to signify the development of caries, its relative association with different factors and subsequently, the management of dental caries by prompt treatment suggestions to the participants. The findings of this study could help patients in seeking appropriate treatment when needed and hence the prevalence of caries could be effectively managed. It is important for parents, schools, and healthcare providers to work together to promote good oral health practices and ensure the well-being of children [10].

MATERIAL AND METHODS

The research type was descriptive cross-sectional research The sample size in this research was 250 participants ranging in age from 6 to 15 years reporting to the outpatient department of Ayub College of Dentistry from November 2023 till April 2024. The sampling technique was convenience sampling technique. Ethical approval was taken by the ethical committee of Ayub Medical College, Abbottabad. The confidence interval for sample was kept at 95% with a precision of 0.05 and design impact of 2. The desired sample size calculated for the research was 250.

Dental caries assessment procedure began with the provision of informed written consent given by the research subject/parents. Tools used in this research were DMFT forms for intra oral examination results, cotton, mouth mirror, dental explorer, excavator, mask, gloves, alcohol on the concentration of 70% disinfectant, and flashlight.

The caries status data was obtained by examination using DMFT index. The record obtained was represented as D (decayed) for the carious teeth, where the dental explorer tip was pointed to the cavity; M (Missing) for the revoked teeth due to caries, teeth extraction trace or presence of root residue; and F (Filling) for restored teeth. The designed questionnaire was a proforma that included name, gender (male or female), age (6-9 years, 10-12 years, 13-15 years), tooth brushing (once/twice/rarely or never), and previous dental visits (yes/no). Based on this proforma, DMFT scores were calculated for all the study participants.

Children aged 6-15 years visiting the OPD for dental complaints or routine checkups were included in the study. Children with compromised medical health were excluded from the study. Children undergoing any orthodontic treatment were also excluded from the research.

Data analysis was done by using Statistical Package for the Social Sciences software (IBM, SPSS Statistics, version 24, Chicago, IL, USA). Categorical variables were presented in the form of frequencies and percentages. Numerical variables were presented by means and standard deviation. For comparative variables between and within groups, one-way ANOVA was used. The Chi- square test was applied to determine the correlation between dependent and independent variables such as age group, brushing habits, snacking habits and prevalence and severity of caries. A p-value of < 0.05 was considered to be statistically significant.

RESULTS

Two hundred and fifty children were the participants of this study with a mean age of 9.8±1.1 years. Predominant study population were males (54.8%), whereas female population was 45.2% as shown in Figure 1. Among the study participants, 58% of the children belonged to the 10–12 years age group, however 29.6% participants were below 9 years and above 12 years were found to be 12.4% only as shown in figure 2. As far as the brushing habits were concerned, 64.4% of the children among research subjects brushed once daily, while 22.8% of children brushed two times a day whereas, 12.8% rarely/never brushed their teeth, before. Among the study population, only 42% children had visited the dentist for regular dental checkups and 58% had never undergone dental checkup. While calculating results, it was established that dental caries was prevalent among 79.7% of the research population. The mean DMFT score for this study population was found to be 5.82±4.48. Among individual teeth, mean value for decayed teeth was 3.903±3.69,

whereas mean value of 1.18±1.69 was calculated for missing teeth, and 0.73±1.35 for filled teeth. Male population had higher mean DMFT scores (4.54±1.8) than females (3.68±1.4) with a statistically significant difference (p=0.0014). As far as individual age groups were concerned, the participants in the age group of 13-15 years were noticed to have higher mean DMFT scores of 4.2±1.8, whereas participants among 10–12 years age group had DMFT scores of 3.8±1.7 and 6-9 years had mean scores of 2.7±1.5, with a p value of (0.002. While calculating brushing habits comparison, it was established that the children practicing twice a day brushing had lower DMFT scores (2.67±1.5). In contrast, children who never brushed before had higher DMFT scores (4.5±1.9), and children who brushed only once a day had DMFT scores of 3.24±1.8. The comparison of tooth brushing and DMFT score was statistically significant (p =0.0009). It was observed that children who used to snack on sugary foods or drinks once a day had a low value of DMFT (2.24±1.5). This trend increased with the frequency of snacking with children taking snacks two times a day having a DMFT score of (3.5±1.8), while more than two times snacking took DMFT score to (4.47±1.7). A low DMFT score (3.6±1.24) trend was observed among children who had paid visit to the dentist at least once before, however children who had never seen a dentist before had a high value of DMFT (4.54±1.8), with a statistically significant difference (p =0.0012). The comparison of the DMFT based on gender, age, tooth brushing, and the previous dental visit are summarized in Table-1.

Regarding individual teeth, high DMFT scores were seen in mandibular right second molar, while low value of DMFT was observed for mandibular central incisors. On observation, the most frequently damaged tooth by dental caries was mandibular right first permanent molar, and the less commonly decayed teeth were mandibular central incisors. It was seen that mandibular right first permanent molar was the most frequently filled tooth while less commonly filled teeth were the maxillary canines. Maxillary left primary central incisor was the tooth that was commonly found missing whereas less commonly missing tooth was the maxillary right primary canine.

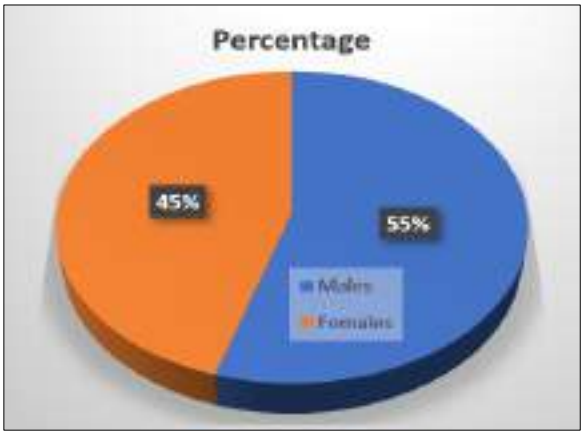

Figure-1: Participants' distribution according to gender

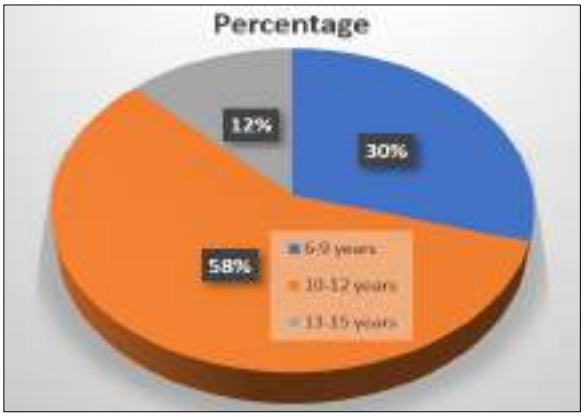

Figure-2: Mean percentage distribution of study participants according to age

Table-1: Comparison of DMFT with age, gender, brushing frequency, snacking habits and previous dental visits

Independent variables	Groups	Percentage (n)	DMFT	*p*-value
o gender	male	137(54.8)	4.54(1.8)	0.0014
	female	113(45.2)	3.68(1.4)	
o age	6-9 years	74 (29.6)	2.7(1.5)	
	10-12 years	145 (58)	3.8 (1.7)	0.0002
	13-15 years	31 (12.4)	4.2(1.8)	
o brushing frequency	once	156 (64.4)	3.24(1.8)	0.0009
	twice	62 (22.8)	2.67(1.5)	
	never/rarely	32 (12.8)	4.54(1.9)	
o snacking habits	once a day	125 (50)	2.24(1.5)	0.001
	twice a day	85(34)	3.5(1.8)	
	more than 2 times	40(16)	4.47(1.7)	
o previous dental visits	yes	105(42)	3.6(1.24)	0.0012
	no	145 (58)	4.54(1.8)	

DISCUSSION

Dental caries remains a significant public health problem worldwide, affecting individuals of all ages.[11] It is a microbial disease of the calcified tissues of the teeth, characterized by demineralization of the inorganic component and destruction of the organic content of the tooth. The prevalence of dental caries is on a surge in many developing countries and remains a matter of deep concern for clinicians. The prevalence of dental caries among school-going children is a growing concern worldwide. According to research studies, children in this age group often face challenges in maintaining good oral hygiene practices, leading to an increased risk of developing cavities.[12]

The results of current research show a high prevalence of dental caries among the study population, with a mean DMFT score of 5.82. This is consistent with previous studies that have reported a high prevalence of dental caries among children and adolescents. The high prevalence of dental caries in this study can be attributed to inadequate oral hygiene practices, frequent snacking, and limited access to dental care.[13]

Sugar consumption and frequency has a direct impact on dental caries development and progression. In the current study, participants who consumed sugary snacks frequently had a higher DMFT score, emphasizing the role of dietary habits in the development of dental caries. Age and gender were also found to be significant predictors of dental caries. The mean DMFT score increased with age, indicating a higher prevalence of dental caries among older children and adolescents. This is consistent with previous studies that have reported an increase in dental caries with age.[3] Gender-wise, males had a higher DMFT score compared to females, which may be attributed to differences in oral hygiene practices and dietary habits.[14]

Previous dental visits were also found to be associated with dental caries. Participants who had regular dental visits had a lower DMFT score compared to those who had not visited a dentist in a long time. This highlights the importance of regular dental check-ups in preventing and detecting dental caries. Previous researchers have emphasized on the importance of regular dental checkups and oral health.[15] Participants who visited dentist at least once earlier had a better oral hygiene status than the ones who never visited the dentist before. Thomson *et al*. reported that regular dental check-ups might be associated with better oral health.[16] Paying visit to the dentist has a multifactorial benefit, therapeutic as well as incorporating awareness among the people about good oral hygiene practices. It is of prime importance to take children to a pediatric dentist on a regular basis as soon as the first tooth appears in oral cavity.

This study reported that the most decayed teeth were mandibular 1st and 2nd molars followed by maxillary 1st and 2nd molars. Previous studies reported that mandibular first molars were the most frequently affected by carious lesions.[17] Another study reported that the most frequently involved teeth in dental caries were molars. The rate of caries was higher in the mandibular teeth than in the maxillary teeth.[18] This may be attributed to the effect of gravity on mandibular teeth which leads to plaque deposition at a more rapid pace than maxillary teeth. Pertaining to the type of tooth involved, mandibular right second molars were discovered to have higher dmft scores, while the mandibular central incisors had lower dmft scores. This is in accordance with previous study conducted in Saudi Arabia who observed similar results.[19]

The findings of this study indicate a significant association between brushing habits and dental caries. Participants who brushed their teeth twice a day had a significantly lower DMFT score compared to those who brushed less frequently. This highlights the importance of regular toothbrushing in preventing dental caries.[20] Mean DMFT scores of at least once brushing participants were low as compared to those who never/rarely brushed their teeth. This is in accordance with the previous studies conducted in China, Hong Kong, and Ireland. Another study also reported that children with poor brushing habits had higher caries rates and plaque deposits.[21] These findings are in agreement with the present study. The results of the present study suggest that tooth brushing habit is one of the substantial factors that can have a profound impact on DMFT scores of the participants.

CONCLUSION

In conclusion, this study highlights the high prevalence of dental caries among children and adolescents and its association with brushing habits, snacking habits, age, gender, and previous dental visits. The findings of this study emphasize the need for promoting good oral hygiene practices, healthy dietary habits, and regular dental check-ups to prevent and control dental caries. It is important for parents, teachers, and caregivers to be aware of the signs and symptoms of dental caries, as well as the preventive measures that can be taken to protect children's oral health. Regular dental check-ups, proper oral hygiene practices, and a healthy diet low in sugar are key factors in preventing dental caries in elementary school students. By promoting good oral health habits from a young age, we can help children maintain healthy smiles and avoid unnecessary pain and discomfort associated with dental caries. It is crucial to prioritize oral health in children to ensure their overall well-being and quality of life. Dental awareness campaigns and surveys must be carried out among schools frequently to timely

asses the development of caries and their early management and prevention.

Recommendations for future research:

Prevention and management of dental caries are crucial to ensure the overall well-being of children. It is essential to focus on both prevention and occurrence of dental caries with the aim of effective management it if it develops. Scheduling regular dental check-ups for children is key to early detection and prevention of dental caries. Dentists can identify any signs of tooth decay and provide necessary treatment to prevent further progression. Dental sealants are protective coatings applied to the chewing surfaces of the back teeth to prevent decay. Fluoride treatments can also help strengthen the enamel and make it more resistant to acid attacks. If the decay is in its early stages, fillings can be used to restore the tooth and prevent further decay. For more extensive decay, crowns may be recommended to cover and protect the affected tooth. In severe cases where the decay reaches the tooth's pulp, root canal treatment may be necessary to save the tooth followed by crowning procedure.

AUTHORS' CONTRIBUTION

AR, HA: Conceptualization of the study design, Literature search. NM, RS: Data collection, data interpretation. AR, KN, AT: Write-up, proof reading.

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Submitted: May 16, 2024	*Revised: August 1, 2024*	*Accepted: November 24, 2024*

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ORIGINAL ARTICLE

PREVALENCE OF CARDIORENAL SYNDROME IN PATIENTS ADMITTED FOR ACUTE DECOMPENSATED HEART FAILURE AND ITS CORRELATION WITH IN-HOSPITAL OUTCOMES

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Background: Cardiorenal syndrome is the prevalent form of the syndrome in Pakistan. Despite the rising importance of CRS, more information is needed to understand comorbidities and hospital outcomes. This research study explores the prevalence, and In-hospital outcomes of patients admitted for Acute Decompensated Heart Failure at the tertiary care hospital of Islamabad at the age of above 18. **Methods:** This cohort study was conducted at the tertiary care hospital in Islamabad from January to June 2024. Data were collected from 200 known ADHF patients who visited the CCU (OPD) and ward through a structured questionnaire. The data were analyzed using SPSS version 25. **Result:** The majority of the sample was diagnosed with Type 1 Cardiorenal Syndrome, which accounted for 30% of the total. Cardiorenal Syndrome Types 3 and 5 had a prevalence of 20% each among the patients, while Types 2 and 4 had a prevalence of 15% each. This suggests that Type 1 was more prevalent, but the other types were equally distributed. The mortality rate in the Hospital was highest for Type 5 CRS at 15% and Type 3 CRS at 13%. During this period, Type 2 CRS exhibited the lowest mortality rate. Type 3 CRS had the most extended average hospitalization duration. **Conclusion:** It was concluded in our study that cardiorenal syndrome is the prevalent form among admitted patients with ADHF, and the government needs to increase awareness about health and health-related risk factors related to the communities.

Keywords: Prevalence; Cardiorenal syndrome; In-hospital; Tertiary care

Citation: Yaqoob N, Khalid F, Khan MF, Anwar W, Khan MF, Iqbal MH. Prevalence of cardiorenal syndrome in patients admitted for acute decompensated heart failure and its correlation with in-hospital outcomes. J Ayub Med Coll Abbottabad 2024;36(4):773–7.

DOI: 10.55519/JAMC-04-13921

INTRODUCTION

Cardio-renal syndrome (CRS) encompasses a range of illnesses that affect both the heart and kidneys. In this syndrome, malfunction in one organ, whether acute or chronic, can lead to dysfunction in the other organ, whether it is also acute or chronic.[1] In 2008, the Acute Disease Quality Initiative (ADQI) introduced the current conceptual description of CRS, which categorizes it into five subtypes: Type 1 CRS, also known as acute cardiorenal syndrome, is defined by the sudden deterioration of cardiac function that results in acute kidney injury (AKI).[2] Approximately 25% of patients admitted for acute decompensated heart failure (ADHF) experience Type 1 CRS.[3] CRS type 2 is distinguished by persistent irregularities in the functioning of the heart, which result in injury or failure of the kidneys. Type 3 CRS is distinguished by an acute deterioration of kidney function that results in cardiac disease. Chronic Reno cardiac illness, commonly known as Type 4 CRS, is identified by cardiovascular complications in individuals with CKD at any stage. CRS type 5 is a newly identified clinical illness; comprehensive epidemiological information must still be included. Type 5 cardiorenal syndrome refers to the simultaneous occurrence of cardiac and renal impairment. This typically happens in cases of sepsis, where both the heart and kidneys are affected due to a shared underlying pathogenic origin.[2]

Cardiorenal syndrome (CRS) frequently arises during the management of acute decompensated heart failure (ADHF) and is linked to unfavourable clinical prognosis.[4] Approximately 14–34% of patients diagnosed with acute decompensated heart failure (ADHF) experience the development of worsening renal function (WRF). The wide range of values can be mainly attributed to differences in the threshold values for changes in renal function, the duration of observation, the population being studied, and the severity of the initial renal function. Furthermore, the admission creatinine measurements, considered "baseline creatinine" values, may not accurately represent the baseline in patients who previously experienced some decline in their renal function before admission. While the majority of

studies have indicated that WRF (Worsening Renal Function) in Acute Decompensated Heart Failure (ADHF) typically begins soon after admission to the Hospital, WRF can develop in the short- and medium-term following hospitalization.[5]

Acute decompensated heart failure is a prevalent cardiac condition in Pakistan for hospitalization, with various precipitants significantly impacting the severity of decompensation, especially in resource-poor settings.[6] Individuals suffering from heart disease often require hospitalization as a result of acute decompensated heart failure (ADHF), which can be associated with either preserved or diminished left ventricular systolic function.[7] The study conducted by Zaidi *et al*.[8] focused on cardiorenal syndrome type 1 in children admitted to the Hospital with acute heart failure. In addition, Naqvi[9] examined a case series involving individuals who experienced Acute Kidney Injury (AKI) and Cardiorenal Syndrome (CRS). The aim was to record multiple factors contributing to CRS and the subsequent prognosis in this group of patients. The aetiologies of CRS encompassed acute myocardial infarction with ST elevation, congestive heart failure, infective endocarditis, and dilated cardiomyopathy. Moreover, the main factors that increase the likelihood of kidney damage in the context of heart failure or cardiac dysfunction include high blood pressure, diabetes, and substantial underlying atherosclerotic vascular disease. A considerable percentage of diabetic patients eventually develop clinically severe nephropathy, and diabetes is a known risk factor for cardiovascular disease (CVD).[10]

Limited published literature exists on cardiorenal syndrome in Pakistan. This study is conducted to fill the literature and knowledge gap for future studies. This research aimed to determine the prevalence of cardiorenal syndrome in hospitalized patients with acute decompensated heart failure.

MATERIAL AND METHODS

The sample was comprised of N=200 patients with ADHF. Acute decompensated heart failure (ADHF) is the sudden worsening of chronic heart failure symptoms, often requiring immediate medical care. It is marked by symptoms like severe shortness of breath, fluid buildup, and fatigue due to the heart's reduced ability to pump blood effectively. Patients who were above the age range of 18 were included in this study, which was conducted over the span of 6 months (January–June 2024). The existing criteria served as the foundation for the definitions of ADHF. Patients with active infections, those who had undergone heart surgery for emergency coronary revascularization, or those with a history of end-stage renal illness necessitating renal replacement treatment were not included in our analysis.

This study was carried out at the tertiary care Hospital in Islamabad, using a retrospective cohort design. This facility is located in the metropolitan area. This tertiary care and sees a mix of patients from wealthy and lower and middle-class backgrounds.

The study was undertaken following approval from the Hospital's ethical and research council. This study covered all patients who were admitted for acute decompensated heart failure. After stabilizing and treating these patients, formally informed consent was obtained from them. Data was collected through the Hospital's computerized information system. Standard clinical, physiological, and demographic data were gathered. Age, sex, body mass index, weight (kg), height (cm), and duration of hospital stay were among the demographic data. Primary diagnoses and other comorbidities were included in the clinical data.

The data was recorded and analyzed using SPSS version 25.0. The mean and standard deviation (SD) were computed for numerical variables such as age and BMI. Categorical characteristics such as gender, professions, hypertension, chronic kidney disease, diabetes mellitus, ischemic heart disease, NYHA Class 1–11, NHYA Class III-IV, and ADHF were analyzed to determine frequencies. ADHF was examined by stratifying data based on age and gender. The findings were displayed in the form of tables and charts.

RESULTS

The study involved 200 patients admitted for Acute Decompensated Heart Failure (ADHF). The majority of these patients were diagnosed with Type 1 Cardiorenal Syndrome, accounting for 30% of the sample. Types 3 and 5 of Cardiorenal Syndrome each affected 20% of the patients. In comparison, Types 2 and 4 affected 15% of the patients, indicating a higher prevalence of Type 1 and an equal distribution of the other types.

The gender distribution showed a predominance of males, with 130 patients (65%) compared to 70 females (35%). Regarding age groups, the most affected were those aged 40–50 years, comprising 45% of the total sample. The second largest group was patients under 40 years old, representing 35% of the cohort. The age group over 50 years old was the least represented, making up only 20% of the study population.

Table 2 showed the comorbidities based on types of cardiorenal syndrome in 200 patients. It classifies 110 individuals with diabetes, with Type 1 accounting for the largest number (40), followed by Type 5 (30). There are 140 cases of hypertension, with

Type 1 accounting for the largest number, followed by Type 2, and Type 5. Seventy patients have chronic kidney disease (CKD), with Type 1 accounting for the majority of cases. There are 120 individuals with ischaemic heart disease (IHD), with the highest number of type 1, type 5 and type 2. New York Heart Association (NYHA) functional classes are used to categorise patients according to the degree of their heart failure. There are 70 cases in Class I–II, with the majority falling into Type 1 (20) and Type 5 (15). There are 130 people in Class III–IV, with Type 1 (45) and Type 5 (40) having the greatest groupings. This distribution shows how common certain comorbidities are and how severe heart failure is in distinct patient groups.

The table provides a summary of in-hospital outcomes for each of the five patient categories, including in-hospital mortality, average length of stay, and 30-day readmission rates. Type 5 patients had the greatest in-hospital mortality rate (15%). The typical length of stay varies by patient category; Type 3 patients spend the longest, on average, for 15 days. Additionally, the 30-day readmission rate is highest for Type 3 patients (38%), followed by Type 5 patients (35%). This data reflects differences in in-hospital outcomes as well as differences in mortality, length of hospital stay, and readmission risk among the different patient categories.

Table-1: Demographic distribution based on types (N = 200)

Category	Total Patients (N)	Type 1 (N)	Type 2 (N)	Type 3 (N)	Type 4 (N)	Type 5 (N)
Total ADHF Patients	200	60	30	40	30	40
Gender						
Male	130	40	20	30	15	25
Female	70	20	10	10	15	15
Age Group						
< 40	70	15	10	10	20	15
40-50	90	30	15	20	5	20
> 50	40	15	5	10	5	5

Table-2: Comorbidities based on types of cardiorenal syndrome (N=200)

Comorbidities	Total Patients (N)	Type 1 (N)	Type 2 (N)	Type 3 (N)	Type 4 (N)	Type 5 (N)
Diabetes	110	40	25	5	10	30
Hypertension	140	50	40	8	6	36
Chronic Kidney Disease (CKD)	70	20	13	15	7	15
Ischemic Heart Disease (IHD)	120	40	25	10	15	30
Severity of Heart Failure						
NYHA Class I-II	70	20	16	9	10	15
NYHA Class III-IV	130	45	30	8	7	40

Table-3: In hospital outcomes based on types of cardiorenal syndrome (N=200)

In Hospital Outcomes	Type 1 (N)	Type 2 (N)	Type 3 (N)	Type 4 (N)	Type 5 (N)
In-Hospital Mortality (%)	10%	8%	13%	11%	15%
Average Length of Stay (days)	14	8	15	8	12
30-Day Readmission Rate (%)	30%	25%	38%	26%	35%

DISCUSSION

This study aimed to determine the prevalence of various forms of Cardiorenal Syndromes (CRS) in Acute Decompensated Heart Failure (ADHF) patients and co-morbid diseases, severity of heart failure, and post-hospitalization outcomes. This study described the frequency and features of Cardiorenal Syndrome (CRS) among 200 admitted patients with Acute Decompensated Heart Failure (ADHF). According to the data, among all types of CRS, Type 1 affects 30% of participants. As Ronco *et al*.[11] Ronco & Lullo (12**),** and Zarbock *et al*.[13] state, Type 1 CRS is an acute cardiorenal syndrome that is most common. Types 3 and 5 affected twenty percent of subjects, whereas fifteen percent were affected by Types 2 and 4. The Distribution of CRS amongst ADHF patients is highly nonuniform, with Type 1 being more prevalent, although other types are also discernible.

There were more men than women, 65% and 35%, respectively, in terms of gender and age distribution of the participants. A relation between heart failure prevalence rate vis-a-vis sex disparity has been reported elsewhere.[14] The most harshly hit age group was participants in their forties and fifties, which constituted 45%. After that, 35% were for those under 40. Another twenty percent comprised individuals aged fifty or above. Thus, it is essential to raise awareness and implement early intervention measures to address the higher incidence of heart failure and CRS among those below the age of fifty years. These results might help halt the progression of cardiovascular insufficiency and CRS.

Different types of CRS have distinct patterns of coexisting diseases, with diabetes being the most common in Type 1 CRS (40 patients) and Type 5 CRS (30 persons), suggesting a strong link between these comorbidities.[15] In a study by Prothasis *et al*.[16] Type 1 CRS was highest among the 140 participants affected by hypertension at 50 individuals, followed by Type 2 at 40 people. Liu *et al*.[17] found that CKD had subtypes: Type 3, Type 1 (20 patients), and Type 5, but there were only patients within each subtype comprising fifteen individuals. Silva & Diógenes[18] observed IHD in fifty cases of Type 1 CRS, while thirty cases out of them had Type 5 CRS. The complex interaction between cardiac and renal dysfunction is highlighted by this condition, which underscores the necessity to employ balanced care approaches targeted towards both heart failure and its most commonly associated ailments.

A remarkable increase in the severity of heart failure was noted as 130 study participants were classified as NYHA Class III-IV. The New York Heart Association (NYHA) Classes I-II [20 patients] and Classes III-IV [45 patients] represent incidences and grades of Type 1 CRS, respectively. This is indicated by 40 patients from 5 CRS being placed in the category of NYHA Class III-IV, which suggests that severe heart failure is common in this condition. Consequently, the statement asserts a need for prompt identification and intervention against HF to prevent it from progressing into severe CKD.[19,20]

Regarding CRS type within the hospital setting, a significant difference was observed in patient prognosis. In Type 5 CRS, this rate was higher at 15% compared to Type 3 CRS (13%). The death rate linked with Type 2 CRS is less than other types of syndromes described above. Different death rates are associated with various types of cardiorenal syndrome due to different pathophysiological processes and different levels of organ dysfunction caused by them.[21,22]

Those with Type 3 CRS stayed an average of 15 days, and those with Type 2 or 4 CRS just eight days. The degree of kidney failure linked to Type 3 CRS necessitates intense and continuous medical therapy that cannot be adequately handled in a shorter amount of time, which is why patients with this condition require longer hospital stays. For Type 3 CRS, the 30-day readmission rate was the highest at 38%. Type 2 CRS was next highest at 25%. A readmission rate of 35% was seen among people with Type 5 CRS. The high readmission rates for Type 3 and Type 5 CRS underscore the symptoms' recurrent, intractable nature. Therefore, comprehensive treatment programs are significant.[22] Chronic renal insufficiency (CRS) is present in patients with acute decompensated heart failure (ADHF), and it is associated with worse outcomes following hospitalization; these subjects require specialized care. Immediate consultation with other specialties, such as cardiologists and nephrologists, is crucial to ensure adequate treatment of this portion. Three strategies should be emphasized to increase patient results: early diagnosis of kidney function impairment, combat the burden by taking outstanding comorbidities, and thinking about specific care plans.

CONCLUSION

The study concentrated on the significant differences in incidence, severity, and comorbidities in various CRS types among ADHF patients. CRS Type 1 (day of surgery type) has a poorer prognosis but expresses less frequently, Chronic cardiorenal syndrome, or CRS Type 2, on the other hand, is linked to chronic heart failure that progressively impairs kidney function over time. In contrast to the abrupt deterioration observed in CRS Type 1, patients with CRS Type 2 typically have more stable and controllable symptoms, which may account for the comparatively improved short-term prognosis. Nevertheless, patients with CRS Type 2 have substantial long-term difficulties in spite of this seeming stability. Over time, these individuals are at a higher risk of death and frequent hospitalisations due to the chronic progression of both renal and heart disease. Higher death and readmission rates result from this. The findings underline the importance of creating protocols for each phenotypically distinct CRS to improve patient outcomes and reduce hospital readmissions.

AUTHORS' CONTRIBUTION

Conceptualization NY. Data curation: FK, MHI Formal analysis: WA, MFK, MFK Investigation: NY Methodology: FK, WA Validation: NY, MFK, WA Writing –original draft: MHI, MFK, MFK. Writing – review & editing: NY, MHI

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Submitted: July 8, 2024	*Revised: October 6, 2024*	*Accepted: November 5, 2024*

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ORIGINAL ARTICLE

MOLECULAR CHARACTERIZATION OF MBL IN UROPATHOGENIC *E. COLI* ISOLATED FROM PATIENTS OF TERTIARY CARE HOSPITAL

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Background: Antibiotic resistance is on an increasing trend, particularly in gram-negative bacteria. The production of metallo β-lactamase (MBL) puts the health sector at great risk as it further limits the treatment option for MDR strain. The current study aims to determine the prevalence, antibacterial sensitivity pattern, and molecular characterization of MBL in Uropathogenic *E. coli* from clinical samples of hospitalized patients in Khyber Pakhtunkhwa. **Methods:** From tertiary care hospitals in Peshawar, 250 Urine samples were collected from indoor hospitalized patients. Gold standard microbiological methods were used to identify UPEC from these clinical samples.For that,urine samples was inoculated onto Cysteine Lactose Electrolyte. Deficient (CLED) agar plate, and MacConkey Agar.Positive growth of *E. coli* identified through Gram staining, colony morphology, Biochemical Tests and *E.coli* 16srRNA gene amplification .Antibiotic sensitivity was determined by the disc diffusion method on Muller Hinton agar. For the detection of MBL production double disc synergy, and a combination disc test of the antibiotics were used. Furthermore, multiplex PCR was used for the molecular characterization of the MBL (bla_{IMP}, bla_{VIM}, and $bla_{NDM)}$ genes. **Results:** Of the 250 samples, only 110 samples were confirmed as Uropathogenic *E. coli* based on colonial morphology, biochemical testing, and molecular level by targeting the 16SrDNA. Female was found more susceptible to UTI compared to male. High prevalence was found in the age group 45–65 years. UPEC was found highly resistance to Ciprofloxacin (90%), followed by Cefotaxime and Ceftriaxone (86%), Ceftazidime and Augmentin (81%), Tazobactam (61%). while the lowest resistance was reported against Meropenum (20%) Imipenem (18%) and Amikacin (37%). PCR-based confirmed prevalence of MBL encoding genes was $bla_{NDM\ (}$42%), bla_{VIM} (32%), and bla_{IMP} (26%). **Conclusion:** The study proposed a higher prevalence of urinary tract infections (UTIs) in females aged group 54–65 years compared to males. An analysis of antibiotic sensitivity revealed Imipenem and Meropenem to be the most effective antimicrobial agents, while Ciprofloxacin, Cefotaxime and Amoxicillin were found to be the less effective. UPEC were found highly resistance to Ciprofloxacin 91%, and ceftazidime 86%, while comparatively less resistance to meropenem, and imipenem,20% and 18% respectively. Genotype BlaNDM of the MBL is highly prevalent (42%) among UPEC.Furthermore, the presence of MBL genes was detected in over 19% of UPEC, and in different combinations.The upraise of the MBLs resistance in uropathogenic *E. coli* is an alarming sign for clinicians to decide on treatment options for complicated UTIs.

Keywords: Urinary tract infection; *Escherichia coli*; Extended spectrum Beta lactamase (ESBL); Metallo beta lactamase (MBL)

Citation: Asghar S, Khuwaj AA, Arfat M, Taj N, Akhtar M, Ihsanullah. Molecular characterization of MBL in uropathogenic *E. coli* isolated from patients of tertiary care hospital. J Ayub Med Coll Abbottabad 2024;36(4):778–82.

DOI: 10.55519/JAMC-04-13466

INTRODUCTION

Urinary tract infection (UTI) is a common public health problem particularly in developing countries due to the lack of health education and hygiene practices. It is the second leading cause of morbidity after respiratory tract infection worldwide. Predisposing factors for UTI include prolonged hospital stay, catheterization, female gender, diabetes, children, and very old age. UTI is mostly caused by uropathogenic *Escherichia coli* (UPEC).[1] The UPEC is responsible for more than 95% of community-acquired, and about 80 % of hospital-acquired UTIs while it also causes 3.6–12.6% of complicated UTIs that often lead to urosepsis.[2]

For a long time, the empirical therapy of UTI due to *E. coli* was relayed on the β-lactam antibiotics. However, its widespread uses in agriculture, veterinary and human medicine resulted in the emergence of drug-resistant bacterial strains.[3] These drugs resistance bacteria particularly the ones that produce extended-spectrum β-lactamase (ESBL), and Metallo- β-Lactamase (MBL) also known as carbapenemase

pose a great risk to public health all over the world.[4] Therefore, antibiotic resistance surveillance on a regular basis is necessary to report the newly emerging and dissemination of drug resistance mechanisms and to refine the treatment guideline for empirical antimicrobial therapy.[8] According to the Amber classification, beta-lactamases are classified into (A, B, C, and D). MBL falls in class B, which further subdivides into B1, B2, and B3. Most commonly reported MBLs like IMP, VIM, SIM, GIM, and NDM belong to the B1 class.[5,6]

Initially, it was proposed that the MBLs encoded genes are found on chromosomes, but now plasmid-mediated MBLs have also been reported around the globe.[7] The MBLs enzyme renders the activity of beta-lactam antibiotics by hydrolyzing the amide bond that links with the beta-lactam ring. Thus, they not only degrade the carbapenem group of antibiotics but also the rest of the beta-lactam antibiotics excluding the monobactam antibiotics (9). Furthermore, the worldwide spread of MBL is due to horizontal gene transfer and the lack of proper MBL inhibitors. Thus MBLs act as a potential weapon of bacteria against the antibiotics that enable the bacterial community to survive in the presence of antibiotics.[10]

Keeping the importance of the drug resistance issues, the current study aimed to determine the prevalence of the MBLs encoding genes in uropathogenic *E. coli* and to find the association of the MBL genotypes with commonly prescribed antibiotics for UTI.

MATERIAL AND METHOD

One hundred and ten **(**110) positive *E. coli*. Calculated by sample size calculator with prevalence of MBL producing *E.coli* as 7.0% based on reference study(8)with assumption of 95% confidence interval and margin of error as 5%.

It was a cross-sectional study carried out at Hayatabad Medical Complex, Peshawar and processed in microbiology laboratory of IPDM, Khyber Medical University, Peshawar in a duration of six months. In the study the Non-probability convenient sampling techniques were used.Inclusion criteria: Patients having UTI due to Uropathogenic E. coli. Patients willing to participate in the study.

Exclusion criteria:Gram Negative bacteria other than E-coli. Patients under the treatment of antibiotics. Patients not willing to participate.

Ethical clearance was taken from ethical committee of KMU, Peshawar and the concerned hospital and consent was taken from hospitalpatient/attendant.

A total of 250 urine midstream samples were collected from hospitalized patients in a leak-proof sterile urine container at Hayatabad Medical Complex (HMC) Peshawar. The samples were transported to the microbiology lab of the Khyber Medical University (KMU) Peshawar for further analysis.

All the samples were processed for the identification of uropathogenic *E. coli* following a standard technique that is colonial morphology, gram staining, motility, and biochemical tests.[11] Antibiotic susceptibility tests (AST) were performed using the Kirby-Bauer disc diffusion method (12). The antibiotic discs used in the study were Meropenem, (MEM-10ug), Imipenem (IMP-10ug), Pipra/Tazobactum (TZO-100/10 ug), Ciprofloxacin (CIP-30ug), Ceftriaxone (CRO-10ug), Cefotaxime (CXT-30ug), Ceftazidime (CAZ-30ug), Ampicillin (AMP-10ug), and Amikacin AK -30ug) provided by thermos-Scientific™ Oxoid™ UK. The result of the AST was interpreted according to the recommendation of the Clinical and Laboratory Standard Institute 2022 (CLSI-2022) (13) using *E. coli* ATCC25922 as a standard.

Double disc diffusion synergy was used for the identification of MBL production following the CLSI-2022 guideline. Carbapenem (Meropenem, and Imipenem) was selected for this. The zone of inhibition was measured by comparing the zone of meropenem alone with that of Meropenem + EDTA.

For detection of MBLs genotype in *E. coli*, the plasmid was extracted via thermos scientific plasmid DNA extraction kit, following the manufacturing guideline. The confirmation of plasmid was done on 1.5% agarose gel and was stored at -20 ^{0}C for further use. Polymerized chain reaction (PCR) was performed to determine the Metallo beta lactamases enzyme genes using specific reaction conditions, and primers. The primers used for MBL genes were blaVIM, blaIMP, and blaNDM.[14] The details of the primer sequence and PCR reaction condition are listed in the below table. The MBLs genes were confirmed on the basis of their product size by running it on 1.5% agarose gel with 100 pb ladder as control.

RESULTS

Out of 250 samples, 110 samples were confirmed for UPEC with the help of colonial morphology, gram staining, biochemical testing, and molecularly PCR based by targeting the 16SrRNA of UPEC. The prevalence of UTI was found higher in females

(62%) compared to their male counterparts (38%), with the most susceptible age groups being 55–64 years which was 32.7%, (36) followed by the age group 45–54 years at 23.6% (25), while the lowest incidence of UTI was reported in the age group 15–24 years is 5.5% (6).

The antibiotics susceptibility profile of UPEC was checked against the nine antibiotics that are commonly prescribed for the treatment of UTI both in hospital setup and community. UPEC shows high resistance to Ciprofloxacin 90% followed by 86% to cefotaxime and ceftriaxone, 81% to co. amoxiclav, 81% to ceftazidime, 61% to tazobactam, and 37.2% to amikacin, while lowest although comparatively high resistance to meropenem 20% and Impenum 18%. Out of 110 UPEC samples, 21(19.09%) were phenotypically confirmed as MBL producers. A total of 21 uropathogenic *E. coli* were screened for the presence of plasmid-mediated metalo- beta-lactamases genes ($bla_{IMP,}$ $bla_{VIM,}$ and $bla_{NDM).}$ The genome size of the Bla_{IMP} (260bp), bla_{VIM} (350bp), and bla_{NDM} (740bp). The Amplified product of the gene bla_{IMP} is compared with the 100bp DNA ladder shown in the below figure.

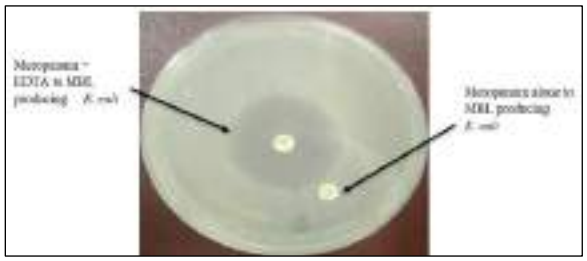

Figure-1: Molecular detection of MBL producing genes in uropathogenic *E. coli*

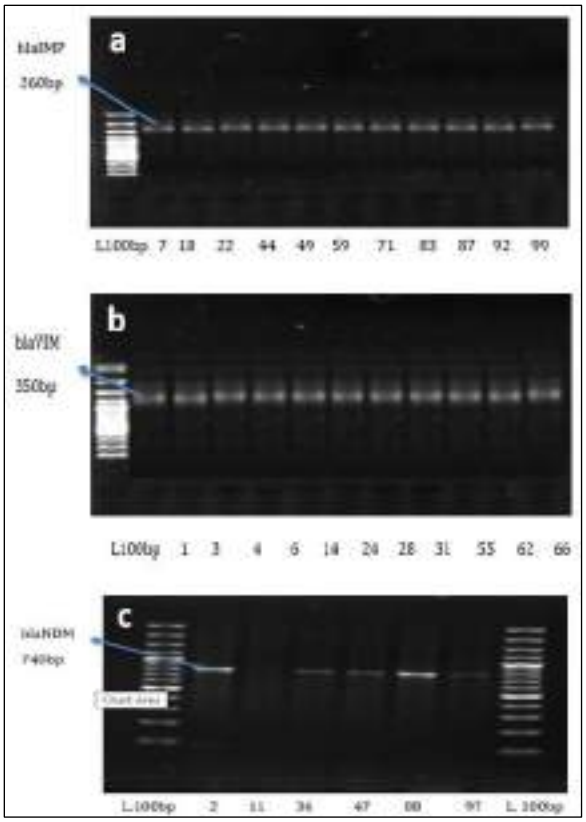

Figure-2: (a), shows the PCR amplified product (260bp) of IMP gene against 100bp leader, (**b)**, VIM gene products (350bp) with 100bp leader, and (**c)**, are of NDM gene products (740pb) with 100bp leader run on 1.5% agarose gel. Among the 110 UPEC isolates, 19% were phenotypically confirmed as MBL producers which harbored $bla_{NDM,}$ gene(42%), blavim gene(32%) harbored bla_{IMP} (26%).

Table-1: Details of primer size, annealing temperature, and target genes.

Target Gene	Primers	Primer Sequence (5-3P)	Size	Annealing Temp	Reference
NDM	NDM	F: GGTTTGCGATCTGGTTTTC R: CGGAAATGGCTCATCACGATC	780bp	53C	(7,14)
VIM	VIM	F: CGAATGCGCACCAG R: TGGTGTTTGGTCGCAAT	350bp	52C	(7,14)
IMP	IMP	F: GTTTAACAAAACAACCACC R: GGAATAGAATGGCTTAACTCT	260bp	52C	(7,14)

Table-2: Frequency and distribution of UTI among males and females with respect to different age groups:

Parameters	Frequency of UTI	Frequency of UTI	Male (%)	Female (%)
Gender		38%	62%	
Age wise prevalence	15-24 years		0 %	5.5 %
	25-34 years		0 %	9%
	35-44 years		4.5%	10%
	45-54 years		9%	14.5%
	55- 64years		10%	22.7%
	65 years and above		14.5 %	0%

Table-3: Antibiotic susceptibility profile of Uropathogenic *Escherichia coli*.

Antibiotics name	Sensitivity	Intermediate sensitive	Resistance
Amikacin	63 (57.2%)	6 (5.45%)	41 (37.2%)
Imepenum	88 (80%)	2 (1.8%)	20 (18.1%)
Meropenem	86 (78.1%)	2 (1.8%)	22 (20%)
Ceftazidime	17 (15.5%)	3 (2.7%)	90 (81.8%)
Ceftriaxone	15 (13.6%)	0 (00%)	95 (86.3%)
Cefotaxime	15 (13.6%)	0 (00%)	95 (86.3%)
Amoxicillin and clavulanic	18 (16.3%)	3 (2.7%)	89 (80.9%)
Piperacillin/tazo	40 (36.3%)	2 (1.8%)	68 (61.8%)
Ciprofloxacin	9 (8.1%)	2 (1.8%)	99 (90%)

DISCUSSION

Urinary tract infection is a global health problem that is most prevalent in females and children. The emergence of drug resistance particularly the acquisition of MBL among the pathogen that causes UTIs puts the human population at great risk mainly in the developing world where health facility is already in overwhelming situation.[15] Uropathogenic *E. coli* is the predominant organism that causes UTI, in all age groups male, and female, both in the community population and in hospital setup. Surveillance study on antimicrobial among uropathogenic organism is scars in developing countries.[16] In this study high prevalence of UTI was found in females (62%) compared to males (38%), particularly at the reproductive stage of life with the predominant organism being *E. coli* as 44%. This finding is in agreement with a study conducted in Iran 43.5, Nigeria 44.1%, and India 44%, but lower than a study in Poland where UPEC was 58% in HIV-positive patients (17–19, 23). In the current study, UPEC shows high resistance to Ciprofloxacin 90% followed by 86% to cefotaxime, ceftriaxone, and 81% to co. amoxiclav, 81% to ceftazidime. In close proximity results to this study were reported from India, and Turkey where resistance to Ciprofloxacin was above 90%, while to cephalosporin 2nd, 3rd, and 4th generation was between 75% to 88%. Although a slightly lower rate of resistance was reported among UPEC to cefotaxime 77%, ceftriaxone, 78%, and ceftazidime 72% from other parts of Pakistan.[20–21]

Resistance to imipenem and meropenem was among the lowest 18% and 20% respectively. Higher resistance was reported to Imipenem 34.5% in India.[23] While the lowest 8% resistance to each antibiotic has been reported from Mexico.[24] In the current study, MBL production was confirmed phenotypically among 21 (19.09%) of the clinical isolate in contrast to our study a high result was reported from Saudi Arabia 62.5% phenotypically while Mexico, had the lowest resistant rate of 8%, and 10% although Iran, and India having similar resistance pattern 26% and 34%.

Metalo-beta-lactamase synthesis is an important mechanism for the resistance to carbapenem group of antibiotics, several genes are responsible for the synthesis of such enzyme. We included three genotypes of this enzyme in our study that is $bla_{NDM,}$ $bla_{VIM,}$ and $bla_{IMP.}$ The prevalence of different MBL genotypes in this study is bla_{NDM} 42%, $bla_{VIM,}$ 32%, and bla_{IMP} 26%. Different MBL genotype prevalence has been reported from different countries even different centers. But a similar pattern of MBL genotype prevalence has been reported from India where Bla_{NDM} at 63% followed by Bla_{VIM} at 18.6% and less than 10% $Bla_{IMP.}$[23] In China higher prevalence was found of Bla_{NDM} 83% and Bla_{IMP} 17% while Bla_{VIM} was not included in the study.[25]

CONCLUSION

Based on the data, there is a higher prevalence of urinary tract infections (UTIs) in females aged group 54-65 years compared to males. An analysis of antibiotic sensitivity revealed Imipenem and Meropenem to be the most effective antimicrobial agents, while Ciprofloxacin, Cefotaxime and Amoxicillin were found to be the less effective. UPEC were found highly resistance to Ciprofloxacin 91%, and ceftazidime 86%, while comparatively less resistance to meropenem, and imipenem,20% and 18% respectively. Genotype BlaNDM of the MBL is highly prevalent (42%) among UPEC. Furthermore, the presence of MBL genes was detected in over 19% of UPEC, and in different combinations. Additionally, some isolates indicated the phenotypic and genotypic occurrence of carbapenem resistance genes. This situation is a cause for concern, highlighting the need for antibiotic prescriptions to be based solely on clinical diagnosis via urine culture. The current situation is worse, required surveillance study across the country. Antibiotics prescription must be made based on culture sensitivity to avoid spread of

Recommendations:

Animal husbandry practices should be closely monitored for antibiotic usage, and routes of transmission should be identified to prevent transmission between animals and humans. Over-the-

counter availability of antibiotics is a major concern in the generation of drug resistance among pathogens. Furthermore, environmental dissemination of antibiotics through various routes could lead to the emergence of XDR and MDR pathogens.

AUTHORS' CONTRIBUTION

SA, AAK: Conceptualization of the study design, literature search. MA, NT: Data collection, data analysis, interpretation. SA, MA, IU: Write-up, proof reading.

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Submitted: June 6, 2024	*Revised: November 19, 2024*	*Accepted: November 20, 2024*

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ORIGINAL ARTICLE

CHARACTERIZATION OF BETA THALASSAEMIA MUTATIONS IN PATIENTS HAVING BORDERLINE HAEMOGLOBIN A2 LEVELS

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Background: The occurrence of a single beta thalassaemia allele is frequently related with microcytic hypochromic red blood cells and a rise in HbA2 levels. In some beta thalassaemia carriers, the outcome of this allele or its collaboration with other acquired or genetic defects may result in normal or borderline Haemoglobin bA2 levels. Objective was to establish the importance of molecular analysis in borderline HbA2 individuals and its significance in a population screening program. **Methods:** It was a cross-sectional study conducted over a period of six months, from July-December 2023. All 123 individuals with borderline HbA2 levels between (3–3.9%) diagnosed by High-performance liquid chromatography (HPLC)/Capillary Zone Electrophoresis underwent molecular testing using multiplex amplification refractory mutation system-Polymerase Chain Reaction (ARMS-PCR) to detect common beta thalassaemia mutations: Fr8-9, IVS1-5, Fr41-42, Cd15, Cd5, IVS1-1, IVS1-1, Cd30, Cd30, Fr16, IVSII-1, Del619, and CAP+1 in the Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi .Statistical tests were applied to compare Red Blood Cell indices and Haemoglobin A2 values among beta thalassaemia carriers and non-carriers. **Results:** Among those tested, 47.1% (n=58) were found to carry Beta thalassaemia mutations. The most prevalent mutations were IVS1-5 (n=19,15.4%) and Fr8-9 (n=19,15.4%) followed by Fr41-42 (n=08,6.5%). Subjects with mutations exhibited significantly lower mean corpuscular volume and mean corpuscular haemoglobin compared to those without mutations (*p*-value= <0.001). Beta thalassaemia mutations were seen more frequently when HbA2 was in range of 3.5-3.9% (n=37,63.8%), as compared to HbA2 that was 3-3.4% (n=21,36.2%) and this difference was found to be significant (*p*-value= <0.001). The CAP+1 mutation was associated (n=02,1.6%) with normal mean MCV and MCH compared to other identified mutations. **Conclusions**: It is concluded that molecular study for the common beta thalassaemia mutations in Pakistani population plays a pivotal role in confirmation of borderline HbA2 thalassaemia carriers, specifically in areas with a high prevalence of the disease. Molecular testing for beta thalassaemia should be offered to all individuals with borderline HbA2 with values especially between 3.4–3.9% and having microcytic hypochromic indices.

Keywords: Borderline HbA2; Silent carriers; Beta Thalassaemia mutation; Red Cell Indices; Molecular analysis

Citation: Noor A, Bozdar M, Malik HS, Mahmood R, Khurshid A, Khan A, Seema N. Characterization of beta thalassaemia mutations in patients having borderline haemoglobin A2 levels. J Ayub Med Coll Abbottabad 2024;36(4):783–7.

DOI: 10.55519/JAMC-04-14046

INTRODUCTION

The occurrence of a single beta thalassaemia allele is frequently related with microcytic hypochromic red blood cells and a rise in HbA2 levels. In some beta thalassaemia carriers, the outcome of this allele or its collaboration with other acquired or genetic defects may result in normal or borderline Haemoglobin bA2 levels.[1] Borderline HbA2 levels refers to values between (3.0–3.9%).[2] Those beta thalassaemia carriers having borderline HbA2 levels may be missed on haemoglobin studies and may only be diagnosed after the birth of diseased child. Hence, these borderline cases are vulnerable for having offspring with beta thalassaemia if their spouse is also a beta-thalassemia carrier.[3] Red blood cell indices and HbA2 levels may be normal in silent beta thalassemia carriers and their status can only be confirmed by DNA analysis.

Borderline HbA2 levels are not rare in countries like Thailand[4] China[5] Italy[6,7] and Greece[8] with a high prevalence of beta-thalassaemia. People with borderline HbA2 levels also have also been reported in Middle Eastern populations[9,10] and India[11]. People with borderline HbA2levels have been reported in 31 different countries worldwide. Migration and inter-marriages between individuals from different genetic backgrounds can lead to the transmission of globin gene defects (like beta-thalassaemia mutations) to populations where these disorders were previously less common or unknown.[12,13] Local literature shows prevalence of beta thalassaemia trait

in Pakistan is 6–7% and the actual numbers may be higher.[14] The present situation of beta-thalassaemia in Pakistan warrants the recognition of individuals with borderline HbA2 levels in our population. Presently, there is lack of information on how to deal with cases having borderline HbA2 levels and information regarding different factors affecting HbA2 levels remains mainly unexplored.[15] Hence, this study was designed to identify silent beta thalassaemia carriers having borderline HbA2 levels by molecular analysis.

MATERIAL AND METHODS

This cross-sectional study was carried out at Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi, over a period of six months, i.e., from July to December 2023 after getting approval from Institutional Review Board under IRB-No: IRB/24/2698. The sample size was 123 and it was calculated by WHO calculator and sampling was done by using non-probability consecutive technique. Individuals with border line HbA2 levels (3.0–3.9%) who were referred for molecular studies at our Institute were interviewed and detailed clinical history and examination findings were recorded. A 3 ml of blood was collected in Ethylene Diamine Tetra Acetic Acid (EDTA) vacutainer from each individual after verbal and written informed consent whereas in children consent was taken from their parents. Our study included 123 individuals above 1 year of age, either gender, and having borderline HbA2 levels already determined by High-performance liquid chromatography (HPLC)/ Capillary Zone Electrophoresis method, while patients with bicytopenia, pancytopenia, other haemoglobinopathies, raised HbA2 levels more than 4%, having recent transfusion history within one month period and low ferritin levels were excluded from the study. The HbA2 cut-off for diagnosis of heterozygous beta-thalassaemia was taken as HbA2 ≥4% and hence these 123 subjects were labelled as borderline HbA2 individuals [3.0–3.9%].

Three milliliters of blood were obtained from the study population by using EDTA vacutainers for subsequent investigation. RBC parameters were assessed using automated Sysmex XP100 Haematology analyzer. The blood samples were processed immediately. DNA extraction from blood samples was performed by mini kit method, as per manufactures protocol with subsequent quantification of extracted DNA samples performed by using a nano-drop spectrophotometer. The target DNA was amplified using primers specific to beta-chain mutations to identify both homozygous and heterozygous states in individuals to identify common, uncommon, and rare mutations prevalent in Pakistan including Fr8-9, IVS1-5, Fr41-42, Cd15, Cd5, IVS1-1, IVS1-1, Cd30, Cd30, Fr16, IVSII-1, Del619(bp), and CAP+1. Multiplex amplification refractory mutation system-Polymerase Chain Reaction (ARMS-PCR) was sequentially conducted. Identification of primary mutations involved multiplex PCR assays labelled as Allelic Discrimination assays (AD1, AD2, and AD3) each employing a distinct set of primers including a control primer. After confirming primary mutations, specific PCR amplification of the DNA fragment was carried out, and the resulting product was visualized on 6% Polyacrylamide Gel Electrophoresis (PAGE) using a 1.0 kb DNA marker.

The data was analyzed on Statistical package of social sciences version 26. Mean & Standard Deviation was calculated for quantitative variables like age, Hb, MCV, MCH, MCHC, RDW, HbA, HbF and HbA2 while frequency and percentages were calculated for qualitive variables like gender, carriers and non-carriers. Tests for statistical significance were t-test (for quantitative) and chi-square test (for qualitative variables). *p*-value of less than 0.05 was considered significant.

RESULTS

A total of 123 individuals were enrolled in our research study. There were 73 (59.3%) males and 50 (40.7%) females with a mean age of 22.0±13.5 years. Out of 123 participants, seven individuals had history of disease of beta thalassaemia major in close family.

We characterized borderline HbA2 into two groups, one group with HbA2 in a range of 3–3.4% and other in a range of 3.5–3.9%. Molecular analysis of these borderline individuals confirmed 58 out of total 123 individuals to be confirmed beta thalassaemia carriers. The comparison of the both groups of borderline HbA2 levels showed a highest number of individuals to be carriers in the group of HbA2 3.5–3.9% vs 3.0–3.4% that is n=37,63.8% vs n=21,36.2% respectively with *p*-value of <0.001. Beta thalassaemia mutations were seen more frequently in HbA2 range of 3.5–3.9%. The non-carriers counted were 65 out of the total 123 individuals having borderline HbA2 levels but with no beta thalassaemia mutation detected by PCR. These were in highest number in the borderline HbA2 range of 3-3.4% with not a single individual seen in the HbA2 range of 3.5–3.9%. The association between these two HbA2 groups and beta thalassaemia carrier status was statistically significant (p = <0.001) Table-1. DNA analysis confirmed that 58 out of 123 individuals were beta thalassaemia carriers. Seven different mutations (IVS1-1, CAP+1, Fr41-42, IVS1-5, Cd-30, Cd-15, and Fr8-9) were identified (Figure 1). The most common mutation identified was IVS1-5 (n=20,16.3%), followed by Fr8-9 (n=1, 25%). The frequency of carriers at different HbA2 levels is shown in Figure-1. The red cell parameters of each individual with or without beta thalassaemia mutation are shown in Table 2. The red cell parameters including Hb, MCV, MCH, MCHC among the carrier's vs non-carriers' individuals were found to be highly significant (p=<0.001), RDW (p=0.03) and only RBC count was found not to be significant (p=0.44). Comparison of the red cell parameters in carriers having beta thalassaemia mutations showed a

significantly lower Hb, MCV, MCH and MCHC value (*p*-value = <0.001) while higher RBC, RDW-SD values (*p*-value= 0.09 and 0.3 respectively). The tests were highly significant as shown in Table-3.

Table-1: Comparison of HbA2 groups among carrier and non-carriers.

HbA2 Groups	Carrier status n (%)		Total	*p*-value
	Carrier	Non- carrier		
3.0–3.4%	21 36.2%	65 100%	86 69.9%	<0.001
3.5–3.9%	37 63.8%	0 0	37 63.8%	<0.001
Total	58 100%	65 100%	123 100%	

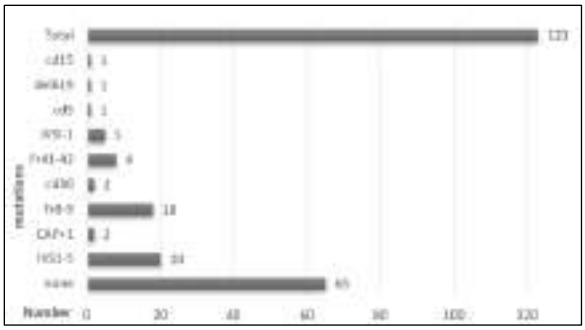

Figure-1: Percentage frequency of beta thalassemia mutations in carriers.

Table-2: Comparison of red cell indices of individuals with carrier status of beta thalassemia

RBC indices	Carrier status	n	Mean	SD	t-test	*p*-value
Haemoglobin	Non-Carrier	65	12.7	2.70	6.75	<0.001
	Carrier	58	9.8	2.08	6.84	<0.001
RBC count	Non-Carrier	65	4.65	1.01	-0.42	0.671
	Carrier	58	4.74	1.37	-0.41	0.676
MCV	Non-Carrier	65	84.4	10.8	8.99	<0.001
	Carrier	58	66.4	11.3	8.97	<0.001
MCH	Non-carrier	65	28.2	4.15	8.71	<0.001
	Carrier	58	20.4	5.72	8.56	<0.001
MCHC	Non-carrier	65	33.3	1.82	7.64	<0.001
	Carrier	58	28.7	4.45	7.33	<0.001
RDW-SD	Non-carrier	65	44.3	13.1	-1.61	0.109
	Carrier	58	47.9	11.2	-1.63	0.105

Table-3: Cross-tab of PCR mutations with in red cell indices of individuals

Red cell indices		PCR mutations, n (%)											*p*-value
		None	IVS1-5	Fr8-9	Fr41-42	IVS1-1	CAP+1	Cd 30	Cd5	Cd15	Del619	Total	
Hb	Low (<11g/dl)	24 36.9%	19 95%	18 100%	6 75%	5 100%	0	2 100%	1 100%	0	1 100%	76 61.8%	
	normal (11-16.5g/dl)	41 63.1%	1 05%	0	2 25%	0	2 100%	0	0	1 100%	0	47 38.2%	<0.001
RBC	Low ($3.5x10^6$/µL	9 13.8%	5 25%	7 38.9%	1 12.5%	0	0	1 50%	0	0	0	23 18.7%	
	Normal ($3.5-5.5x10^6$/µL	40 61.5%	7 35%	2 11.1%	3 37.5%	3 60%	1 50%	1 50%	1 100%	1 100%	0	58 47.2%	0.096
	High >$5.5x10^6$/µL	16 24.6%	8 40%	9 50%	4 50%	2 40%	1 50%	0	0	0	1 100%	42 34.5%	
MCV	low <80fL	10 15.4%	18 90%	15 83.3%	7 87.5%	4 80%	0	2 100%	1 100%	1 100%	1 100%	61 49.6%	
	Normal 80-98fL	50 76.9%	2 10%	3 16.7%	1 12.5%	0	2 100%	0	0	0	0	57 46.3%	<0.001
	High >98fL	5 7.7%	0	0	0	0	0	0	0	0	0	5 4.1%	
MCH	Low 26.5pg	11 16.9%	19 95%	16 88.9%	7 87.5%	4 80%	0	2 100%	1 100%	1 100%	1 100%	62 50.4%	
	Normal 26.5-33.5pg	49 75.4%	1 5%	2 100%	1 12.5%	0	2 100%	0	0	0	0	56 45.5%	<0.001
	High >33.5pg	5 7.7%	0	0	0	0	0	0	0	0	0	5 4.1%	
MCHC	Low <32g/dl	11 16.9%	18 90%	16 88.9%	7 87.5%	4 80%	1 100%	1 100%	1 100%	1 100%	1 100%	61 99.6%	
	Normal 32-36g/dl	49 75.4%	2 100%	2 100%	2 11.1%	1 12.5%	1 20%	0	0	0	0	57 46.3%	
	High >36g/dl	5 7.7%	0	0	0	0	0	0	0	0	0	5 4.1%	<0.001
RDW-SD	Normal 35-56fL	40 61.5%	10 50%	6 35.3%	4 50%	2 40%	1 50%	0	0	1 100%	0	64 52.5%	
	High >56fL	25 38.5%	10 50%	11 64.7%	4 50%	3 60%	1 50%	2 100%	1 100%	0	1 100%	58 47.5%	0.36

DISCUSSION

Haemoglobinopathies represent unique genetic disorders due to the potential to determine carrier status in the majority (approximately 90%) of cases through haematological findings alone.[14] Utility of red blood cell parameters and HbA2 quantification in the diagnosis of beta thalassaemia trait has proved to be effective for disease prevention and is widely applied globally as a carrier screening test.[16] However, challenges such as the lack of standardized optimal HbA2 cut-offs internationally, insufficient local studies defining normal ranges, and the diverse distribution of HbA2 in the Pakistani population suggest that relying solely on red cell parameters and HbA2 may not be sufficient particularly in silent carriers of beta thalassaemia include individuals with hypochromic microcytic RBC parameters but having normal HbA2 levels. These silent carriers account for approximately 2.5% of all beta thalassaemia carriers in Pakistan.[17] Our study underscores the importance of molecular examination in identifying these silent carriers who may be missed by conventional methods.

The study participants primarily included individuals from families with identified patients of thalassaemia and those with family history of haemoglobinopathies. This selection bias could account for the notably increase proportion of beta thalassaemia carriers detected among individuals with borderline A2 levels (47.1%), in contrast to findings from comparable researches in India (32%),[18] Malaysia (30%),[19] and Thailand (5.7%)[20].

Prior research indicates that the IVS1-5 and Fr8-9 mutations are frequently found among beta thalassaemia carriers in Pakistan, with a prevalence ranging from 16.3–14.6%, and it is distributed across all major ethnic groups in our country[14] which are similar to the results of our study of borderline beta thalassaemia carriers. In our study population, 2 (1.6%) individuals with CAP+1 mutation were identified. This mutation involves a point change in the promoter region, leading to a β+ mutation and is commonly observed in the Indo-Asian region. It is classified as a silent mutation, where individuals heterozygous for this mutation typically exhibit nearly normal RBC indices and HbA2 levels, often resulting in it being overlooked during screening tests. When combined with other beta thalassaemia mutations, CAP+1 can contribute to the development of beta thalassaemia intermedia.[21,22] Hence, molecular analysis is crucial for its diagnosis. In our study, individuals affected by the CAP+1 mutation exhibited normal mean MCV and MCH values compared to those with other identified mutations, displaying low MCV and MCH.

Besides IVS1-5 and Fr8-9 other identified mutations included, Fr41-42, IVS1-1 CAP+1, Cd-30, Cd-15, Cd-5, and Del 619 in descending order of frequency. These mutations are similar with that typically found in carriers in Pakistan, where the most prevalent mutations are IVS1-5, Fr 8-9, Del 619, Fr 41-42, and IVS1-1 in descending order[14] only in contrast with one mutation of Del 619 not found to be very common in our study. Study done by Colah R *et al* and Rija T *et al* has shown an opposite trend with CAP+1 being the most common mutations found in borderline A2 cases along with IVS1-5.[23,24] This mutation spectrum varies in other Asian nations; for example, in Malaysia, the most common genetic mutations among silent carriers are Cd19, IVS1-1, and Poly A mutations, with the CAP+1 mutation present in only 2.7% of borderline cases.[25]

The discovery of beta^0 mutations in our research was expected, given that recent studies have indicated their presence in individuals with borderline A2, although at a low frequency.[26] Additionally, in alpha or delta globin gene mutations coinheritance may have led to reduced levels of HbA2 in these individuals with β^0 mutations. It's worth noting that KLF1 mutations can also influence borderline HbA2 levels,[27] although our study did not explore this aspect. We ensured that confounding factors such as iron deficiency[28] and megaloblastic anemia[15] were omitted from our study population.

CONCLUSION

In countries like Pakistan with a high prevalence of thalassaemia, affordable molecular tests like ARMS-PCR are crucial for identifying silent beta thalassaemia carriers in individuals having borderline HbA2 levels. This is especially important for couples where both partners might be carriers, as it allows for preventing the birth of children with thalassaemia major. The detection of these silent carriers will contribute to effective prevention of thalassaemia, once genetic counselling and extended family screening is employed.

Limitations: Further research with large sample size with distribution from different parts of the country is needed to determine the ideal HbA2 cut-off for maximizing carrier identification using this cost-effective method.

Acknowledgement: We would like to acknowledge the support from the staff of AFIP who helped us in the sampling and data collection.

Funding: None.

Conflict of interest: None.

AUTHORS' CONTRIBUTION

AN, MB, HSM: Conceptualization of the study design, literature search, write-up. RM, AK, AK, NS:

Data collection, data analysis, data interpretation, write-up, proof reading, review.

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Submitted: June 4, 2024	*Revised: October 9, 2024*	*Accepted: November 17, 2024*

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ORIGINAL ARTICLE

LABIAL GINGIVAL RECESSIONS AND THE POST TREATMENT PROCLINATION OF MANDIBULAR INCISORS

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Background: Labial gingival recessions are a common periodontal condition characterized by the apical migration of the gingival margin, which can impact dental aesthetics and health. The proclination of mandibular incisors following orthodontic treatment has been implicated as a contributing factor to the development or exacerbation of such recessions. This study investigates the relationship between post-treatment incisor proclination and the occurrence of labial gingival recessions to perform clinical strategies for minimizing periodontal complications. Objectives were to evaluate the relationship between the mandibular incisor's proclination and the emergence of gingival recession. **Methods:** After obtaining ethical committee approval, this prospective cohort study was conducted at the Department of Orthodontics, Frontier College of Dentistry from March 2019 to March 2024, involving 180 participants that met the inclusion criteria and followed up after one year. Assessments included clinical crown height measurements, gingival recession presence, and cephalometric analysis. Crown heights were measured on plaster models at TS, T0, and T5 with an electronic caliper. Recessions were noted at T5 if the labial cement enamel junction was exposed. Cephalometric radiographs marked specific landmarks to assess incisor inclination at TS, T0, and T5. Participants were grouped based on post-treatment incisor inclination: <95°, 95°–100.5°, and >100.5°, with further analysis focusing on the non-proclined (<95°, N=60) and proclined (>100.5°, N=60) groups. **Results:** The mean age of all the patients were 36.99±10.7 years. The mean elevation in clinical crown heights from T0 to T5 for mandibular incisors showed a range of 0.79 to 0.87 mm in the non-proclined group and the proclined group, respectively, with no significant P-value. The mean increase in clinical crown heights for the lower incisors post-treatment (from T0 to T5) varied from 0.58 mm to 1.32 mm in the Proclined group and 0.64 mm to 0.89 mm in the non-proclined group **Conclusion:** It was concluded that the inclination of mandibular incisors did not pose an elevated risk for the occurrence of gingival recession during a five-year observation period when compared to non-proclined teeth.

Keywords: Gingival recession; Proclination; Cemento Enamel Junction (CEJ)

Citation: Zahid H, Ahmad N, Ijaz F. Labial Gingival recessions and the post treatment proclination of mandibular incisors. J Ayub Med Coll Abbottabad 2024;36(4):788–92.

DOI: 10.55519/JAMC-04-13588

INTRODUCTION

Gingival recession is the condition characterized by the exposure of the tooth roots, resulting from the displacement of the gingival (gum) tissue away from the tooth crown. This leads to a lower positioning on the tooth and the potential exposure of the root surface.[1] The cemento-enamel junction (CEJ) is the area where the enamel on the crown meets the cementum on the root of the tooth. It is more commonly observed in older individuals compared to younger ones.[2] Localized gingival recession and the subsequent exposure of the tooth roots can pose aesthetic concerns for patients.[3] The appearance of longer teeth and exposed roots can impact the overall harmony and aesthetics of the smile.[4] The exact etiology of gingival recession may has not been identified however several predisposing factors have been identified.[1] These factors can contribute to the development or exacerbation of gingival recession. Chronic gum inflammation (gingivitis or periodontitis) is a significant contributor to gingival recession. Brushing the teeth too vigorously or using a toothbrush with hard bristles can contribute to the abrasion of gum tissue and enamel, leading to recession.[5] Malocclusion, genetic, tobacco use and trauma are also the most common causative factors.[6] Changes in the shape of the dental arch can indeed result in incisor proclination. The dental arch refers to the curved alignment of the teeth in the upper and lower jaws.[7] If there are alterations in the size or shape of the dental arch, it can impact the positioning of the teeth, including the incisors. Incisor proclination specifically refers to the forward movement or inclination of the incisor teeth.[8] The main aim of the present study is to evaluate the

relationship between the mandibular incisor's proclination and the emergence of gingival recession. The study can contribute valuable insights to dental practitioners, assisting in optimizing treatment approaches to achieve both proper tooth alignment and gingival health.

Objective of the study was to evaluate the relationship between the mandibular incisor's proclination and the emergence of gingival recession.

MATERIAL AND METHODS

The study was designed as a cohort study and conducted at the Department of Orthodontics, Frontier College of Dentistry. A non-probability purposive sampling technique was employed to recruit patients for participation. The inclusion criteria consisted of individuals aged between 18 and 40 years, with fully erupted mandibular incisors prior to treatment and no apparent incisal edge wear. Participants were required to have labial gingival recessions in the mandibular incisors, varying in severity, and must have undergone orthodontic treatment involving the proclination of mandibular incisors. Both male and female individuals were included in the study. Exclusion criteria encompassed participants with severe periodontal disease, pregnant women (due to the potential impact of hormonal changes on gingival health), those who had previously undergone orthodontic treatment specifically for labial gingival recessions, individuals with poor-quality dental casts, especially in the gingival margin area, smokers or tobacco users, and individuals diagnosed with Diabetes Mellitus

After the approval of hospital ethical committee, this prospective cohort study was conducted in the Department of Orthodontics, Frontier College of Dentistry from March 2019 till March 2024. An informed consent was obtained from all enrolled patients, duly signed by the patients and the researcher. The purpose of the study was explained to all participants, and assurances were provided regarding the confidentiality and security of their data. Total of 120 individuals were enrolled after fulfilling the inclusion criteria. All the patients were followed after 1,2,3,4 and 5^{th} year and the data were noted in a predesigned questionnaire. Three categories of evaluations were conducted to assess post-treatment changes: 1. Clinical crown height measurements, 2. Evaluation of gingival recession site presence and clinical crown heights were determined by measuring the distances between the incisal edges and the deepest points of the curvature of the vestibulo-gingival margins. Plaster models of all mandibular incisors were created at TS, T0, and T^5, and measurements were conducted by a single investigator using an electronic caliper with a precision of 0.01 mm. Each tooth's recession at the pre-treatment stage (TS) was individually assessed on plaster models by two calibrated observers, who then provided a Yes or No classification. At the five-year mark after treatment (T5), the assessment focused on identifying gingival recessions in the lower incisors. Any instance of an exposed labial cementoenamel junction resulted in the notation of a recession, categorized as "Yes." Lateral cephalometric radiographs captured at TS, T0, and T5 were utilized to outline specific landmarks, including the incisal edge (ie) and apex (ap) of the lower incisor, Menton (the lowest point of the mandibular symphysis), and Gonion (the most inferior posterior point of the mandibular angle). The angle formed by the line connecting, Menton and Gonion landmarks and the line joining the incisal edge and apex (ie-ap) was employed to approximate the incisor inclination at each of the specified time points.

The sample was split into three groups of similar size based on the mandibular incisors' post- treatment inclination with respect to the mandibular plane (Inc_Incl at T0):

1. Inc_Incl < 95°,
2. Inc_Incl ≥ 95° and ≤100.5°, and
3. Inc_Incl > 100.5°.

For the purposes of the subsequent analysis, only patients with Inc_Incl < 95° (non-proclined group, N = 60) and those with Inc_Incl > 100.5° (proclined group, N = 60) were included.

For statistical analysis SPSS Version 25 were used. The results for all Quantitative variables: age, will be expressed as mean ± standard deviation. Frequency and percentage will be presented for qualitative data. Chi square test was used for comparison between both groups. The relationship between the degree of proclination and age, gender, and group classification were determined using multiple linear regression analysis.

RESULTS

The mean age of all 120 patients was 36.99±10.7 years. 2 increase in clinical crown heights for mandibular incisors from T0 to T5 varied from 0.79 to 0.87 mm, respectively, with a non-significant P-value. In both groups the number of male patients were 31 (51.7%) and 35 (58.3%) while the female patients were 29 (48.3%) and 25 (41.7%) respectively. In our study 18 (66.7%) and 9 (33.3%) patients underwent extraction treatment in non-proclined and proclined group respectively. 42 (45.2%) and 51 (54.8%) patients underwent non-extraction treatment in non-proclined and proclined group respectively. The lower incisors' mean rise in clinical crown heights from T0 to T5 varied between 0.58 mm and 1.32 mm in the Proclined group and 0.64 mm and 0.89 mm in the non- Proclined group following treatment. There were statistically significant variations in the crown height increases for every tooth. According to the results of the regression analysis, there was no significant difference in the clinical crown heights of lower incisors between the independent factors.

Table-1: Mean age of all enrolled patients (n=120)

Variable	
Age (Years)	36.99±10.7

Table-2: Distribution of patients on the basis of gender and treatment alternative of both groups

	Non-Proclined	Proclined	*p*-value
Gender			0.46
Male	31 (51.7%)	35 (58.3%)	
Female	29 (48.3%)	25 (41.7%)	
Treatment			0.04
Extraction	18 (66.7%)	9 (33.3%)	
Non extraction	42 (45.2%)	51 (54.8%)	

Table-3: Characteristics of the patients of both groups

	Non-Proclined	Proclined	*p*-value
Age at Ts	12.5 (0.87)	12.3 (0.76)	0.18
Age at T0	15.5 (0.85)	14.4 (0.76)	0.00
Treatment time (Ts to T0)	3.11 (1.02)	2.18 (0.98)	0.00
Time from Ts to T5	5.43 (1.01)	5.60 (0.99)	0.36
Inc_Incl at Ts	90.5 (2.61)	98.8 (5.52)	0.00
Inc_Incl at T0	91.5 (3.26)	106.2 (2.68)	0.00
Inc_Incl at T5	91.7 (3.34)	106.4 (2.58)	0.00

Table-4: The increase (in mm) of mean clinical crown height of lower incisors after treatment (from T0 to T5)

Tooth No	Non Proclined	Proclined	*p*-value
Tooth 31	0.46 (0.03)	0.71 (0.05)	0.00
Tooth 32	0.87 (0.0.3)	1.32 (0.37)	0.00
Tooth 41	0.67 (0.05)	0.58 (0.05)	0.00
Tooth 42	0.89 (0.04)	0.92 (0.03)	0.001

Table-5: Results of regression analysis

Tooth No.	Proclined	*p*-value
Age at TS	0.200	0.07
Gender	-0.189	0.30
Proclined group	6.293	0.42

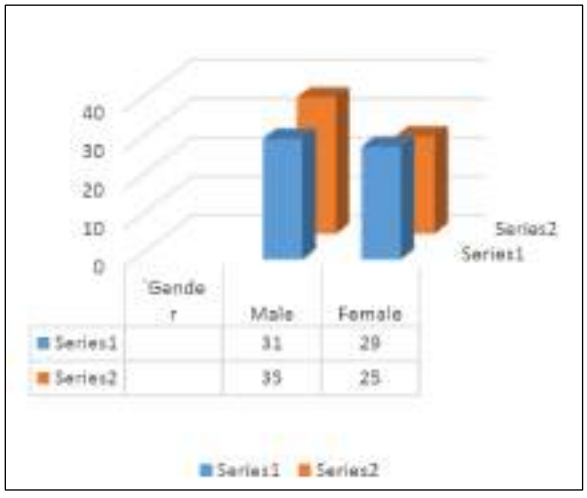

Figure-1: Frequency of gender in both groups

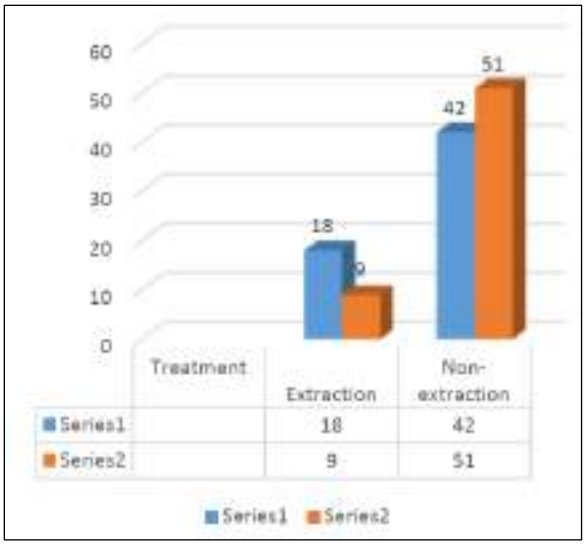

Figure-2: Frequency of extraction/non-extraction in both groups

DISCUSSION

The traditional approach in orthodontics often involved the extraction of certain teeth to create space and align the remaining teeth. But orthodontics is currently witnessing a growing tendency where an increasing number of patients undergo treatment without the need for tooth extraction.

In 1986, it was more common for orthodontic patients in the USA to undergo extraction of teeth as part of their treatment plan. This approach was often used to address issues such as crowding in the mouth. However, by 2008, there was a notable decrease in the percentage of orthodontic patients undergoing extractions.[9] This change is likely associated with advancements in orthodontic techniques. The present study was conducted in order to evaluate the relationship between the mandibular incisor's proclination and the emergence of gingival recession. Gingival recession refers to the exposure of the roots of the teeth due to the loss of gum tissue, leading to the lowering or pulling back of the gum line.

The present study finding could have implications for orthodontic treatment planning and may suggest that achieving a proclined position of the lower incisors may not be a significant risk factor for gingival labial recession. The incidence of recession sites in individuals with mandibular incisors that were proclined at the end of treatment was comparable to those whose mandibular incisors maintained a relatively constant inclination throughout both treatment and the retention phase. There was no difference in the average increase of clinical crown heights between

the proclined and non-proclined groups. In all teeth increase of mean clinical crown height of lower incisors after treatment (from T0 to T5) have a significant *p*-value of ≤0.05. A number of studies support our finding.[10–13]

When compared to non-proclined teeth, proclination of mandibular incisors did not appear to increase the likelihood of gingival recession developing over the course of a five-year observation period, according to a study by Anne-Marie Renkema *et al.*[13] In the findings of our study, we did not identify any elevated risk for the development of gingival recession during a five-year observation period when comparing it to non-proclined teeth. This finding means that after a five-year observation period, there was no evidence to support the idea that the proclination of mandibular incisors was associated with an elevated risk of developing gingival recession.

In other words, individuals with mandibular incisors that were proclined did not experience a higher likelihood of gingival recession compared to those with non-proclined teeth during this specific observation period. This finding may indicate that the proclination of mandibular incisors did not emerge as a significant factor contributing to gingival recession over the specified five-year timeframe. Ruf *et al.*[10] evaluated the impact of Herbst appliance therapy on the development of gingival recession in teenagers in Class II. Proclining lower incisors by nearly 9° did not raise the likelihood of recession, according to the authors' findings. Neither the incidence of recession sites nor the maximal proclination (16 participants; mean = 16.4°) nor the minimal proclination (17 participants; mean = 2.7°) differed significantly between the subgroups in terms of crown height. The incisors' end-of-treatment inclination in relation to the mandibular plane, however, was not disclosed by the authors, therefore it is only reasonable to conclude that the incisors were excessively inclined following treatment. In the present study all participants maintained consistent retention throughout the entire post- treatment duration. We specifically chose individuals with bonded retainers due to a prevailing practice among orthodontists favoring retention methods that do not rely on patient compliance. A number of studies have shown that prolonged use of fixed retention has a restricted impact on periodontal health.[14–16]

CONCLUSION

The proclination of lower incisors at the treatment's end did not seem to have an impact on the occurrence of labial gingival recession or changes in clinical crown heights within this group of patients.

AUTHORS' CONTRIBUTION

HZ: Conception and design, literature search and write up. NA: Acquisition of data, analysis and interpretation. FI: Analysis interpretation and proof reading

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Submitted: July 12, 2024	*Revised: November 19, 2024*	*Accepted: November 24, 2024*

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ORIGINAL ARTICLE

EXPLORING EYE CARE PRACTICES AND SERVICE UPTAKE AMONG DIABETIC INDIVIDUALS - A STUDY FROM A TERTIARY CARE HOSPITAL

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Background: Diabetes mellitus is a leading cause of morbidity and mortality, with many ocular severe complications. This cross-sectional study determined adherence to proper eye care recommendations and regular eye examinations among local diabetic patients and factors associated with non-adherence. **Methods:** This cross-sectional survey assed the knowledge, attitude, and practices of 200 type I and II diabetic patients. The frequency of patients' regular eye examinations, good knowledge of diabetic eye disease, and measures of the association of periodic eye examination with different variables were calculated. **Results:** There were 116 (58%) males and 84 (42%) females (mean age=55.28 years, SD=13.928 years). The majority belonged to the lower socioeconomic group with little education. 114 (57%) had never had any eye examination. 107 were unaware of the importance of eye examination. Only 35 (17.5%) had good knowledge, and 146 (73%) patients had poor attitudes towards diabetes. Periodic eye examination was significantly associated with occupation, area of residence, and overall knowledge of diabetic eye complications. In contrast, it had no significant association with gender, type of diabetes, presence of eye symptoms, or presence of other diabetes complications. **Conclusion:** The knowledge of our local population about diabetic eye disease is very deficient. An extensive campaign of educating diabetic patients about ocular complications is necessary to address this.

Keywords: Eye care; Knowledge; Attitude and practices; Diabetes

Citation: Ullah O, Aurangzeb A, Salam M, Ismail S, Faisal Z, Ahmed I. Exploring eye care practices and service uptake among diabetic individuals - A study from a tertiary care Hospital. J Ayub Med Coll Abbottabad 2024;36(4):793–8.

DOI: 10.55519/JAMC-04-13811

INTRODUCTION

Diabetes mellitus is one of the leading causes of morbidity and mortality worldwide. More than 460 million adults and 1.1 million children and adolescents were known to have diabetes in 2019, with 79% of adult patients residing in developing countries. Accounting for 4.2 million deaths in 2019, diabetes is also a significant cause of death worldwide, and with these figures only expected to rise based on the current trends, it is predicted that by the year 2045, approximately 700 million adults will be living with the condition.[1,2]

Type 1 Diabetes is a condition where the immune system destroys insulin-producing cells, causing complete insulin deficiency, and in Type 2 Diabetes, insulin resistance and reduced insulin production, are often linked to lifestyle factors. Diabetes poses a significant public health challenge for both developed and developing countries, with a much more rapid increase in the prevalence of the disease in developing nations, including those in Asia.[3,4]

Ocular complications of diabetes, including retinopathy, maculopathy, glaucoma, cataracts and ocular surface diseases, are a significant cause of morbidity among diabetic patients, with diabetic retinopathy being one of the most common causes of blindness worldwide, accounting for visual impairment in 2.6 million individuals in 2015.[5,6] Most of type 2 and almost all of type 1 diabetics are expected to demonstrate some degree of retinal involvement after 20 years of the disease [7], and with the ever-increasing prevalence of diabetes, appropriate eye care and effective strategies for prevention, early detection and management of diabetic eye disease are of paramount importance.

It is recommended that a person with type 1 diabetes undergo ophthalmologic examinations at 11 or within 5 years of diagnosis, followed by annual follow-ups. In contrast, type 2 diabetics should have an eye examination with yearly retinal exams upon diagnosis,[8,9] non-adherence to these recommendations usually results from a lack of awareness about diabetic eye complications and the importance of regular examinations[10,11].

Pakistan is among the top 10 countries worldwide for an increase in diabetes prevalence, with the latest figures released by the International Diabetes Federation in 2019 showing that 17.1% of the Pakistani

population is living with the condition.[1] In a recent study, diabetic retinopathy was reported to affect 28.78% of all people with diabetes in Pakistan.[12] Despite this, there is no national public health program for preventing and detecting diabetic eye disease. This study aims to add to the minimal existing literature on preventing diabetic eye disease in Pakistan by determining adherence to proper eye care recommendations and regular eye examinations among local diabetic patients and the factors associated with non-adherence. This study provides valuable information for developing effective public health strategies to prevent diabetic eye complications.

MATERIAL AND METHODS

This hospital-based cross-sectional study was conducted in the Medicine and Endocrinology departments of Ayub Teaching Hospital, Abbottabad, a tertiary care facility in Khyber Pakhtunkhwa, Pakistan. The study was started after approval from the Ethical Review Board of the hospital, and 200 adult diabetic patients (18 years of age or older) consisting of 116 males and 84 females were included in the study during November and December 2020 after obtaining informed consent. Two hundreds consecutive patients attending the outpatient clinics or admitted were included. Unstable/seriously unwell patients, patients with a learning disability, patients who did not understand Urdu, Hindko, or English, and patients with any pre-existing eye condition before the diagnosis of diabetes were excluded from the study. Each patient was given a random.

A detailed questionnaire, consisting of four parts, was used to collect data from each patient. The questionnaire was developed after an extensive literature review, and help was taken from the questionnaires used in previously conducted studies. The first part of the questionnaire covered the patient's demographic characteristics and details about the patient's diabetes (including the type of diabetes, duration, treatment modality, presence or absence of any eye symptoms, presence or absence of any diabetic complications, and control of diabetes mellitus). The second part assessed the patient's practices regarding eye care and prevention/early detection of diabetic eye disease. The third and fourth parts of the questionnaire were used to evaluate the patient's knowledge regarding diabetic eye complications and their overall attitude towards diabetes, both of which were classified as "good" or "poor" based on an overall score. It was pretested twice before adopting a final version for data collection.

The authors administered the questionnaire themselves. Data was entered and analysed using SPSS version 26. Descriptive statistics were obtained, including the frequency of diabetic patients in our study who had regular eye examinations (at least yearly) and patients with good knowledge of diabetic eye disease. Associations between good eye care practices and other factors (such as demographic characteristics, knowledge of diabetic eye complications, and overall attitude towards diabetes) were analysed. Eye care was stratified by independent variables. Post-stratification Chi-square test was applied with 5% level of significance. Similarly, the point bi-serial correlation coefficient was calculated to find out the association of regular eye examinations with the duration of diabetes. The results were presented in tables and graphs.

RESULTS

The subjects of this study included 116 (58%) males and 84 (42%) females. The age of the patients ranged from 19 years to 88 years, with a mean age of 55.28 ±13.928 years. Most 63 (31.5%) patients were illiterate or had only primary education 70 (35%) only 67 (33.5%) were above primary. Regarding the socioeconomic condition of the patients, the vast majority 157 (78.5%) were from a low socioeconomic class, defined as people with a monthly income of less than 50,000 rupees per month. 25 (12.5%) of patients had type 1 diabetes, while 175 (87.5%) of patients had type 2 diabetes.

Looking into the practices regarding eye care revealed that among the patients included in the study, 114 (57%) had never had any eye examination after diagnosis of diabetes. In the 86 patients who had at least one eye examination after the onset of diabetes, the first examination was within three months of diagnosis in 13 (15.1%) patients, within a year of diagnosis in 28 (32.6%) patients, within 5 years of diagnosis in 36 (41.9%) patients and after 5 years in 9 (10.5%) patients. 54 (62.8%) patients had their first eye exam because a healthcare professional advised them to do so, 20 (23.3%) patients went for the exam because of an unrelated eye problem, and 12 (14%) patients went for the exam because they knew the importance of having an eye exam in diabetes. 19 (22.1%) patients had an eye exam within the last year, 43 (50%) had it in the previous 2 years, while 24 (27.9%) had it before 2 years. Only 22 (25.6%) patients had periodic eye exams. 34 (39.5%) patients did not have any repeat eye exams after the first one, and 30 (34.9%) patients had repeat exams only in case of an eye problem. Of the 22 patients with periodic eye exams, only 12 (54.5%) visited an ophthalmologist to prevent or treat diabetic eye complications. In contrast, the rest visited an ophthalmologist, optometrist, or another healthcare professional to check the power of glasses. Only 12 patients had eye examinations at least once a year. 6 patients had exams once every two years, while others had them even less frequently. Among the 178 patients who did not have regular eye examinations, an overwhelming majority (107 patients, i.e., 60.1%) were unaware of the importance of regular eye examinations. Similarly, 33 (18.5%) patients felt no need because they had no eye

symptoms, whereas 12 (6.7%) patients felt no need because their blood glucose levels were controlled. 6 (3.4%) patients could not afford regular eye examinations, while the unavailability of local eye facilities was the reason for the lack of regular visits in 15 (8.4%) patients.

As depicted in Table-1, analysing the knowledge of the 200 subjects of the study about diabetic eye complications revealed that 168 (84%) patients knew that diabetes could involve eyesight. Eight (4%) patients thought that diabetes affected taste function, while 3 (1.5%) patients were certain that diabetes did not involve any organ system. Twenty-one (10.5%) patients responded that they did not know which organ system is applied by diabetes. Of the 168 patients who knew that diabetes could affect eyesight, 141 (83.9%) patients knew that diabetes could affect the posterior layer of an eye, but only 21 (12.5%) patients knew that diabetes could cause blindness. One hundred and nineteen (70.8%) of these 168 patients thought that diabetic eye disease always caused eye symptoms and, therefore, the absence of eye symptoms excludes diabetic eye disease. 51 (30.4%) of these patients thought that patients with good glycaemic control cannot have diabetic eye disease, and 107 (63.7%) patients thought that it is not possible to prevent diabetic eye disease or detect it at an early stage. When asked whether regular eye examinations are important for diabetic patients, 92 (54.8%) of these 168 patients responded that it is essential only if there is an eye problem or uncontrolled diabetes, while 46 (27.4%) patients responded that they are unnecessary. Of the 29 patients who responded that regular eye examinations are important, 14 (48.3%) patients responded that these regular examinations should be at least yearly, 7 (24.2%) said that these should be at least two yearly, and 8 (27.6%) thought that less than one examination every two years is needed.

Based on the patient's responses to the questions about knowledge (see the previous paragraph), an overall knowledge score was calculated for each patient as described in the questionnaire. The results showed that 35 (17.5%) of the 200 patients had good knowledge of diabetic eye complications (defined as an overall score of 5 or more out of 7) and 165 (82.5%) of the 200 patients had poor knowledge (defined as an overall score of 4 or less).

Twenty-six (13%) of the 200 patients said that they had not been previously educated in detail about diabetes mellitus, but 154 (77%) of 200 patients said that they had not been previously educated about eye involvement in diabetes mellitus. One hundred and seventy-nine (89.5%) of the 200 patients said that they were never told by a healthcare professional that diabetes can affect eyes without symptoms, and 178 (89%) said that a healthcare professional never told them about the importance of regular eye examinations. 181 (90.5%) out of 200 patients responded in the affirmative when asked whether they wished they knew more about diabetic eye complications. One hundred and forty-four (72%) patients believed it is okay for people with diabetes to eat sweets once in a while, and 172 (86%) thought that it is okay not to take medications or Insulin regularly or forget to take them if feeling well. Twenty-four (12%) patients did not consider regular sugar level monitoring necessary for all diabetic patients. When specifically asked whether they consider follow-up of diabetes to be important only if they are not feeling well or their blood sugar level is uncontrolled, 69 (34.5%) patients responded in the affirmative.

Of all the 200 patients as shown in Table-2, 112 (56%) said they did not follow a proper diet schedule, while 158 (79%) told us they did not follow an appropriate exercise schedule. 44 (22%) patients responded that they were not compliant with medications or Insulin, whereas 155 (77.5%) patients disclosed that they did not regularly check blood glucose at home (at least twice weekly). Based on all these answers, a combined score was calculated to quantify the overall attitude towards diabetes. Based on this score, 146 (73%) people had poor attitudes towards diabetes (a score of 6 or less out of 9).

The results in Table-3 indicate that the association of Gender, Type of Diabetes, Presence of Eye Symptoms, Presence of other diabetic complications, and Attitude regarding diabetes with Periodic Eye Examination was insignificant. At the same time, occupation was statistically significantly associated with Periodic Eye Examination ($p<0.001$). Moreover, the Area of Residence was found to be statistically significantly associated with Periodic Eye Examination ($p<0.001$), and Overall knowledge of diabetic eye complications was also found to be statistically significantly associated with Periodic Eye Examination ($p<0.001$).

The results as shown in Table-4 indicate that the Periodic Eye Examination was negatively significantly associated with education status $r=-.419$ ($p<.001$); moreover, Periodic Eye Examination was also negatively associated considerably with Socioeconomic Status $r = -.347$ ($p<.001$).

The point bi-serial correlation results shown in Table-5 indicate that the No category in Periodic Eye Examination is positively significantly associated with the Duration of Diabetes, $r_{pb}=.448$ ($p<.001$) and bears a moderate association among the two. Moreover, the other categories are not significantly associated with the Duration of Diabetes. Application of Chi-Square revealed that periodic eye examination was significantly associated with occupation, area of residence and overall knowledge of diabetic eye complications. In contrast, it had no significant association with gender, type of diabetes, presence of eye symptoms or other diabetes complications. The calculation of the point bi-serial correlation coefficient reveals that the "No" category in "Periodic Eye Examination" is positively significantly

associated with the duration of diabetes, r_{pb}=.448 (p<.001) and bears a moderate association among the two. However, the other categories are not significantly associated with the duration of diabetes.

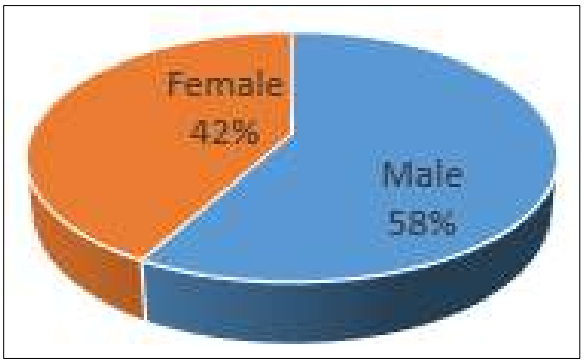

Figure-1: Gender

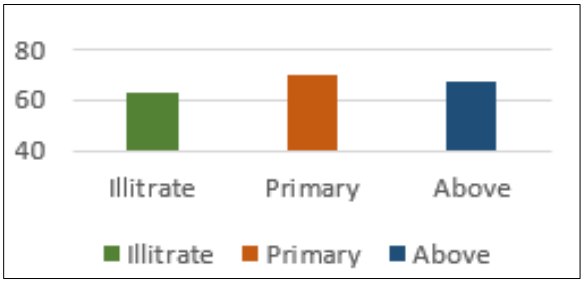

Figure-2: Level of Education

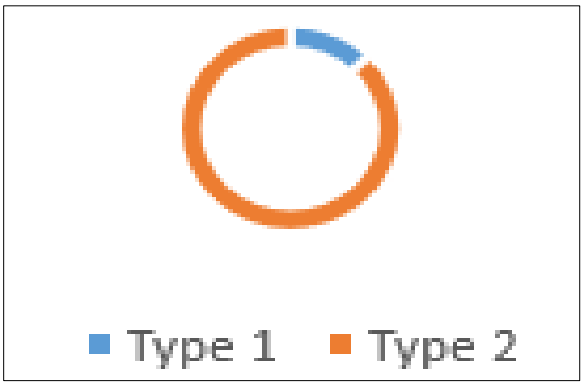

Figure-3: Type of Diabetes

Table-1: Important points of knowledge and percentage

Knowledge	Frequency
Patients knew that diabetes could involve eyesight	168 (84%)
Patients thought that diabetes affected taste function	8 (4%)
Diabetes did not involve any organ system	3 (1.5 %)
Patients responded that they did not know which organ system is applied by diabetes	21 (10.5%)
Patients knew that diabetes could affect the posterior layer of an eye	141 (83.9%)
Patients knew that diabetes could cause blindness	21 (12.5%)
Patients thought that patients with good glycaemic control could not have a diabetic eye disease	51 (30.4%)

Table-2: Important points of practice

Practice	frequency
Did not follow a proper diet schedule	112 (56%)
Did not follow an appropriate exercise schedule	158 (79%)
Not compliant with medications or Insulin	44 (22%)
Did not regularly check blood glucose at home	155 (77.5%)

Table-3: Periodic eye examination chi-square results

	Sig (p-value)
Gender	.853
Occupation	.001
Area of Residence	.005
Type of Diabetes	1.00
Presence of Eye Symptom	.345
Presence of other diabetic complications	1.00
Overall knowledge of diabetic eye complications	.008
Attitude regarding diabetes	.199

Table-4: Periodic eye examination correlation results

Variables	ρ	Sig (p-value)	Remarks
Education Status	-.419**	.000	Negative Correlation
Socioeconomic Status	-.347**	.000	Negative Correlation

Table-5: Duration of diabetes

Response	r_{pb}	Sig (p-value)	Remarks
No	-.070	.323	No Significant Association
Yes	.448	.000	Significantly Associated
Only in case of eye problem	-.122	.085	No Significant Association

DISCUSSION

Pakistan faces a rising prevalence of diabetes, contributing to an increased risk of diabetic retinopathy. The local context is crucial, considering factors such as lifestyle, dietary habits, and genetic predispositions that might impact the prevalence and severity of diabetic eye complications. The specific infrastructure and facilities available in the tertiary care hospital are under consideration. This includes specialized eye care units, state-of-the-art diagnostic equipment, and a team of skilled healthcare professionals, including ophthalmologists and dialectologists.

This cross-sectional study was carried out in the hospital setting. It aimed to investigate the knowledge, attitude and practices of diabetic patients about diabetic retinopathy. Understanding the knowledge, attitudes, and practices of diabetic patients about diabetic retinopathy is foundational for targeted healthcare interventions. Healthcare providers can tailor educational programs, communication strategies, and support mechanisms based on the identified gaps and attitudes, ultimately improving outcomes for diabetic patients and reducing the burden of diabetic retinopathy. Regular assessments and follow-ups are essential to gauge changes in knowledge, attitudes, and practices over time.

The results of this study suggested that the rate of regular eye examinations and ophthalmology follow-

up in diabetic patients in our population is considerably less than that in developed countries. For example, an Australian study published in 1998 showed that 68.2% of patients with diabetes had at least one visit with an ophthalmologist[13] compared to our research, revealing that only 43% of patients had at least one eye examination by any health professional. Similarly, an American study published in 2017 showed that only 128 (5.87%) out of 2179 diabetic patients visiting the ophthalmology clinic did not have a repeat dilated fundus exam within 30 days (these patients were excluded from the study)[14] as opposed to our research showing that 39.5% among the diabetic patients who had at least one eye exam had never gone for a repeat exam.

This study also shows that the practices regarding diabetic eye care in the studied population are significantly deficient compared to the International Council of Ophthalmology recommendations and guidelines on diabetic eye care. These guidelines, published in 2018, state that the minimum screening examination should include a screening vision examination (before pupil dilation if necessary) and a retinal exam. Moreover, the guidelines also mention that this screening examination must be coupled with access to adequate and timely referral for ophthalmological care.[15] However, our study revealed that 57% of the patients with diabetes mellitus never had any screening eye exam. The guidelines also recommend that even for patients with no apparent diabetic retinopathy on screening eye exam, the re-examination or next screening should be in one to two years.[16] But our study revealed that only 18 out of the 200 patients had regular screening in the recommended one to two years.

The statement suggested that the researchers have conducted a literature review to identify existing studies in neighbouring countries that investigated the knowledge and awareness of diabetic patients, similar to the focus of their research. The key findings from the literature review, particularly referencing an Indian study published in 2017, indicate that the researchers found that, akin to their patient population, patients in neighbouring countries (specifically referencing India) also exhibit suboptimal knowledge and awareness about diabetes. The mentioned Indian study, published in 2017, reported that 42% of patients had "good knowledge" about diabetes. It's important to note that the criteria used to define "good knowledge" in the Indian study might not align with the standards or definitions used in the current research.[17]

There are similarities in the level of knowledge and awareness among diabetic patients across borders. However, the researchers acknowledge that differences in criteria for defining "good knowledge" exist between the Indian study and their research. The inclusion of results might suggest that the researchers are aware of the broader context in which their study is situated. The comparative analysis with neighbouring countries adds depth to their understanding of the knowledge landscape among diabetic patients. The mention of differences in criteria for defining good knowledge may also indicate a potential research gap or the need for further investigation. It highlights the uniqueness of the current study and its contribution to understanding the knowledge and awareness of diabetic patients within the specific context or criteria chosen for the research.[18]

In conclusion, this segment of the statement reflects the researchers' effort to contextualize their study within the broader regional landscape, drawing attention to the literature in neighbouring countries and highlighting similarities and differences in the knowledge and awareness among diabetic patients. This comparative approach adds depth to the discussion and underscores the need for a nuanced understanding of knowledge levels in the specific patient population under investigation.[19, 20]

CONCLUSION

In conclusion, our study sheds light on the crucial intersection of diabetes and ocular health within a tertiary care hospital in Pakistan. The findings underscore the significance of eye care and the utilization of related services among diabetic patients in this local setting. Our research reveals a notable gap in the awareness and uptake of eye care services among individuals with diabetes, emphasizing the need for targeted interventions to address this issue. The intricate relationship between diabetes and ocular complications demands proactive measures to enhance preventive strategies, timely screenings, and education about the importance of regular eye examinations.

Moreover, the study underscores the importance of fostering collaborations between healthcare providers, community organizations, and policymakers to develop comprehensive initiatives to promote eye health within the diabetic population. By establishing effective communication channels and educational programs, we can empower healthcare professionals and patients to prioritize and engage in proactive eye care practices. As we move forward, we must integrate our findings into the broader healthcare framework, advocating for policy changes that facilitate increased accessibility and affordability of eye care services for diabetic patients. Additionally, future research should delve deeper into the barriers hindering the utilization of eye care services, allowing for targeted interventions to overcome these challenges.

Ultimately, the insights gained from this study contribute to the ongoing discourse on diabetic care in Pakistan, emphasizing the pivotal role of eye health in the overall well-being of individuals with diabetes. By

addressing the specific needs and challenges outlined in this research, we can work towards a future where diabetic patients receive comprehensive care, preserving their vision and overall quality of life.

AUTHORS' CONTRIBUTION

OU: Conceptualization of study design, write-up, data collection. AA, ZF: Literature review, write-up. MS: Write-up, proof reading. SI: Data analysis, critical analysis of manuscript.

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Submitted: September 6, 2024	*Revised: October 13, 2024*	*Accepted: November 11, 2024*

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ORIGINAL ARTICLE

THE GLOBAL SCOURGE OF GUN VIOLENCE: A CALL FOR ACTION

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Background: Firearm injuries are critically important in criminal proceedings and jurisprudence discussions. The aim of the current study was to reinforce the growing concern of firearm violence in society and authenticate findings through autopsy examinations in the casualty department of Ayub Teaching Hospital Abbottabad. **Method**: This retrospective observational study was conducted in the casualty department of Ayub Teaching Hospital Abbottabad. Data was collected from registers spanning 1st September 2023 to 31st May 2024, after obtaining permission from the hospital administration. **Result**: Data from 56 cases were analyzed using SPSS 22. Among these, 50% suffered from firearm injuries, while the remaining 50% died due to sharp weapons, blunt weapons, poisoning, hanging, strangulation, road traffic accidents, electric shocks, or unknown causes. Of the total cases, 45 (80.4%) were male and 11 (19.6%) were female. The most affected age group was 20–40 years, comprising 36 (64.2%) cases. Furthermore, 42 (75%) cases were homicidal, 2 (3.6%) were suicidal, and 12 (21.4%) were accidental. **Conclusion:** The most common weapon used in homicidal deaths is firearms. Firearm violence should be prioritized as a critical issue in global health discussions.

Keywords: Firearms; Homicide; Gun violence

Citation: Jadoon OK, Shazia S, Ullah I, Haroon M, Adnan, Inam F. The Global Scourge of Gun Violence: A Call for Action. J Ayub Med Coll Abbottabad 2024;36(4):799–802.

DOI: 10.55519/JAMC-04-14150

INTRODUCTION

Gun violence is one of the most pressing public health and human rights crises of our time. According to Amnesty International, it claims more than 600 lives daily, threatening the fundamental right to life and security.[1] Easy access to firearms–both legal and illegal–exacerbates this epidemic, with devastating effects on individuals, families, and communities worldwide.

Globally, there are over one billion firearms in circulation, with 85% in the hands of private individuals. This widespread availability, coupled with socioeconomic challenges, creates conditions where firearms fuel crime, violence, and systemic inequality. Inadequate regulation further amplifies these risks, making firearms easily accessible to individuals who pose a danger to society.[2,3]

Gun violence is a clear violation of fundamental human rights, including the rights to life, security, and health. Former President Barack Obama's "Now is the Time" plan (White House, 2013) emphasized the need for research to identify causative factors. However, many governments fail to recognize this epidemic as a human rights issue, focusing instead on political and economic considerations. This lack of recognition hinders efforts to implement effective gun control measures and evidence-based violence prevention strategies, as highlighted by the Institute of Medicine & NRC's 2013 report.[4]

Globally, more than 250,000 deaths per year are attributed to firearms. The psychological, economic, and social impacts of gun violence shatter communities and strain public resources. Despite these significant consequences, the true danger of gun violence remains underrecognized, particularly in low-income urban areas where the crime is disproportionately prevalent.[5]

Gun violence is violence committed with different types of weapons, including shotguns, rifles, handguns, and other automatic and semiautomatic firearms. An interesting fact is the prevalence of this crime among low-income individuals, especially in urban areas.

In our legal system, the intent of the crime is a vital factor to consider under the concepts of *Mens Rea* and *Actus Reus.* These principles are similarly applied to firearm-related injuries. Studies show that in the United States, the rate of firearm crimes is 19.5% higher than in 23 other countries of similar status. Another report indicates that in America, half of all crimes involve firearm injuries, a statistic comparable to countries of African origin, Albania, Thailand, and other similar nations.[6]

Despite the significant impact of firearm-related crimes on criminal records, accurate data is unavailable even in countries where firearms are notoriously prevalent, particularly in the developing world. The lack of data is attributed to reasons such as political instability and ongoing conflicts.[7]

Firearm violence accounts for 71% of all homicides globally, with six countries–Brazil, the United States, Venezuela, Mexico, India, and Colombia–contributing to two-thirds of these deaths.[7] Shockingly, the United States has a firearm homicide rate that is 19.5 times higher than the average of other high-income nations.[6] In low-income urban neighborhoods plagued by inadequate policing and high crime rates, gun violence is particularly prevalent, exacerbating social inequalities.[1]

Youth are disproportionately affected by firearm violence. Firearm injuries have been identified as the leading cause of death among young people in countries such as the U.S., Brazil, and Mexico.[8,9] Globally, gun violence results in 28,000 youth deaths annually, with over 60% occurring in the Americas.[10-13]

MATERIAL AND METHODS

This descriptive cross-sectional study was conducted in the casualty department of Ayub Teaching Hospital Abbottabad, Pakistan. Data was collected from the casualty department spanning from 1st September 2023 to 31st May 2024, after obtaining permission from the hospital administration. A total of 56 cases were assessed during the prescribed time period that were reported to the accident and emergency department of Ayub Teaching Hopsital, Abbottabad. Data was entered and analysed using SPSS 22. Data was expressed in terms of frequencies and percentages for categorical variables like gender, types of firearm injuries etc.

RESULTS

Data from 56 cases were analyzed using SPSS 22. The most affected age group was 20–40 years, comprising 36 (64.2%) cases. Furthermore, 42 (75%) cases were homicidal, 2 (3.6%) were suicidal, and 12 (21.4%) were accidental of the total cases included to the study, 45 (80.4%) were male and 11 (19.6%) were female.

Among these, 50% suffered from firearm injuries, while the remaining 50% died due to sharp weapons, blunt weapons, poisoning, hanging, strangulation, road traffic accidents, electric shocks, or unknown causes.

Table-1

Age		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	0–10years	2	3.6	3.6	3.6
	10–20years	6	10.7	10.7	14.3
	20–30years	18	32.1	32.1	46.4
	30–40 years	18	32.1	32.1	78.6
	40–50years	4	7.1	7.1	85.7
	>50 years	8	14.3	14.3	100.0
	Total	56	100.0	100.0	

Table-2

Sex		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	male	45	80.4	80.4	80.4
	female	11	19.6	19.6	100.0
	Total	56	100.0	100.0	

Table-3

weapon		**Frequency**	**Percent**	**Valid Percent**	**Cumulative Percent**
Valid	Firearm	28	50.0	50.0	50.0
	Sharp weapon	5	8.9	8.9	58.9
	Blunt weapon	2	3.6	3.6	62.5
	Poisoning	1	1.8	1.8	64.3
	Hanging	1	1.8	1.8	66.1
	Strangulation	6	10.7	10.7	76.8
	RTA	10	17.9	17.9	94.6
	Cause unknown	2	3.6	3.6	98.2
	Electric shock	1	1.8	1.8	100.0
	Total	56	100.0	100.0	

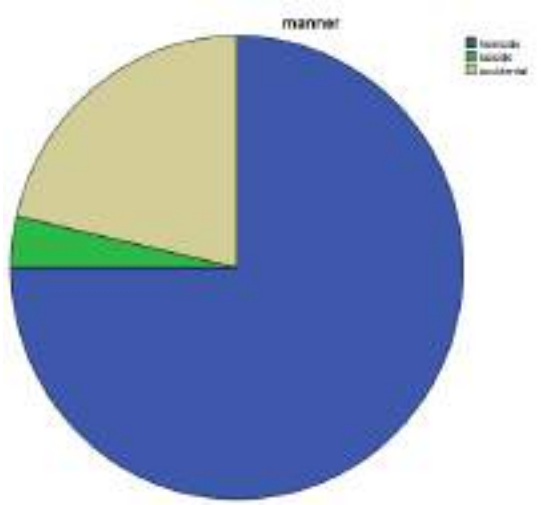

Figure-1

DISCUSSION

Guns are not a necessary or sufficient cause of violence and can be used legally for a variety of sanctioned activities, i.e., to defend against criminals. The presence of a gun may frighten a criminal away, thereby reducing the likelihood of loss of property, injury, or death. But on the other hand, they are openly used for criminal purposes by the people. These are the most lethal weapons. In Pakistan, underscoring their easy accessibility and cultural significance are contributors to the normalization of violence

Our study shows the most common age group is between 20–40 years which is in continuity with most of the studies done world-wide.[14] Homicide is the manner which is mostly adopted as in studies done in United States and Pakistan.[15–20]

While men are the primary perpetrators and victims of gun violence, women face unique risks, particularly from intimate partners with firearms. Firearms are frequently used to perpetrate sexual violence and enforce control, reflecting deeply ingrained gender norms (Arooj Azhar, 2024). The cultural association of guns with masculinity perpetuates harmful stereotypes, fostering environments where violence is normalized and even glorified. Our study shows that males are more the victims to firearms which is against a study done in Peshawar, which states that females are mostly affected.[21]

Gun violence is not confined by borders; it is a global issue that requires a global response. Governments, civil society, and international organizations must work together to tackle this crisis, using research, policy innovation, and collaboration to prevent firearm-related deaths and injuries. The stakes are too high to ignore. Every day that action is delayed, more lives are lost, families are shattered, and communities are devastated. It is time for leaders to step up and confront gun violence with the urgency and commitment it demands.

Programs that address the underlying causes of violence, such as poverty, inequality, and lack of education are vital. Community engagement and support systems can reduce the prevalence of gun violence and its impact on vulnerable populations.

CONCLUSION

It is concluded from this study that the most common weapon of homicidal deaths is firearm. The firearm violence should be discussed on priority basis in the field of global health.

AUTHORS' CONTRIBUTION

OKJ, SS: Conceptualization of the study design, write-up, proof reading. IU, MH, Adnan, FI: Literature search, data collection, data analysis, data interpretation.

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Submitted: February 3, 2024	*Revised: October 9, 2024*	*Accepted: November 13, 2024*

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ORIGINAL ARTICLE

OUTCOME OF GPLLB/LLLA INHIBITORS IN TOTALLY OCCLUDED CORONARY ARTERY IN PATIENTS PRESENTING WITH ACUTE MYOCARDIAL INFARCTION LATE FOR THROMBOLYSIS OR PRIMARY PERCUTANEOUS CORONARY INTERVENTION

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Background: Acute coronary ischemia is one of the most fatal cardiovascular events, presenting with tremendously high morbidity and mortality, especially in cases involving a completely occluded artery, leading to acute myocardial infarction (AMI). The study aimed to ascertain the efficacy and safety of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in Pakistani patients who present late for thrombolysis or primary percutaneous coronary intervention (PCI). **Method:** The trial was conducted at a tertiary care hospital in Islamabad, including 200 patients, with GP IIb/IIIa inhibitors used in 40% of infarct-related artery (IRA) cases. **Results:** The analysis revealed that GP IIb/IIIa inhibitors reduced major adverse cardiac events (MACE) by 9%, recurrent myocardial infarction (MI) by 7.5%, and improved thrombus resolution by 25%, as well as myocardial salvage by 12%. However, there was a higher rate of bleeding complications ($p<.05$) associated with their use. No other significant adverse events, such as in-hospital mortality, length of stay, or renal complications, were identified. **Conclusions:** These results suggest that GP IIb/IIIa inhibitors should not be used as a one-size-fits-all therapy. Proper patient selection, along with robust monitoring under dose-adjusted Eptifibatide or Tirofiban infusion regimens to target coagulation levels appropriately, is crucial. Although this treatment could be valuable in managing AMI, particularly in regions where advanced cardiac care is less accessible, further large-scale, multicenter studies are needed to determine its long-term safety and efficacy. This study provides a framework for further investigations into the use of GP IIb/IIIa inhibitors in similar patient populations.

Keywords: Acute myocardial infarction; GP IIb/IIIa inhibitors; Thrombolysis; Primary percutaneous coronary intervention; Renal Complication

Citation: Khalid F, Khan MF, Anwar W, Khan MF, Iqbal MH, Yaqoob N. Outcome of GP llb/llla inhibitors in totally occluded coronary artery in patients presenting with acute myocardial infarction late for thrombolysis or primary percutaneous coronary intervention. J Ayub Med Coll Abbottabad 2024;36(4):803–7.

DOI: 0.55519/JAMC-04-14013

INTRODUCTION

Acute Myocardial infarction (AMI) is a critical cardiovascular event with immense potential morbidity and mortality. However, one of the difficult presentations is the one with a totally occluded coronary artery, especially those who present later for thrombolysis or primary PCI. At this point, such patients are left as a grey area after their presentation delayed thrombolysis or the expected primary PCI outcome compromised because of their delayed presentation. At this point, glycoprotein IIb/IIIa inhibitors have been presented to offer a promising adjunction to therapy seeking to improve outcomes in this category of patients.

An AMI is most commonly caused by atheromatous plaque rupture with superimposed thrombus, leading to coronary artery occlusion and myocardial tissue ischemia. The longer the myocardium is deprived of blood flow, the more severe the damage due to ischemia; therefore, a timely reperfusion strategy is essential. If reperfusion is delayed, larger areas of myocardial necrosis can develop, increasing the risk of adverse outcomes, such as heart failure or death.[1] The situation is even more critical in patients who present late with a fully occluded coronary artery. No-reflow is a phenomenon of myocardial tissue reperfusion failure despite successful recanalization of an occluded vessel. This may be the consequence of microvascular obstruction (MVO) with more severe endothelial dysfunction in cases of prolonged ischemia.[2] Therefore, using standard reperfusion strategies such as thrombolysis or PCI in these cases may not always be enough, leading clinicians to investigate alternative therapeutic options, such as GpIIb/IIIa inhibitors.

GP IIb/IIIa inhibitors are a class of antiplatelets that inhibit the final common pathway in platelet aggregation, which is mediated by the GP Gertrude (IIIA Receptor on Since you DO) surface. Blocking this receptor prevents the crowding of platelets to make thrombi that further suppresses coronary artery occlusion particularly through AMI disease.[3] GpIIb/IIIa inhibitors have been used in MI specifically those associated with a completely occluded coronary artery, owing to their potent anti-thrombotic effects. Recent clinical trials suggest that these agents reduce rates of major adverse cardiac events (MACEs) -- a composite endpoint including death, myocardial infarction, or urgent revascularization. The advantage is all the more established in patients undergoing PCI, with a reduced rate of procedural complications including distal embolization and no-reflow.[4]

The utility of GpIIb/IIIa inhibitors in the setting of late presentation with AMI and totally occluded coronary artery involvement has been evaluated by several studies. In the TARGET trial, for example, the administration of abciximab, a GpIIb/IIIa inhibitor, in high-risk patients undergoing PCI decreased MACE compared to placebo.[5] It has been suggested that abciximab might be especially beneficial in patients with AMI undergoing primary PCI, based on the results of the CADILLAC trial, which demonstrated an enhancement of outcomes associated with its use compared to the placebo group among high-risk features, including a totally occluded artery.[6]

Yet the data is not unambiguously good. Indeed, studies reported that the efficacy of GpIIb/IIIa inhibitors may be attenuated in patients presenting late especially with significant myocardial necrosis or no-reflow.[7] The results sought to emphasize caution when applying GpIIb/IIIa inhibitors in that setting, depending on the patient selection and timing of intervention."

The success of GpIIb/IIIa inhibitors depends on patient selection and, especially, the timing of intervention in the case of an occluded coronary artery. Early administration, particularly at the pre-hospital stage, might improve their effectiveness in preventing thrombus propagation and reduce the no-reflow phenomenon during PCJ.[8] However, in those presenting very late, there may be less benefit because so much myocardial damage has already occurred.[9]

Also, not all GpIIb/IIIa inhibitors are the same, and patient selection is paramount, as benefits with these agents appear stronger in high-risk patients that may have a large thrombus burden, elevated troponin, or complex coronary anatomy. The potent antithrombotic effects of GpIIb/IIIa inhibitors could tip the balance in favor of successful reperfusion and, hence, better clinical outcomes among these patients.[10]

Acute Myocardial infarction management is fraught with a variety of problems in Pakistan due to prevalent healthcare infrastructure and socio-economic factors. Of note, a substantial proportion of patients with AMI present late to medical facilities and often have a coronary artery that is already occluded when they are first treated. This translates into significantly delayed delivery of established therapies like thrombolysis and primary percutaneous coronary intervention (PCI), with associated adverse outcomes. GpIIb/IIIa inhibitors might be a useful therapeutic strategy in this high-risk patient group based on these arguments.

GpIIb/IIIa inhibitors act by inhibiting the final common pathway for platelet aggregation, which is a central component of thrombus formation in AMI. Due in large part to their potent antiplatelet effects, glycoprotein IIb/IIIa inhibitors have shown utility either adjunctively or constitutively, most commonly following percutaneous coronary intervention (PCI) with the aim of reducing major adverse cardiac event (MACE) rates. In a patient population such as in Pakistan, where time delays to PCI are quite common, GpIIb/IIIa inhibitors, theoretically, because of late presentation making thrombolysis less effective, might at least play an intermediary role by limiting to some extent the unfavorable sequelae associated with belated reperfusion, such as the no-reflow phenomenon and distal embolization.

The use of GpIIb/IIIa inhibitors is particularly relevant in Pakistan, where not all AMI patients can be offered timely PCI due to common healthcare resource scarcity. In rural and underserved areas with limited availability of advanced interventional procedures, these inhibitors could be a feasible and possibly life-saving option. Their intravenous administration allows for use in a variety of healthcare institutions, including those lacking full PCI capabilities. Additionally, considering the limited fiscal resources in Pakistan, GpIIb/IIIa inhibitors might be an affordable approach to improving patient outcomes, particularly among high-risk patients with a large thrombotic burden or complex coronary anatomy.

Moreover, it is important from a research standpoint to investigate the results of GpIIb/IIIa inhibitors in the Pakistani patient group as well. The recruitment of patients from South Asia, including Pakistan, has been poor in global clinical trials, yet the region carries a heavy burden of cardiovascular disease. Assessment of efficacy and safety in our region is useful for clinical practice by Pakistani

physicians. Possible longer-term effects: Ultimately, this might lead to individualized treatment strategies acknowledging the particular difficulties of AMI management in these settings and thus a better survival rate.

Thus, the impetus to study GpIIb/IIIa inhibitors in Pakistani patients with a totally occluded coronary artery who present late for thrombolysis or PCI stems from significant delays in treatment and limited access to advanced cardiac care. This will, therefore, be of great help to the current treatment strategies for AMI in Pakistan, contributing towards enhancing survival and diminishing the cardiovascular illness populace here.

MATERIAL AND METHODS

The sample was comprised of N=200 patients with AMI. Patients who are above the age range of 18 were included in this study. This research study was conducted over the span of 6 months (Dec 2023- May 2024). The inclusion criteria of the study was The inclusion criteria are as follows: patients aged 18 years and above, those presenting with a confirmed diagnosis of AMI, and patients with evidence of a totally occluded coronary artery on angiography. Additionally, the study will focus on patients who present more than 6 hours after the onset of symptoms, classifying them as late presenters for thrombolysis or primary percutaneous coronary intervention (PCI), and who have received GpIIb/IIIa inhibitors as part of their treatment regimen. Exclusion criteria will consist of patients with contraindications to GpIIb/IIIa inhibitors, those with incomplete medical records, and patients who received alternative antiplatelet therapies other than GpIIb/IIIa inhibitors.

This study was carried out at the tertiary care Hospital in Islamabad, using a retrospective cohort design. This tertiary care facility is located in the metropolitan area. It serves the entire city as a referral center for patients in need of high-intensity tertiary care and sees a mix of patients from wealthy backgrounds as well as those from lower- and middle-class backgrounds

The study was undertaken following approval from the Hospital's ethical and research council. This study covered all patients who were admitted for AMI. After stabilizing and treating these patients, formal informed consent was obtained from them. Data were collected through the computerized information system of the hospital. Standard clinical, physiological, and demographic data were gathered. Age, sex, and duration of hospital stay were among the demographic data. Primary diagnoses and other comorbidities were included in the clinical data.

The data was recorded and analyzed using SPSS version 25.0. The frequencies, percentages, and chi square were computed for numerical variables such as age, age, efficacy outcomes, and Safety and Clinical Outcomes of GP IIb/IIIa Inhibitors. The findings were displayed in the form of tables.

RESULTS

The study sample consisted of 200 patients who were treated with GP IIb/IIIa inhibitors in Islamabad's tertiary care hospitals. The analysis includes different frequencies of treatment, such as GP IIb/IIIa inhibitor types used and their efficacy outcomes. Besides, bleeding complications and other clinical outcomes have been statistically evaluated to determine the safety profile of these inhibitors.

Table 1 shows that sample comprised of 200 patients. Out of 200 patients 57% were men and 43% were women. It also shows that 80 patients received Glycoprotein IIb/IIIa inhibitors. 35% of patients show late presentation for thrombolysis or PPCI. Out of 80 patients 50% received Abciximab, 30% Eptifibatide and 20% received Tirofiban. Table 2 depicts the efficacy outcomes of Glycoprotein inhibitors IIb/IIIa. After giving inhibitors there was 9% reduction in adverse cardiac events. Additionally, a 7.5% reduction in recurrent myocardial infarction and 25% thrombus resolution was improved. Lastly, 12% of myocardial salvage enhancement occurred.

Table 3 reveals that there is a significant increase both in bleeding (p=0.03) and minor bleeding complications (p=0.02) associated with the use of GP IIb/IIIa inhibitors. However, administration timing, in-hospital mortality, length of stay, renal complications, need for blood transfusion, and overall clinical benefits did not have statistically significant differences (p>0.05). Thus, this finding implies that utilization of GP IIb/IIIa inhibitors may increase bleeding risk but does not adversely influence other clinical outcomes.

Table 1: Study Population and Treatment Frequencies in Pakistan (n=200)

Characteristics	n	%
Total number of patients	200	
Male	114	57
Female	86	43
Patients Receiving GP IIb/IIIa inhibitors	80	40
Late presentation for thrombolysis /PPCI	70	35
Use of specific GP IIb/IIIa	Abciximab: 40	50
	Eptifibatide: 24	30
	Tirofiban: 16	20

Table-2: Efficacy outcome frequencies in tertiary Care Hospital of Islamabad (n=200)

Outcome Measure	Frequency	%
Reduction in Major Adverse Cardiac Events	18	9
Reduction in Recurrent Myocardial infarction	15	7.5
Improved Thrombus Resolution	50	25
Enhanced Myocardial salvage	24	12

Table-3: Safety and Clinical Outcomes of GP IIb/IIIa Inhibitors in Tertiary Care Hospitals of Islamabad (n=200)

Outcome measure	Category	Count	Chi-square value (χ^2)	*p*-value
Bleeding	Yes	8	4.56	0.03
	No	192		
Minor bleeding	Yes	15	5.12	0.02
	No	185		
Effective timing of administration	Yes	60	1.78	0.18
	No	140		
In-hospital mortality	Yes	10	2.89	0.08
	No	190		
Length of stay	Yes	12	3.46	0.06
	No	188		
Renal complication	Yes	80	2.94	0.17
	No	120		
Need for blood transfusion	Yes	4	1.97	0.16
	No	196		
Overall clinical benefits	Yes	160	2.55	0.11
	No	40		

Note= $p<0.05$

DISCUSSION

Recent advances in the management of acute myocardial infarction (AMI) have markedly improved patient outcomes. This study, conducted at a tertiary care hospital in Islamabad, evaluated the efficacy and safety of glycoprotein IIb/IIIa (GP IIb/IIIa) inhibitors in conjunction with other therapeutic interventions. Our findings offer important insights into the efficacy of these inhibitors and highlight critical safety concerns. The study included 200 patients with 40% treated in the GP IIb/IIIa inhibitor arm. Among these 60% of inhibitors were Abciximab, 30% were eptifibatide and other 10-15% was tirofiban. This distribution was in accordance with current clinical practice, where Abciximab is often favored because of its proven effectiveness.[11] Clinical trials have proved Abciximab effective when used in combination with Aspirin and Heparin, reducing ischemic events by 30-50% within 30 days of percutaneous coronary intervention.[12]

In this study, the GP IIb/IIIa inhibitors showed a 9% major adverse cardiac event reduction and 7.5%, recurrent myocardial infarction improvement; and a more so remarkable number of thrombus resolution in almost all cases or >25%; as well as an impressive myocardial salvage increase of 12%. These results are consistent with published evidence on the efficacy of these inhibitors and reinforce their use to enhance crucial outcomes in patients with AMI.[13] The safety profile of GP IIb/IIIa inhibitors should be weighed against these benefits. Our analysis detected a significantly increased bleeding (p=0.03) and minor bleeding complication rate (p=0,02). These findings are consistent with previously known risks of GP IIa/IIIb inhibitors documented in other investigations.[14,15] The increased bleeding risk emphasizes the necessity for vigilant patient monitoring and management to balance the therapeutic benefits with potential adverse effects. It is also noted that administering GP IIb/IIIa inhibitors during the initial stage of infarction can be particularly effective. At this stage, the higher concentration of platelets in the blood clot and the presence of viable myocardium enhances the therapeutic benefits of the treatment, potentially mitigating the increased bleeding risk.[16]

As for other clinical outcomes like effective timing of administration, in-hospital mortality, length of stay, renal complications, and the need for blood transfusion, there were no significant differences noted with $p>0.05$. The average door-to-needle time of 10 minutes achieved in our study is within the recommended optimal range, showing efficient care in emergency cases. Insignificant differences in these parameters suggest that, though GP IIb/IIIa inhibitors may increase the risk of bleeding, they do not negatively affect other important indices of AMI management. Furthermore, GP IIb/IIIa inhibitors have substantial efficacy in improving outcomes for patients with acute myocardial infarction, and there are associated bleeding risks that need careful management. Specifically, the study illustrates how any therapy needs to balance benefits against risks and how there needs to be continued vigilance in the use of GP IIb/IIIa inhibitors.

This paper presents some limitations. To begin with, the number of patients included in the study was restricted to one tertiary care facility, which limits how far the conclusions can be applied. Additionally, there is no follow-up study to evaluate the long-term effects of glycoprotein inhibitors. Finally, while bleeding complications are maintained at a statistically significant level, however, more quality studies are needed in this regard.

This study demonstrates the importance of GP IIb/IIIa inhibitors in clinical practice. However, we must not assume they are effective solely because they can lower coronary events and improve clot resolution. The healthcare providers must evaluate them together with the likelihood for bleeding problems caused by administering them. GP IIb/IIIa antagonists do show some effectiveness but their use ought to be individualized based on patient-specific risk factors and continuous monitoring for possible haemorrhage side effects. For this reason, further studies need to have large multicenter trials that are conducted over long periods so that the effectiveness of these agents can be assessed more thoroughly along with ways of maximizing their safety. Lastly, this research will work as a baseline for other researchers to carry out more research on glycoprotein inhibitors.

CONCLUSION

In general, GP IIb/IIIa inhibitors can reduce serious heart problems and enhance myocardial salvage, but they often cause bleeding issues. The results also show that when these inhibitors are given the other clinical outcomes have not worsened by these inhibitors. Even though these findings show that GP IIb/IIIa inhibitors are useful for treating heart attacks, they also suggest that doctors should consider the benefits and risks of bleeding and monitor patients more closely.

Ethical approval: The study was initiated after obtaining ethical approval from the Ethical Review Committee of the HBS Medical and Dental College, Islamabad, Pakistan.

Patients' consent: A written informed consent was obtained from the patients. COMPETING INTEREST: The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION

FK: Conceptualization of the study design, write-up. MFK: Literature search. WA, MFK: Data collection. MHI: Data analysis, proof reading. NY: Write-up.
All of the authors equally contributed in the paper. All authors approved the final version of the manuscript to be published.

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Submitted: July 8, 2024	*Revised: October 29, 2024*	*Accepted: November 10, 2024*

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REVIEW ARTICLE

THE INTERPLAY OF THE ANGIOTENSIN RECEPTOR BLOCKERS AND HAEMATOLOGICAL ABNORMALITIES: INSIGHTS AND IMPLICATIONS

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Antihypertensive medications known as angiotensin receptor blockers (ARBs) have become increasingly popular for treating conditions beyond hypertension. The reason for this widespread use is mainly due to their Reno protective and cardioprotective properties in patients with congestive heart failure and diabetes mellitus. There have been conflicting studies on the relationship between ARBs and haematological abnormalities. Using the supplied search terms, we carried out a thorough search for relevant papers written in English and published before July 2023. All of the studies that met the selection criteria were searched for on PubMed, Cochrane Library, and Google Scholar. Based on the examined data from the searched literatures, it has been demonstrated that angiotensin II is essential for stimulation of erythropoiesis and inhibition of it by drugs such as ARBs can lower haematocrit levels, leading to anaemia. Accordingly, dose reduction or stopping administration of ARBs could be a choice for correction of anaemia. However, such decision is based on the clinical situation and the requirements for other management options.

Keywords: Angiotensin receptor blockers; Haematological abnormalities; Anaemia

Citation: Ahmed GM, Alassaf FA, Abed MN. The interplay of the angiotensin receptor blockers and haematological abnormalities: insights and implications. J Ayub Med Coll Abbottabad 2024;36(4):808–15.

DOI: 10.55519/JAMC-04-12507

INTRODUCTION

Renin-angiotensin-aldosterone system (RAS) activation is a key factor in a number of prevalent clinical disorders, such as hypertension, heart failure, and kidney disease. RAS blockers were initially created to treat hypertension, but in addition to being successful at lowering blood pressure, they are also commonly used because of their potential for protecting the kidneys and the heart, independent of their blood pressure-dropping effects.[1,2] Numerous investigations have discovered a connection between RAS and haematological disorders, such as alterations in the number of red blood cells that cause secondary erythrocytosis. However, it has been demonstrated that angiotensin receptor blockers (ARBs) lower haemoglobin levels in people who are at risk for erythrocytosis. Experimental investigations have shown that RAS blockage lowers haemoglobin and haematocrit levels, presumably because angiotensin II is involved in the release of erythropoietin or because of its direct stimulation of erythroid progenitors.[3–6] Clinical investigations, however, have yielded conflicting findings regarding whether RAS blockers lower haemoglobin levels. Some studies implied that angiotensin converting enzyme inhibitors (ACEis) have a greater impact on lowering Hb levels than do ARBs,[7] while other studies suggest the contrary[8]. Thus, the objective of this review is to explore any possible associations between the use of ARBs and haematological abnormalities, including variations in haemoglobin levels and red blood cell synthesis (erythropoiesis), with an aim to establish the potential role for ARBs in the onset or treatment of haematological abnormalities by examining the existing researches.

Renin-Angiotensin System

The renin-angiotensin system, or RAS, is a polypeptide hormone system that has been extensively studied and is connected to a number of physiological and pathological processes. The single precursor of all angiotensin peptides, angiotensinogen (AGT), is created and secreted by the liver. Renin-proteinase, which cleaves AGT to create angiotensin I (Ang-I), is released by the kidneys in response to variations in blood pressure or plasma sodium levels. Ang-I is transformed into Ang-II by the angiotensin-converting enzyme (ACE), a vital part of the RAS with a variety of functions.[9] Angiotensin II stimulates the angiotensin type 1 receptor (AT1-R) and angiotensin type 2 receptor (AT2-R), two different types of G protein-coupled receptors.[10] Additionally, aminopeptidases A and N can further alter Ang-II to create angiotensin III (Ang-III) and angiotensin IV (Ang-IV), respectively. While Ang-IV has its own receptor, AT4-R, Ang-III binds to both AT1-R and AT2-R.[9]

The ability of Ang-II to be broken down into angiotensin 1-7 (Ang 1-7) by Ang-converting enzyme 2 is demonstrated. Ang 1-7 molecule interacts with the G protein-coupled receptor Mas (MasR) to counterbalance the cardiovascular impacts of Ang-II.[11,12] Additionally, cathepsin G, CAGE, or chymase can create Ang-II from Ang-I 8 via a different mechanism. Through the AT-1R, Ang-II produces vasoconstriction, raises plasma aldosterone, retains sodium and water, and intensifies thirst and salt cravings. This preserves fluid and salt equilibrium and raises blood pressure as a result. Hypertension in particular is associated with cardiovascular illnesses when the system is de-regulated or hyper-activated.[9] In addition to the classical RAS, numerous organs, including the brain, kidneys, heart, and blood vessels, can locally produce RAS components that can function alone or in conjunction with circulating RAS molecules. Angiotensins made locally are anticipated to influence tissue homeostasis and dysfunction.[13]

Angiotensin Receptors

Angiotensin receptors are essential for many body activities in conjugation with different agents, including the growth of the kidney.[14–16] Both AT1-R and AT2-R are present and remain throughout embryonic life during embryogenesis. At embryonic day 20, AT1-R reaches its peak expression level and maintained until maturity, but AT2-R is not seen until day 28 of the postnatal period.[17,18] Their expression is noticeably decreased in adult kidneys. While AT2-R also focuses on actively differentiating cortical cells, both receptor types are co-localized in differentiated nephrons and blood vessels.[18] Human kidneys contain the majority of the AT1-R, which has an 8–10-fold higher mRNA expression than AT2-R. AT1-R is normally found in human glomeruli, interlobular arteries, and their surrounded tubule-interstitial fibrous regions. On the other hand, AT2-R is located in large preglomerular vessels of the human cortex and by interlobular endothelial arterial cells of healthy adult.[19] Additionally, Ang-II drives proximal tubule cell proliferation via the AT1-R receptor,[20] and it triggers neo-angiogenesis, apoptosis, and tubular cell proliferation through AT2-R[21].

Angiotensin Receptor Blockers

Angiotensin receptor blockers selectively target and block the AT-1 receptor, resulting in effective inhibition of the harmful effects of angiotensin II. Losartan was the first ARB introduced to the market for hypertension treatment, with subsequent marketing of other ARBs such as valsartan, irbesartan, candesartan, telmisartan, eprosartan, and olmesartan worldwide.[22] The blood pressure-lowering effects of ARBs result from their displacement of angiotensin II from the angiotensin I receptor, thereby they inhibit angiotensin II-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic response.[23] At therapeutically effective doses, telmisartan exhibits peroxisome proliferator-activated receptor gamma activity, which may have positive impact on hyperglycaemia, independent of renin RAS blockade. Treatment with telmisartan was linked to reduced visceral fat, reduced vascular inflammation, and increased serum adiponectin,[24] with decreased growth of cardiovascular (CV) cells[25]. In contrast to valsartan and candesartan, telmisartan and losartan both show platelet anti-aggregatory activity. Moreover, losartan lowers uric acid, a byproduct of purine metabolism linked to the development of hypertension in children as well as increased CV risk and renal disease progression.[26] As a group, ARBs have strong anti-inflammatory properties through localized inhibition of cytokine synthesis, reduction of leukocyte accumulation, and direct regulation of interactions between leukocytes and endothelium.[27]

Angiotensin receptor blockers and haematopoiesis of red blood cells

Following studies that revealed the manipulation of ACE activity could impede erythropoiesis, it was evident that the involvement of the RAS in erythropoiesis is complicated, encompassing nearly every stage between the hematopoietic stem cell and the fully differentiated erythrocyte. Upon closer examination, it was demonstrated that the activation of the AT1 receptor promoted the development of early erythroid progenitors, which necessitated the presence of erythropoietin (EPO).[28] Furthermore, genetically induced AT1a receptor over-activity in mice resulted in an elevation in haematocrit.[29] On the other hand, when compared to wild-type animals, AT1-receptor-knockout mice exhibit a reduction in haematocrit values.[30] The activating function of AT1 receptors in erythropoiesis carries clinical significance, similar to ACEis, treatment with ARBs was found to impede erythropoiesis in both healthy individuals and patients undergoing haemodialysis.[31]

The precise pathways through which AngII regulates erythropoiesis are still not well understood, however it seems that it has primary impact in the early stages of erythropoiesis.[28,31] Investigators suggest that AngII indirectly affects erythropoiesis by influencing EPO levels or sensitivity.[32,33] The JAK/STAT (signal transducer and activator of transcription) pathway, which is stimulated by AngII and is essential to the erythrocyte-stimulating activity of EPO, is another potential second messenger mechanism that AngII used to alter erythropoiesis.[34,35]

Haemoglobin concentrations are influenced by plasma volume, haematocrit/packed cell volume. While the RAS and antidiuretic hormone are acknowledged to

play significant role in controlling plasma volume, EPO is believed to be the primary regulator of red blood cell synthesis. The RAS's function in modulating erythropoiesis is less clear, though. Although the mechanism through which the RAS increases red blood cell mass is not fully known, the most recent research indicates that angiotensin II is essential for controlling erythropoiesis. Angiotensin II may be able to accomplish this via acting as an EPO secretagogue. This happens as a result of a mechanism in which angiotensin II constricts the efferent arteriole, reducing blood flow in the peritubular capillaries, and ultimately causing ischemia in the renal parenchyma. Additionally, angiotensin II can directly affect hypoxia-inducible factor 1, which controls the production of EPO, to enhance the secretion of EPO.[36] In patients with renovascular hypertension, cardiac failure, and non-diabetic hypertension, studies have shown that serum EPO concentrations and renin levels are directly correlated.[37–40] Serum EPO levels were reduced after RAS inactivation by ACEis or ARBs in healthy volunteers, chronic kidney disease (CKD) patients, and patients with heart failure. However, compared to wild-type controls, serum EPO levels and kidney EPO messenger RNA expression were significantly higher in double-transgenic mice expressing the human renin and angiotensinogen genes. This suggests that angiotensin II may have a role in controlling the production of EPO.[41] The AT1 receptor appears to mediate the stimulatory effect of the RAS on EPO secretion, as losartan has been shown to fully block the EPO over-secretion induced by angiotensin II infusion in healthy volunteers.[42] However, angiotensin II may also act as a direct growth factor for erythroid progenitors by activating specific AT1 receptors on their surface, as demonstrated by *in vitro* experiments conducted by Mrug *et al*.[28] Given that angiotensin II can stimulate the production of red blood cells, therefore, it is not unexpected that this substance might also affect iron metabolism and the function of iron transporters. Rats given angiotensin II led to greater ferritin levels and a buildup of iron in different tissues, including the kidney, heart, and liver, according to Ishizaka *et al*. Losartan, a selective AT1 receptor blocker, could be used to prevent this effect.[43] In human glomerular endothelial cells, angiotensin II enhanced the protein expression of the transferrin receptor, divalent metal transporter 1, and ferroprotein 1, according to research by Tajima *et al*.[44] Additionally, studies on mice revealed that angiotensin II decreased hepcidin levels while increasing the expression of duodenal iron transporters. The effects of pre-treating with ARBs could be enhanced.[45] Therefore, the prevalent use of ARBs, in conjunction with the common occurrence of low-grade inflammation among heart failure patients, may serve as the primary pathophysiological factor responsible for the emergence of iron deficiency in this group.

Angiotensin receptor blockers and hematopoiesis of white blood cells and platelets

Studies have demonstrated that *in vitro*, AngII is capable of inducing the proliferation of mouse bone marrow and human cord blood hematopoietic stem cells (HSCs). This impact is partially mediated by the direct activation of HSCs in the presence of colony-stimulating factor (CSF) and through the stimulation of bone marrow stromal cells. Losartan blocks this effect, indicating that it is mediated by AT1-R. The presence of AT1 receptors in both HSCs and stromal cells is consistent with this dual pathway. Additionally, AngII/AT1 receptor signalling can promote the differentiation and proliferation of bone marrow monocyte lineage cells mediated by monocyte colony-stimulating factor (M-CSF).[46]

By acting on the bone marrow and blood vessels, AngII can play a role in regulating the production of white blood cells. However, under normal physiological conditions, AT1 receptor signalling appears to be of limited importance for hematopoiesis. It has been demonstrated through research on ACE-Knockout mice that the lack of ACE, which is required for the generation of AngII, results in a block in terminal granulopoiesis and a decrease in segmented neutrophils. Even while monocytes and macrophages are present in both ACE-Knockout and AT1 receptor-Knockout mice at normal levels, they show functional immaturity.[47,48] This suggests that the lack of reduction in WBC levels with ARB treatment may be because AngII/AT1 receptor signalling does not play a major role in WBC production under normal physiological conditions. However, it has been shown that under hematopoietic stress conditions, such as chemotherapy or irradiation, AngII/AT1 receptor signalling has noticeable effects. In these situations, infusion of AngII can improve the re-population of BM with HSCs, thereby accelerating the restoration of WBC counts.[47,49]

Concerning platelets, under normal conditions, Ang II counterbalances the antithrombotic properties of the endothelium by inducing platelet activation and promoting platelet aggregation through the AT1-receptors expressed on the surface of platelets. Blocking the action of Ang II using ARBs can potentially have direct anti-platelet effects. These drugs inhibit platelet aggregation, which is thought to be partly due to the inhibition of thromboxane A2 release and improvement of calcium dynamics. This action is evident in several studies.[50,51]

Clinical Implication

RAS activation in diabetes could be caused by a number of different methods. First off, sodium glucose cotransporters link glucose reabsorption in the proximal tubule to sodium reabsorption, which

decreases sodium delivery to the macula densa and boosts renin release.[52,53] Secondly, experimental evidence suggests that insulin may cause RAS activation in subjects with insulin resistance and hyperinsulinemia, which is common in individuals with metabolic syndrome or diabetes.[54,55] Acute hyperinsulinemia has been shown to elevate renin and circulating Ang II levels even in healthy subjects. Finally, there may be a connection between diabetes, RAS activation, and systemic hypertension via GPR91, a metabolic receptor in the kidney that can cause the activation of the renin-dependent RAS system and subsequent elevation of systemic blood pressure.[56,57]

It is anticipated that Ang II will increase intraglomerular pressure and filtration fraction while concurrently reducing oxygen delivery to the tubulointerstitium through the postglomerular peritubular capillary bed since it works as a selective vasoconstrictor for efferent arterioles. Furthermore, Ang II can promote proximal sodium reabsorption, increasing the need for oxygen in tubular cells. As a result, following RAS activation, the tubulointerstitium experiences parenchymal hypoxia, which causes the release of EPO due to a combination of decreased oxygen supply and increased oxygen demand.[58] Additionally, Ang II can directly influence HIFs and promote EPO secretion. Ang II promotes HIF-1 expression in human placental explant cells, both at the mRNA and protein levels.[59] Furthermore, the growth factor Ang II can directly promote the development of erythrocytes in erythroid progenitors in the bone marrow.[58] Hepcidin and iron transporter expression are both changed concurrently, promoting iron uptake and utilization.[45]

For hypertensive, cardiac, and renal patients with T2DM, pharmacologically disrupting the RAS with ACEis or ARBs can have positive effects, according to a number of seminal research. Medications or treatments that inactivate RAS may likely cause a haematocrit-lowering impact and/or anaemia if RAS up-regulates erythropoiesis as stated above.[42] Significant anaemia is present in ACE or angiotensinogen gene knockout mice, which is treated with Ang II infusion for two weeks.[41,60] The renin-angiotensin system may not significantly affect erythropoiesis in normal or nearly normal circumstances, such as those with simple hypertension and T2DM,[61] RAS may have no discernible effect on erythropoiesis. However, the action of RAS is more obvious in conditions where the bone marrow needs every stimulus to increase erythropoiesis, such as in individuals with severe renal insufficiency, congestive heart failure, or immunosuppression. Giving ACEi or ARB to patients with altitude polycythemia, post-transplant erythrocytosis, or polycythemia linked to chronic obstructive pulmonary disease can help normalize haematocrit levels.[6,62,63] An estimated 16% rise in anaemia prevalence was observed over the period of time from 1979 to 2002, when RAS inhibition became a mainstay of management, according to a community study looking at anaemia and heart failure.[64] RAS inhibition reduced haemoglobin levels in CKD patients by about 0.6–0.9 g/dL, even though no changes in haemoglobin levels were seen in CKD patients on other traditional anti-hypertensive medications.[65]

The majority of patients who have both anaemia and heart failure do not have a discernible underlying cause for their anaemia. Consequently, this condition is referred to as chronic disease anaemia. Anaemia can develop in individuals with heart failure for a variety of reasons. Some of these causes include haemodilution, iron depletion (either absolute or relative), decreased EPO production, pro-inflammatory cytokine activation, aspirin- or anticoagulant-induced blood loss, and uremic toxin-induced bone marrow suppression. Most patients with heart failure do not have iron, B12, or folate deficiency as the main underlying cause of anaemia.[66,67] There is an increase in pro-inflammatory cytokines, as seen in heart failure and CKD, and decreased hematopoiesis in anaemia may be caused by a large drop in the number of progenitor cells. This might be because pro-inflammatory chemicals in the bone marrow are having a direct effect. In bone marrow culture, the proliferation of burst-forming units-erythroid is suppressed by TNF-alpha and interleukin-6, this is also applying to colony-forming units-erythroid.[68] High amounts of pro-inflammatory substances and inflammation can cause reticulo-endothelial blockade and decrease the uptake of iron by raising serum hepcidin levels. These factors collectively contribute to the development of anaemia.[69,70] It has been speculated for a while that people with CKD may have specific inhibitory uremic toxins present that could affect erythropoiesis. Indoxyl sulphate is one of these toxins and is recognized as a prototype uremic toxin that has received a lot of attention. It can hinder the development of erythroid colonies, interfere with tubular cells' oxygen metabolism, and weaken oxygen-sensing systems, all of which contribute to insufficient *in vitro* EPO production.[71] Additionally, it is negatively correlated with haematocrit values in some clinical studies, although not in all.[72,73] Nevertheless, it is important to note that in patients with heart failure and CKD, the widespread use of RAS inhibition may also contribute to the emergence or progression of anaemia. Therefore, the administration of ARBs could be a potential iatrogenic cause of anaemia in these patients.

Anaemia has a significant and independent prognostic impact, raising the likelihood of

hospitalizations and mortality by 20–50% in patients with heart failure with reduced ejection fraction (HFrEF) or Heart failure with preserved ejection fraction (HFpEF).[74–77] The development of hemodynamic and non-hemodynamic compensatory mechanisms that have a detrimental effect on myocardial function and viability is a consequence of decreased tissue oxygenation caused by anaemia.[78]

Through a number of different pathways, the inactivation of RAS caused by the use of ARBs may contribute to the onset of anaemia. RAS inhibitors can firstly worsen renal function, which can result in uremic toxin buildup, bone marrow suppression, salt and water retention, and haemodilution. Additionally, RAS inhibitors may prevent hemopoiesis by preventing EPO release and preventing angiotensin II from acting directly on erythroid progenitor cells. The natural stem cell suppressor tetrapeptide Ac-SDKP (goralatide), which is degraded more slowly by ACEis in particular, may rise in concentration,[79] although the comparable reduction in haematocrit values observed with ARBs suggests that the impact of this oligopeptide on the haematocrit-lowering effect may not be significant. Finally, RAS inhibitors could potentially have an adverse effect on iron absorption and utilization.[45] Therefore, the inhibition of RAS via the use of ARBs is related to a reduction in haematocrit and/or anaemia in various clinical circumstances. RAS inhibition has been utilized to regulate haematocrit levels in secondary erythrocytosis patients, such as those with post-transplant erythrocytosis, altitude erythrocytosis, and erythrocytosis linked to chronic obstructive pulmonary disease.[63,80] A meta-analysis encompassing seven studies and 29,061 patients demonstrated that the use of RAS inhibitors resulted in a greater than 50% increase in the risk of anaemia in patients.[5] It is worth noting that other smaller studies revealed a slight or no reduction in haematocrit following RAS inhibition.[8,81] It is unclear why the results are inconsistent, but it is possible that patient population variances, variations in the kind and severity of the underlying illness, variations in the type, dosage, and duration of RAS inhibition, as well as variations in study design and statistical analysis, are contributing factors.

Haematocrit readings often fall after RAS blockage, albeit this depends on the medication's dosage. The nadir haematocrit value is typically attained within the first month of treatment and remains steady throughout long-term follow-up. Haematocrit readings may progressively revert to pre-treatment levels for three months after stopping ARB treatment. The patient's clinical situation's severity and the availability of other treatments should be taken into account when deciding whether to change the dosage or withdraw these medications.[82] It has not been determined whether correcting iron deficiency through intravenous iron administration or correcting anaemia using drugs that stimulate erythropoiesis is beneficial for patients with cardiorenal syndrome (CRS) and anaemia.[83,84] Individuals with CKD or heart failure were previously treated with medications that induce erythropoiesis to normalize their haemoglobin levels, but the results did not enhance their cardiovascular prognosis. Similar to this, intravenous iron administration to patients with heart failure improved their clinical state but did not lower death rate.[85]

Although the rate of change in estimated glomerular filtration rate was marginally greater in the through-collective therapy group after the first six months of the SPRINT study, which involved patients over 50 years old with increased cardiovascular disorders but no diabetes, there was a higher incidence of acute renal failure (2 times more frequent) and the development of CKD (3–4 times more frequent) of the through-collective therapy group. These undesirable renal outcomes in the through-collective therapy group may be attributable to the overuse of diuretics and ACEis or ARBs, which may have an intraglomerular hemodynamic effect.[86,87] However, following the administration of ARBs to patients with cardiac failure, the drop in GFR is typically reversible upon medication discontinuation.

Although the majority of ARBs are predominantly processed in the liver and are not necessarily nephrotoxic medications, care must be taken when administering them to individuals with CRS. The ideal dose of RAS inhibition in these patients has not been studied in a randomized, placebo-controlled experiment. There is a considerable percentage of patients who need a reduction in post-randomization dose, mostly because they are older, have hypotension, hyperkalaemia, or renal failure, even in cardiac focused studies that have excluded patients with severe CKD.[88] To effectively block the RAS in patients with CRS, it is best to start them on a low dose of ARBs and progressively increase it, following the 2016 ESC guidelines for heart failure patients. Potassium levels and renal function should be closely monitored. If hyperkalaemia cannot be controlled or baseline creatinine levels rise by more than 20–30%, the ARBs should be temporarily stopped with dose reduction later.[89] Even though ARBs are not inherently nephrotoxic, individuals with CRS should use them with caution because there is no solid trial for the optimum dose of RAS inhibition in CRS patients. Many patients required a dose minimization after randomization in cardiac focused trials that already exclude individuals with severe CKD, mostly because of advanced age, hypotension, hyperkalaemia, and kidney impairment.[90] Physicians might decide to discontinue ARBs therapy in patients who are approaching end-stage renal disease as a policy for improvement of kidney function levels and transplantation avoidance.[91]

In conclusion, it has been repeatedly demonstrated that anaemia, which is common in patients with CRS, raises hospitalization and mortality rates. RAS inhibition is a crucial component of both cardiovascular and renal disease therapies. However, RAS inhibition can lower haematocrit levels, lead to anaemia, and compromise renal function in patients with CRS since angiotensin II is essential for controlling GFR and stimulating erythropoiesis. The choice to reduce the dose or stop administrating such medications should be based on the clinical condition and the presence of other management options. Preventing cardiovascular complications in patients with CRS is essential, and RAS inhibition can be helpful.

Conflict of interest

The authors declare that they have no conflicting interest.

Acknowledgement

We are sincerely grateful to the University of Mosul, the College of Pharmacy and the Health Directorate of Nineveh for their utmost scientific support.

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Submitted: September 20, 2023	*Revised: October 10, 2023*	*Accepted: November 8, 2023*

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CASE SERIES

PATTERN OF CHEMOTHERAPY INDUCED TOXICITIES IN CHILDREN WITH EWING SARCOMA: A CASE SERIES

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Background: Ewing sarcoma is a rare and aggressive bone or soft tissue cancer that primarily affects children and adolescents. Estimated incidence of Ewing sarcoma is reported to be 1.2–2.9 in one million individuals in England and 1 in one million in the US. Objective of the study was to determine the pattern, and influence of gender and age on chemotherapy-induced toxicities in children with Ewing sarcoma. This descriptive case series was carried out at the Department of Paediatric Oncology, CMH Rawalpindi, from January 2014 to June 2023. **Methods:** Children of either gender aged less than 18 years and diagnosed cases of Ewing Sarcoma were enrolled. All patients were given VIDE (vincristine, ifosamide, doxorubicin, etoposide) chemotherapy and patients were observed for chemotherapy induced toxicities. Chi square test was used to analyze significance of age and gender on toxicity. **Results:** In a total of 59 children 35 (59.3%) were male and 24 (40.7%) females. Out of these 11 children expired. The mean age was 7.59±3.87 years. Younger age was strongly associated with higher occurrence of toxicity specifically children under 5 years being most affected (p<0.05). Neutropenia, nausea and vomiting, thrombocytopenia, and diarrhoea were the most frequent adverse events observed in 53 (89.9%), 37 (62.7%), 36 (61.0%), and 36 (61.0%) patients respectively. There was no association of gender with chemotherapy induced toxicity. Neutropenic sepsis and diarrhoea were positively associated with mortality in the 11 children who expired (p<0.05). **Conclusion:** Neutropenia, nausea and vomiting, mucositis, thrombocytopenia and diarrhoea were the most frequent chemotherapy induced toxicities in children with Ewing sarcoma. Younger children specifically under 5 years have a higher chance of chemotherapy induced toxicities however gender did not seem to influence related toxicities. Neutropenic sepsis was the major predictor of mortality warranting higher vigilance and aggressive management of infections.

Keywords: Ewing sarcoma; Antineoplastic combined chemotherapy protocols; Chemotherapy; Adverse effects; Neutropenia

Citation: Manzoor R, Naz S, Ali S, Tariq R, Shamraiz I, Siddiqui W. Pattern of chemotherapy induced toxicities in children with ewing sarcoma: A case series. J Ayub Med Coll Abbottabad 2024;36(4):816–20.

DOI: 10.55519/JAMC-04-13292

INTRODUCTION

Ewing sarcoma is a rare and aggressive bone or soft tissue cancer that primarily affects children and adolescents. Estimated incidence of Ewing sarcoma is reported to be 1.2–2.9 in one million individuals in England and 1 in one million in the US.[1] Ewing sarcoma originates from the neural crest cells as a result of chromosomal aberrations and consequent formation of EWS-FLI1 fusion gene which promotes oncogenesis in 85% cases of Ewing sarcoma.[2]

The treatment of Ewing sarcoma often involves a combination of surgery, radiation therapy, and chemotherapy.[3] While chemotherapy is an integral component of the treatment regimen, it is known to be associated with a range of toxicities that can significantly impact the well-being of young patients.[4] These toxicities can lead to treatment interruptions, compromised quality of life, and potential long-term health consequences.[5] Understanding the pattern of chemotherapy-induced toxicities specific to the Pakistani paediatric population with Ewing sarcoma is crucial for optimizing treatment protocols, improving patient outcomes, and enhancing the overall management of this aggressive malignancy. Limited studies have investigated the pattern of chemotherapy-induced toxicities in children with Ewing sarcoma, particularly within Pakistan. International studies have indicated that bone marrow suppression, including anaemia, neutropenia, and thrombocytopenia are frequently observed in paediatric Ewing sarcoma patients undergoing chemotherapy.[6] Nausea, vomiting, and gastrointestinal symptoms are also reported side effects. Hair loss (alopecia), fatigue, and increased susceptibility to infections have been observed across different paediatric cancer populations.[7]

Given the unique genetic, environmental, and healthcare factors in Pakistan, it is imperative to conduct

research that specifically addresses the Pakistani population. This research focused on determining the pattern, and influence of gender and age on chemotherapy-induced toxicities in children with Ewing sarcoma in Pakistan, addresses a critical gap in the literature. The impact of Ewing sarcoma on young patients and their families can be substantial due to its aggressive nature and potential long-term effects. The incidence or treatment outcomes of any type of cancer is not well documented in the country due to the lack of a cancer registry. This research will not only provide insights into the impact of chemotherapy on patients with Ewing sarcoma but will also guide the development of tailored supportive care strategies to mitigate toxicities and enhance treatment adherence. By investigating the specific toxicities experienced by these young patients within the Pakistani context, the study aims to contribute to the optimization of treatment protocols and the improvement of patient care. This research holds the potential to inform clinical practice and policy decisions related to paediatric Ewing sarcoma treatment in Pakistan, ultimately enhancing the quality of life and outcomes for affected children and their families.

MATERIAL AND METHODS

The study was a descriptive case series undertaken in the department of Paediatric Oncology, CMH, Rawalpindi, Pakistan, from January 2014 to June 2023. Approval from Institutional Ethical Committee was obtained. Informed and written consents were acquired from parents/guardians of all patients. Admitted children of either gender aged less than 18 years and known cases of Ewing sarcoma were analyzed. Parents or guardians of children who refused to be part of this study were excluded from this study. Non-probability consecutive sampling technique was adopted and all cases fulfilling the inclusion criteria were included. All patients were given VIDE (vincristin, ifosamide, doxorubicin, etoposide) chemotherapy before local control according to EURO EWING 2012 protocol.[8] Chemotherapy was given during the inpatient stay and patients were observed for chemotherapy induced toxicities and managed accordingly as per institutional protocols. The use of granulocyte-colony–stimulating factor (GCSF) was encouraged but was not mandatory. Neutropenia was labelled as absolute neutrophil count below 1.5 x 10^9/l. Thrombocytopenia was named when platelet count was below 150 x 10^9/l. Anaemia was labelled as haemoglobin below 10 g/dl.

Data was analyzed using SPSS-26.0. Nominal data were shown as frequency and percentages while quantitative data were given mean and standard deviation representation. Chi-square test was applied to compare data between various chemotherapy induced toxicities to identify any possible significant associations. *p*-value below 0.05 was taken as significant.

RESULTS

In a total of 59 children with Ewing sarcoma, there were 35 (59.3%) male and 24 (40.7%) female, representing a male to female ratio of 1.5:1. The mean age was 7.59±3.87 years, ranging between 3 months to 18 years. The details about the gender and age distribution are shown in table-1.

Table-1: Gender and Age Distribution of Children with Ewing Sarcoma (n=59)

Characteristics		Number (%)
Gender	Male	35 (59.3%)
	Female	24 (40.7%)
Age (years)	<5	15 (25.4%)
	5–12	37 (62.7%)
	13–18	7 (11.9%)

Evaluation about the chemotherapy induced toxicities revealed that neutropenia, nausea and vomiting, thrombocytopenia, and diarrhoea were the most frequent, noted in 53 (89.9%), 37 (62.7%), 36 (61.0%), and 36 (61.0%) patients respectively. The details about the frequency of chemotherapy related toxicities among children having Ewing sarcoma are shown in figure-1. There were 29 (49.2%) patients who reported administration of red cell concentrates. Granulocyte-Colony Stimulating Factor (GCSF) had been given in 34 (57.6%) patients.

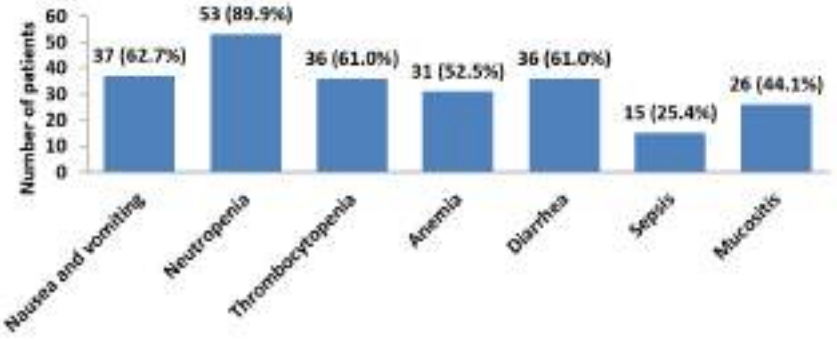

Figure-1: Frequency of chemotherapy induced toxicities in children with Ewing Sarcoma (n=59)

We observed that children below 5 years of age were adversely affected by chemotherapy related toxicity. It was found that Gastrointestinal related toxicities (nausea, vomiting, diarrhoea) were significantly more common in children aged below 5 years (p<0.05). Furthermore, anaemia and mucositis were also significantly associated with younger age as almost 80% of children under 5 years of age suffered from these toxicities (p<0.05). Although we found a larger number of children under 5 years of age suffering from thrombocytopenia and neutropenia but this was not found statistically significant in analysis. There were 12 (80.0%) children below 5 years of age who were administered red cell concentrates versus 14 (37.8%) between 5–12 years, and 3 (42.9%) between 13–18 years and the difference was found to be significant (p=0.021). There was no statistical difference in age and gender on the possibility of child having sepsis post chemotherapy. No significant association of gender with any of the chemotherapy induced toxicities was found (p>0.05). Comparison of gender and age with respect to various chemotherapy induced toxicities and tendencies towards red cell concentrates and GCSF administration are shown in table-2 and 3. Mortality was reported in 11 out of 59 patients (18.6%). Neutropenic sepsis was observed in all children who expired. (Diarrhoea (90.9% vs. 54.2%, p=0.024), as well as sepsis (100% vs. 8.3%, p<0.001) were found to have significant association with mortality (table-4).

Table-2: Stratification of gender and age with respect to chemotherapy induced toxicities (n=59)

Toxicities	Gender			Age (years)			
	Male (n=35)	Female (n=24)	*p*-value	<5 (n=15)	5-12 (n=37)	13–18 (n=7)	*p*-value
Nausea and vomiting	23 (65.7%)	14 (58.3%)	0.565	14 (93.3%)	19 (51.4%)	4 (57.1%)	0.017
Neutropenia	31 (88.6%)	22 (91.7%)	0.699	13 (86.7%)	34 (91.9%)	6 (85.7%)	0.792
Thrombocytopenia	21 (60.0%)	15 (62.5%)	0.847	12 (80.0%)	22 (59.5%)	2 (28.6%)	0.067
Aanemia	20 (57.1%)	11 (45.8%)	0.393	13 (86.7%)	15 (40.5%)	3 (42.9%)	0.009
Diarrhoea	24 (68.6%)	12 (50.0%)	0.151	13 (86.7%)	18 (48.6%)	5 (71.4%)	0.033
Sepsis	9 (25.7%)	6 (25.0%)	0.951	7 (46.7%)	6 (16.2%)	2 (28.6%)	0.072
Mucositis	15 (42.9%)	11 (45.8%)	0.821	12 (80.0%)	12 (32.4%)	2 (28.6%)	0.005

Table-3: Association of age and gender with respect to tendencies towards red cell concentrates and GCSF administration (N=59)

Characteristics	Gender			Age (years)			
	Male (n=35)	Female (n=24)	*p*-value	<5 (n=15)	5-12 (n=37)	13-18 (n=7)	*p*-value
Red cell concentrates given	10 (28.6%)	19 (79.2%)	0.341	12 (80.0%)	14 (37.8%)	3 (42.9%)	0.021
Granulocyte-colony–stimulating factor given	13 (37.1%)	21 (87.5%)	0.656	8 (53.3%)	19 (51.4%)	7 (100%)	0.053

Table-4: Association of mortality with various chemotherapy induced toxicities (N=59)

Chemotherapy induced toxicities	Mortality		*p*-value
	Yes (n=11)	No (n=48)	
Nausea and vomiting	9 (81.8%)	28 (58.3%)	0.146
Neutropenia	11 (100%)	42 (87.5%)	0.216
Thrombocytopenia	8 (72.7%)	28 (58.3%)	0.377
Anemia	7 (63.6%)	24 (50.0%)	0.414
Diarrhoea	10 (90.9%)	26 (54.2%)	0.024
Sepsis	11 (100%)	4 (8.3%)	<0.001
Mucositis	6 (54.5%)	20 (41.7%)	0.438

DISCUSSION

This study highlights that younger age has a significant association with chemotherapy induced toxicity in children with Ewing sarcoma while the influence of gender is not statistically significant. The high incidence of chemotherapy-induced toxicities observed in this study is consistent with the broader international literature on Ewing sarcoma treatment in paediatric populations. Similar findings have been reported in studies conducted in other countries.[9,10] These toxicities not only impact the quality of life of paediatric patients but can also necessitate dose modifications or treatment delays, potentially affecting treatment outcomes.[11]

Ewing sarcoma is typically observed more frequently in children aged 10 years and older, and it traditionally exhibits a higher incidence in males, with a male-to-female ratio of 1.5.[12–14] This research also observed that 74.6% children with Ewing sarcoma were aged between 5–18 years with male predominance. There was no significant association between gender and chemotherapy-induced toxicities in our study. Contrary to our findings a study by Paioli *et al* in Italy found gender to significantly affect bone marrow toxicity with males having lower incidence of cytopenia and febrile neutropenia.[15] Safety data from another large muti-

centre EUROE.W.I.N.G.-99 study also reported females to have a higher incidence of adverse reactions regarding haemoglobin and platelets.[16] We found young age as a strong predictor for chemotherapy related toxicities with children under 5 years having worst outcome. Previous research has also shown young age as an independent risk factor for chemotherapy related adverse events.[15,16] This increased toxicity in young age could be attributed to variation in drug metabolism, pharmacokinetics and body fat distribution.

The study's findings regarding mortality due to neutropenic sepsis emphasizes the life-threatening nature of this complication in paediatric oncology.[17] This highlights the urgent need for robust infection control measures, early intervention, and vigilant monitoring, especially in patients at higher risk. Furthermore, the significant association between mortality and diarrhoea underscores the importance of gastrointestinal toxicity management at an earlier stage. The relationship between diarrhoea and mortality has been observed in other studies as well, emphasizing the need for effective prophylaxis and treatment of chemotherapy-induced diarrhoea.[18,19]

Conducting this study in Pakistan adds valuable regional context to the understanding of chemotherapy-induced toxicities in paediatric Ewing sarcoma in Low- and Middle-Income countries. It highlights the need for tailored supportive care strategies and resources to address the specific challenges faced by children with cancer in LMIC, including access to specialized medications and monitoring. Moreover, the study emphasizes the importance of developing comprehensive oncology care programs in LMIC which may face unique healthcare challenges. Collaboration between international and regional healthcare organizations and the adaptation of treatment protocols to local contexts could further improve outcomes for paediatric cancer patients in Pakistan. Being a single centre study conducted on a relatively small sample size without any longer follow up data were some of the limitations of this study.

CONCLUSION

Neutropenia, nausea and vomiting, thrombocytopenia, and diarrhoea were the most frequent chemotherapy induced toxicities in children with Ewing sarcoma. Relatively young age (below 5 years) was having strong association with chemotherapy induced adverse events including nausea and vomiting, anaemia, diarrhoea, and mucositis. Gender did not seem to influence related toxicities. Neutropenic sepsis and gastrointestinal adverse effects can be further investigated as predictors of mortality in these cases.

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Submitted: April 26, 2024	*Revised: October 3, 2024*	*Accepted: November 11, 2024*

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CASE REPORT

CUTANEOUS MANIFESTATIONS OF MIGRAINE: FIRST OF ITS KIND, TWO CASE REPORTS FROM PAKISTAN

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Migraine is a common clinical entity; however, its dermatological manifestations are rarely reported. We report two young Pakistani female patients with asymptomatic, linear and round erythematous non blanchable patches on their forehead that were temporally associated with their migraine attacks. The local and systemic examination as well as extensive investigations, of both the patients, were all normal. The lesion resolved within a few days following abortion of migraine attacks in these patients. With Pathophysiology of cutaneous manifestations of migraine is still unknown due to their rare presentation, research is required to establish their significance in the long-term outcome of migraine.

Keywords: Migraine; Red dot syndrome; Cutaneous manifestations of migraine

Citation: Muhammad A, Iftikhar N, Iftikhar A, Abbasi AS. Cutaneous manifestations of migraine: First of its kind, two case reports from Pakistan. J Ayub Med Coll Abbottabad 2024;36(4):821–3.

DOI: 10.55519/JAMC-04-12925

INTRODUCTION

Migraine is a well explored neurological entity, characterized by episodic unilateral or bilateral attacks of headaches with signs and symptoms of aura such as dizziness, nausea and photophobia with a diagnostic criterion that helps in its diagnosis.[1] There are other manifestations, reported over the course of time; rare entities like "primary erythromelalgia in facial region" and "red ear syndrome" found in association with migraine have been reported[2], however rest of the cutaneous manifestations of migraine are reported sparsely[3,4]. We report two Pakistani young women who presented separately over a period of six months, with asymptomatic erythematous linear and round patches respectively, on their foreheads at the time of migraine attacks. The presentations of these lesions were directly related to the severity of migraine attacks in both the patients.

CASE-1

A 37 years of age dextromanual female homemaker, married, two kids for eight years with no other comorbid, presented to dermatology outpatient department with complaints of multiple episodic red linear streaks on her forehead appearing for four years off and on. These lesions were asymptomatic however they were associated with severe unilateral throbbing headache that upon further inquiry, fulfilled the criteria of migraine without aura. She had been suffering from these episodic attacks of headache, for the past four years without being labelled as a case of migraine by any doctor. She used oral non-steroidal anti-inflammatory medications to relieve her attacks. There were no other local or systemic complaints or any indicators of focal neurological deficit. On examination, her vitals were found to be within normal range, i.e., temperature 98.6 °F, pulse rate 90 beats/min, breathing rate 15 breaths/min and blood pressure was 135/85 mmHg. Her general physical examination was unremarkable while cutaneous examination revealed multiple erythematous, asymptomatic, linear non blanchable, vertical patches on her forehead, the longest streak being 6 cm in size while the smallest, 2.5 cm in size. She refused to get photographed during the initial attack due to cultural preferences however later agreed when she had another episode of migraine with similar skin manifestations, where the erythematous patch was again linear but single, measuring around 7 cm in length (Figure-1). Rest of her systemic examination including cardiovascular, neurological and abdominal examination was unremarkable.

The patient was reassured and placed in a dark room. She was given oral NSAID (Ibuprofen) for headache. Her baseline investigations including blood complete picture, liver & renal function tests, electrocardiogram and urine routine report were sent which were later found to be normal. Her MRI brain study was also found to be normal. After thorough counselling and consent, a punch biopsy of the cutaneous lesion was taken and sent for histopathological analysis which showed epidermis hyperkeratosis. Subcutaneous tissue showed red blood cells extravasation. Focal crusted vessels were also seen. There were no lymphocytes/ eosinophils, extravasation and the collagen bundles were found be normal looking (Figure-2,3,4). The headache subsided

considerably in the ensuing hours. The cutaneous markings, however persisted longer, gradually fading in colour and length until completely resolved in the next 36 hours in all of her clinical presentations. After 2 weeks, the patient reported with complaints of headache, of lesser intensity with proportionately less marked forehead markings than the initial attack. Following oral medications which abolished the migraine attack, the cutaneous markings resolved on second day of resolution of headache. With all her investigations being normal, the patient was referred to neurological OPD to start her on migraine prophylaxis treatment. She was counselled about the rarity and seemingly benign nature of these lesions. She agreed to be followed up on term basis and remain in touch with dermatologist reporting this case.

CASE-2

A 27 years of age dextromanual female student, known case of migraine, with no other comorbid, presented to dermatology outpatient department with complaints of multiple episodic discoid erythematous lesions on her forehead (Figure-5) appearing for three years off and on. Like the first case, these lesions were asymptomatic associated with severe unilateral throbbing headache that fulfilled the criteria of migraine without aura. She used abortive therapies for her migraine attacks as she didn't meet the criteria to put her on migraine prophylaxis and ignored her skin markings until recently as she planned to get married soon. There were no other local or systemic complaints or any indicators of focal neurological deficit. Her vitals, general physical and systemic examination were all unremarkable while cutaneous examination revealed four asymptomatic erythematous discoid patches with surrounding oedema.

The two larger patches measuring 2x3 cm in size while the other two were much smaller and fainter. The baseline investigations including blood complete picture, liver & renal function tests, electrocardiogram and urine routine and MRI brain study, were all normal like the first patient. She refused to get biopsied despite counselling. The cutaneous markings, followed a course, similar to the first case where they persisted longer than the headache and gradually faded in colour and size until completely resolution in the next two days. With all her investigations being normal, the patient was counselled in detail about the rarity and seemingly benign nature of these markings and also advised a close follow-up in dermatology and neurology outpatient departments.

The differential diagnosis in both cases included migraine, primary erythromelalgia presenting as migraine, *morphea en coup de sabre*, a space occupying lesion and vascular tumour. The history, examination and investigations in both cases ruled out other differentials. Both the fulfilled the diagnostic criteria of migraine without aura and hence were diagnosed as cases of migraine with cutaneous manifestations.

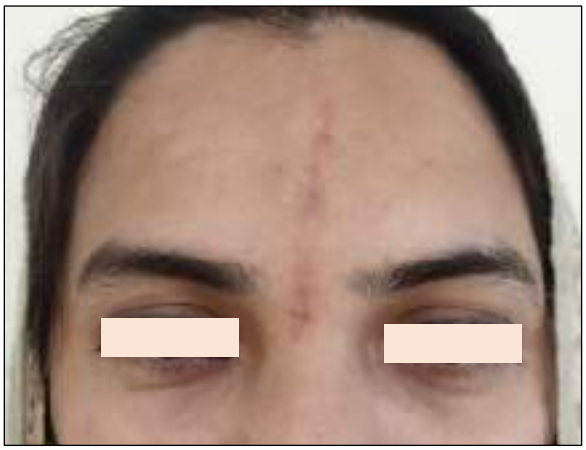

Figure-1: Patient #1, presenting with episodic red linear streaks on her forehead appearing for four years off and on.

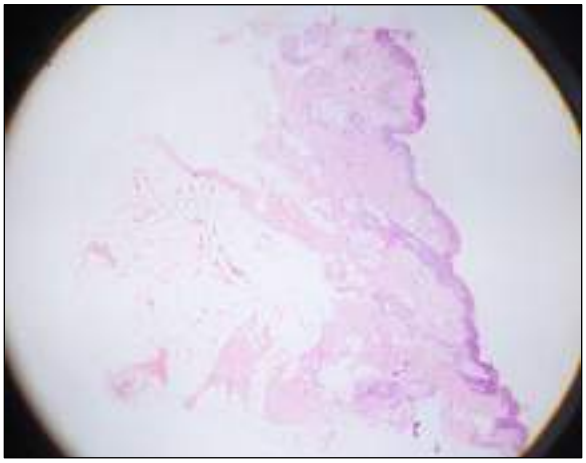

Figure-2

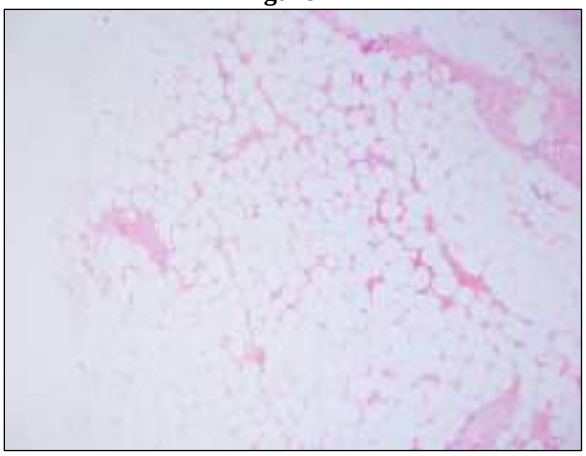

Figure-2

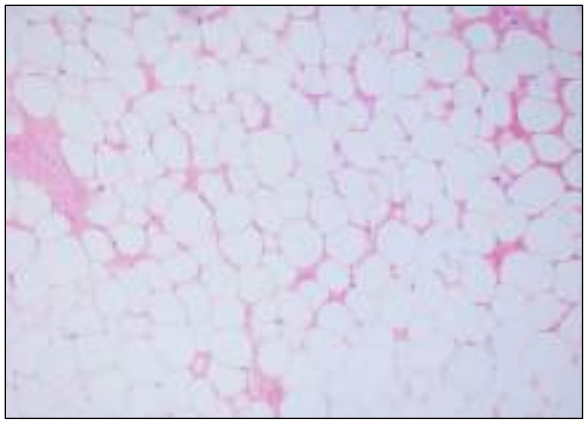

Figure-2,3,4: Biopsy of lesions from patient #1, showing subcutaneous tissue with red blood cells extravasation. Focal crusted vessels are also seen.

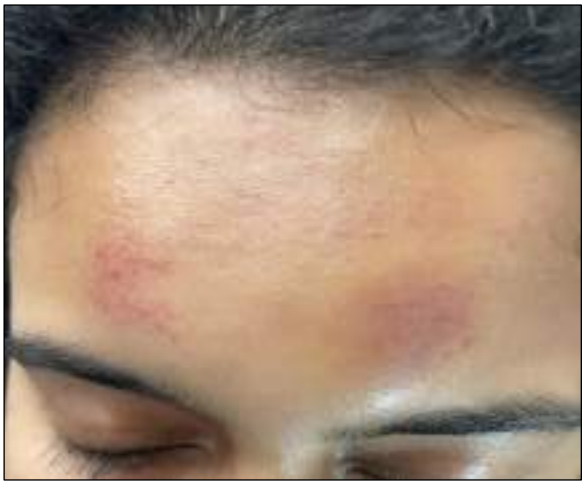

Figure-5: Patient #2 with multiple episodic discoid erythematous lesions on her forehead.

DISCUSSION

The cutaneous manifestations of migraine have been reported via only a few case reports.[3,4] While differentials like *morphea en coup de sabre* and vascular tumours were ruled out with cutaneous biopsy, the CT brain ruled out any intracranial SOL. The important differential of Primary Facial Erythromelalgia of Migraine[2] was rule out with history and examination as the lesions, although associated with migraine, were completely asymptomatic, had no known triggering/aggravating factors and would resolve completely, only following the resolution of migraine attacks. To the best our knowledge this is the first instance where two female patients of migraine with such extensive cutaneous involvement are reported. These are also the first case reports of such nature from Pakistan.

Interestingly, of the total seven cases reported so far, three patients are of Pakistani origin. The cutaneous manifestations in our first case are similar in distribution and behaviour to an earlier report of a UAE based male of Pakistani origin, not limited to V1 distribution of trigeminal nerve.[3] The earliest reports have described the cutaneous manifestations of migraine as a red dot in a female of Turkish and European origin, both in the distribution of the frontal branch of trigeminal nerve.[3-5] The Biopsy findings in our sample corroborate the previous suggestions regarding the nature of these cutaneous manifestations being vascular in origin.[4]

CONCLUSION

The cutaneous manifestations of migraine are rare and need further exploration and research regarding their pathophysiology and association with migraine severity and prognosis. Based on the so far higher frequency of these cutaneous manifestations of migraine in eastern Mediterranean ethnicities in general and Pakistani population in particular, we hypothesize that such cutaneous findings may have a predilection to a specific ethno-geographic distribution. There may also be a predilection of such findings in female patients. Clinicians need to be aware of such manifestations and may follow such patients on long term basis to understand the outcome of their illness.

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Submitted: February 5, 2024	Revised: June 25, 2024	Accepted: September 8, 2024

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CASE REPORT

PAEDIATRIC HEPATIC HAEMANGIOMA-A RARE CAUSE OF PYREXIA OF UNKNOWN ORIGIN

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Pyrexia of unknown origin (PUO) has remained a diagnostic challenge for medical professionals for decades as its aetiology remains elusive and requires extensive investigation. Hepatic Haemangioma (HH) is generally not considered a possible cause of PUO. HH is the most frequent, non-cancerous tumour in children usually presents as vague abdominal pain. We describe a case of 4-year-old female presented with the complaint of dull abdominal pain associated with low grade fever. Extensive workup was done to find out the cause. Her haemoglobin also dropped suggestive of bleeding haemangioma. She was treated with steroids (prednisolone) which significantly reduced her inflammatory markers prior to surgery. Later, hepatectomy was done after informed consent. The surgery was uneventful, and her PUO was also resolved.

Keywords: Pyrexia of unknown origin; Hepatic Haemangioma; Bleeding haemangioma

Citation: Nasir H, Bashir H, Asghar I, Tahir I, Seerat I. Paediatric hepatic haemangioma-a rare cause of pyrexia of unknown origin. J Ayub Med Coll Abbottabad 2024;36(4):824–6.

DOI: 10.55519/JAMC-04-12918

INTRODUCTION

Pyrexia of unknown origin (PUO) was first described in 1961 by Petersdorf and Beeson in adults as fever above 38 °C or 101 °F for longer than 3 weeks without an established diagnosis after a week of inpatient investigations. In children fever lasting more than 10 days without a definite cause can also be labelled as PUO.[1] Infections remain the most common cause of PUO in paediatrics age group. Other possible subcategories for causes include inflammatory disorders, malignancies and miscellaneous.[2] Hepatic Haemangioma is a very rare cause of PUO and there are very few cases that have been reported. Hepatic Haemangioma is the most common benign tumour in children often presenting as vague abdominal pain. We report here a case of preschool child presented in outpatient clinic with the complaints of dull abdominal pain and fever.

CASE

A 4-year-old developmentally normal, vaccinated girl with weight at 5th percentile and height at 10th percentile for age was admitted to Pakistan Kidney and Liver Institute and RC Lahore with complaints of gradually increasing swelling in right hypochondrium for last one month associated with dull abdominal pain, distention, occasional vomiting, persistent low-grade fever highest documented spike was of 37.8, anorexia, and weight loss. No previous medical or surgical history. Family history was unremarkable. On physical examination patient has a firm non tender single mass extending from right hypochondrium crossing midline extend up to left lumbar region 7cm below the costal margin. There was conjunctival pallor but no jaundice, ascites, or pedal oedema. No remarkable findings on CVS, CNS, and respiratory examination.

Blood tests done are as follow:

LABS	UNITS	Before Surgery	After Surgery
Total Bilirubin	mg/dl	0.24	0.18
Direct Bilirubin	mg/dl	0.14	0.09
Indirect Bilirubin	mg/dl	0.1	0.09
ALT	U/L	48	20
AST	U/L	30	25
ALP	U/L	170	150
GGT	U/L	90	80
ALBUMIN	g/dl	2.93	3.94
Haemoglobin	g/dl	9.7	10.8
WBC	10^9/L	12.9	12.5
Platelets	10^9/L	534	639
CRP	mg/dl	15.9	0.6
Procalcitonin	ng/ml	0.03	0.46

Blood tumour markers were, Serum LDH 542 IU/l (normal range 105 to 333 IU/l), Serum alpha fetoprotein 2.96 ng/ml (normal range <8.2 ng/ml), serum b-hcg less than 0.1 mIU/ml (normal range <5 mIU/ml).

As part of partial septic screening, Viral markers HbsAg, anti HCV, anti-HIV were done and came out to be non-reactive, NS 1antigen, covid 19 PCR, Quanteferon Tb were all negative and malarial parasite were not seen. All Blood, Urine and Stool cultures came out to be negative. Chest X-ray was unremarkable. All other possible causes of persistent fever were ruled out.

Ultrasound done revealed A huge heterogeneous predominantly hypoechoic mass is

noted replacing the left lobe of the liver with few internal areas of necrosis.

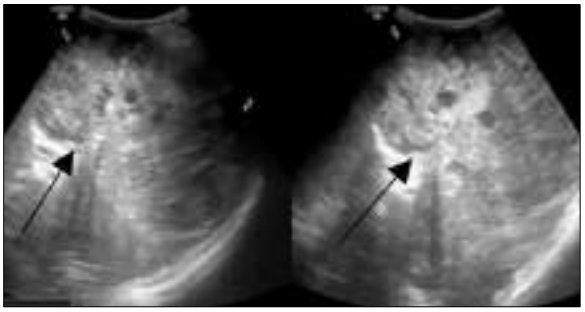

Figure-1: Ultrasound Liver (Black Arrows:Hemangioma)

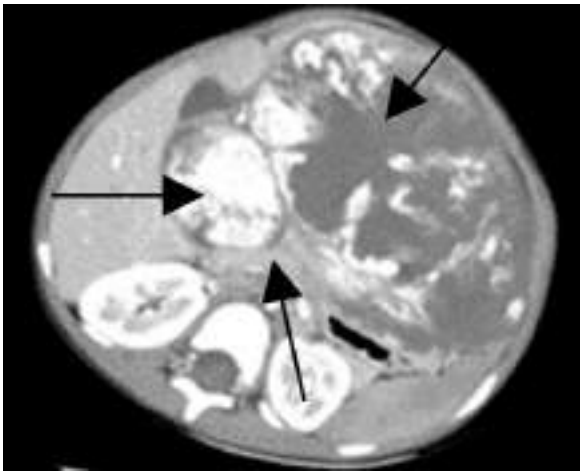

Figure-2: CT Abdomen (Black Arrows:Hemangioma)

Ct scan showed a large left hepatic lobe haemangioma measuring approximately 10×15×16 cm is re-demonstrated with peripheral contrast puddling and progressive peripheral enhancement with central area of necrosis. Left hepatic vein is severely attenuated however patent. Spleen, pancreas, gall bladder, stomach, gut loops appear unremarkable however compressed due to mass effect.

Histology was done to confirm the diagnosis. A lobulated tumour measuring 16×11×10 cm. Cut surface shows haemorrhage and some grey white areas. The tumour is 0.3 cm from the nearest parenchymal resection margin.

The sections show liver tissue involved by a vascular neoplasm composed of narrow vascular channels lined by plump endothelial cells. The cells have vesicular nuclei. Intervening spindle cell proliferation is also present. Some of the lining cells are forming papillary structures with entrapped bile ducts. There is central necrosis with some cavernous differentiation towards Centre of the lesion. There is variable nuclear atypia and mitotic figures. And CD31 was positive in tumour cells.

Patient was discharged 4 days after the surgery with no complications, without any episode of repeat fever or antibiotic requirement. Condition fairly improved. On follow up after 6 months, she was completely asymptomatic and her growth was satisfactory.

DISCUSSION

For many years, diagnosing PUO has been difficult. There have been numerous changes made to the definition, particularly in terms of the temporal criteria, which has gone from the original definition's 1 week of inpatient investigation to Durack and Street's 3 days of outpatient or inpatient investigation to Knockaert *et al*.'s most recent definition of the "pragmatic investigation period" and a structured diagnostic checklist without a time limit.[1,3,4]

After making a thorough and laborious effort to rule out the most prevalent causes of PUO, the diagnosis of exclusion for giant HH as the cause of PUO was made in our instance. The majority of benign hepatic tumours, or 70% of them, are HH.[5,6] HHs are blood-filled cavities lining the liver parenchyma that are supplied by a branch of the hepatic artery and lined with endothelial cells.5,6 0.4 to 20% of people are said to have HH.[5,6,8]

Small HH can be conservatively handled. In cases of sudden growth, unbearable pain, huge HH, or consequences including rupture, hemorrhage, or Kasabach-Merritt syndrome, surgery may be an option.[7,9] There are two peculiar characteristics of this case that demand notice; hence it is being reported. First, a low-grade fever that persisted for more than a month was the main clinical manifestation of the patient's massive haemangiomatous liver. Second, moderate dosages of prednisone had a substantial effect on the fever, and other clinical measures gradually improved as well. These improvements persisted for a long time after the use of steroids was stopped. The literature hardly ever refers to fever as a manifestation of this mass.

Although its exact mechanism of action is unknown, corticosteroid medication is the treatment of choice for young patients with severe cavernous haemangiomas of the skin and subcutaneous tissues.[10] Steroid therapy for hepatic haemangiomas has sometimes been documented as very useful. The quick reduction in fever together with the steady improvement in anaemia, weight, and work capacity show that the prednisone medication was effective above and beyond only serving as a generic antipyretic.

It is speculative how the fever developed and how prednisone might have had a positive effect. It is tempting to assume that damage to blood cells, particularly polymorphonuclear leukocytes, within the bounds of haemangioma results in the release of

pyrogens and, as a result, fever occurs. It is well recognized that haematomas themselves could be the source of fever, and it is undeniable that clotting frequently happens in haemangiomas, occasionally leading to calcifications in the lumens.[11,12]

Corticosteroids are long recognized to have anti-inflammatory and anti-pyretic effects. Although the exact mechanism of this fever suppression is unknown, experimental evidence supports both central effects on the hypothalamic centre that controls body temperature[13] and peripheral effects on leukocytes' production of pyrogen[14].

CONCLUSION

Patient was medically optimized with propranolol and steroid therapy successfully, prior to surgery after which her inflammatory markers, WBC count was in decreasing trend as well as the size of her haemangioma was reduced. Medical optimization with propranolol and prednisolone significantly improved her Anaemia and general wellbeing, indicating their prime significance in treatment of hepatic haemangioma. Hepatic haemangioma was the main cause of her Pyrexia of unknown origin (PUO). After surgery, her inflammatory markers were completely back to normal, no episode of fever was reported and patient's compression symptoms due to huge mass were relieved.

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Submitted: February 1, 2024	*Revised: November 21, 2024*	*Accepted: November 21, 2024*

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CASE REPORT

AMPHETAMINE-INDUCED PSYCHOSIS LEADING TO HOMICIDE, SUICIDAL ATTEMPTS, AND DISORIENTATION: A CASE REPORT

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Amphetamine abuse leads to severe psychiatric and cardiovascular complications–psychosis, hallucinations and aggressive behavior. A 34-year-old male of five years noted history of amphetamine abuse and presented with amphetamine psychosis characterized by hallucinations, violent ideations and a recent suicide attempt is described in this case report. Previously under the influence of amphetamines, two years prior, the patient committed homicide. Patient had periods of very severe disorientation and agitation, history of suicidal ideation and violent thoughts toward others. Toxicology screenings were done, all were consistent with amphetamine presence. Diagnostic studies included cardiac biomarker elevations and abnormal electrolyte levels. Management was immediate and involved sedation, antipsychotic therapy and cardiovascular support, followed by long term psychiatric care and substance abuse rehabilitation. Here, chronic amphetamine abuse is shown to have profound psychiatric and behavioral effects and to require integrated treatment strategies to meet the complex needs of such patients.

Keywords: Amphetamine abuse; Psychosis; Hallucinations; Suicidal behavior; Violent ideations

Citation: Azad AH, Khan SA, Bibi I, Ali I, Wazir P, Umar SA. Amphetamine-induced psychosis leading to homicide, suicidal attempts, and disorientation: A case report. J Ayub Med Coll Abbottabad 2024;36(4):827–9.

DOI: 10.55519/JAMC-04-14128

INTRODUCTION

Amphetamine abuse has become a pressing public health problem of global prevalence and severity. Methamphetamine and other synthetic stimulants as well as amphetamines, known for their euphorigenic stimulating properties, have a high abuse and addiction potential.[1,2] Amphetamine use increase on global basis is due to factors ranging from the increased availability, to both societal and social stressors and the improvement of cognitive and physical performance to which amphetamine use is linked.[1] Severe psychiatric conditions have followed chronic use of amphetamines, including amphetamine induced psychosis, characterized by hallucinations, paranoia and severe agitation.[3] Substantial disruptions in dopaminergic systems are the neurochemical mechanisms underlying amphetamine induced psychosis. Amphetamines are proving to be particularly good at releasing dopamine, especially from and in the mesolimbic pathway, which is critical to reward processing and reinforcement learning.[4] Whereas conventional drugs simply adjust pharmaceutical neurotransmitters based on a blood test to treat these symptoms, this is a possibility that impedes on other areas like this alteration in neurotransmitter function, which can have a full spectrum of psychiatric symptoms from mild paranoia to severe psychotic episodes.[5] The long-term psychiatric manifestations seen in users of amphetamines are made more complicated by the induction of chronic changes in structure and function of the brain by amphetamines.[6] Amphetamine use is typically chronic, and over time, these neurochemical imbalances tend to become more persistent, worsening the psychiatric symptoms.[7] Amphetamine induced psychosis often resembles acute primary psychotic disorders including schizophrenia but can be differentiated on the basis of its drug use history.[8] This condition is not easy to deal with when the possibility of aggressive behavior, violence, and even self-destructiveness in chronic users is considered. It is therefore paramount to know these manifestations so as to start developing ways of handling it. In a study it was found that psychosis, which is left without treatment, may result in severe deficits in activities of daily living and social interactions, as well as the increased level of dangerous behaviour.[9] The complexity of the disorder requires that management approach be multimodal which involves psychiatric evaluation, pharmacological treatment, and substance use treatment.[10]

CASE REPORT

Male patient aged 34-years with a history of amphetamine was brought to emergency ward, Amna Hospital Sialkot after he survived a suicidal attempt. He had been using amphetamines daily for the last five years, which gradually progressed. Two years before

the current presentation, the patient killed his 10 years old nephew during psychosis due to amphetamines use. During that period, he had perceptual disturbances, in the form of hallucinations and delusional manifestations that precipitated acts of violence. The patient was arrested but was later detained in a jail for a short time because he was declared mentally unfit to stand a trial. He was prescribed antipsychotic medication but was non-compliant; this together with substance abuse and psychiatric instability persisted. The patient was taken to the emergency department after attempting to commit suicide by jumping off the roof of a two storied building. It has been a few weeks since his family received complaints about him screaming and telling them false things, and physical aggression toward them. In this period, he used to talk nervously about the violent intentions towards his family members and used to believe that his family members have ill intentions against him. He had severe paranoid symptoms and high levels of impulsiveness, which degenerated into suicide measures before the study. At admission, the patient was noted to be severely agitated, paranoid. He was incoherent and would often go from agitated activities. Psychomotor agitation was noted with difficulty maintaining focus in Mental Status Examination. The conditions he had included were delusions of persecution and auditory hallucinations that the voices commanded him to harm others. His behavior varied from irritable to tearful. He became intermittently disoriented to time and place and every now and then announced that he was aware of what he was doing. The patient was agitated and restless, alternately sitting and reclining, and was unable to sit still, as Physical Examination showed. He probably had some form of hypertension and tachycardia with the onset owing to his psychotic state and substance use. During the examination there were no focal neurological deficits. The following investigations were conducted to assess the extent of the patient's condition and to guide treatment.

Test	Result	Normal Range
Urine Toxicology	Positive for amphetamines	Negative
Complete Blood Count (CBC)	WBC: 10.2 x 10^9/L	4.5–11 x 10^9/L
	Hemoglobin: 13.8 g/dL	13.0–17.0 g/dL
Liver Function Tests (LFTs)	ALT: 38 U/L	10–40 U/L
	AST: 42 U/L	10–40 U/L
Electrolytes	Sodium: 140 mmol/L	135–145 mmol/L
	Potassium: 4.0 mmol/L	3.5–5.0 mmol/L
Brain MRI	No acute abnormalities	-
EKG	Sinus tachycardia	60–100 bpm
Psychiatric Evaluation	Amphetamine-induced psychosis; high risk of self-harm and aggression	-

The patient confirmed a history of amphetamine use that had become increasingly frequent and intense over the past 5 years. The patient's family stated that over the past year, they had observed escalating aggression, followed by a pattern of erratic behavior, then bad compliance with psychiatric treatment, only to have it fail. In addition, the patient reported multiple failed attempts to quit, only partially complying with psychiatric treatment. In the past the family had sought psychiatric help but were unsuccessful due to the noncompliance of the patient. The patient also had amphetamine induced psychosis, with recurrent episodes of severe paranoia and hallucinations. Severe agitation and drug induced sedation were managed with a combination of antipsychotic medications risperidone and olanzapine and benzodiazepines to stabilize the patient. In addition to treatment of evident hypertension and tachycardia, the patient was also given cardiovascular support. The patient was stabilized first and then admitted to psychiatric ward for further management. An overall treatment plan was established consisting of continuing antipsychotic therapy, cognitive behavior therapy, and a didactic structured substance abuse rehabilitation program. Rehabilitation program was based on motivational interviewing and recovery prevention strategies, emphasizing both psychological aspects of addiction and behavioral modification necessary to keep one abstained from addiction.

DISCUSSION

This case illustrates the great effect of chronic amphetamine abuse on mental health, with an academic approach to amphetamine psychosis with hallucination, ideation of violence, and a suicide attempt. Vulnerable patients like this with a history of prior violent behavior, including the murder of his nephew, have severe risks in this context, provoked by untreated psychotic episodes exacerbated by stimulant use. Amphetamines are known to primarily act in the brain by causing an enormous increase in dopamine release, thereby raising mood and alertness.[11] However, when it is used chronically this disrupts normal dopaminergic function, causing a variety of psychotic symptoms, including hallucinations and paranoia. Amphetamine induced psychosis is primarily a result of over dopaminergic activity in the mesolimbic pathway, a critical brain circuit responsible for emotional and reward responding, although other neurotransmitter systems contribute.[5,12] It results in robust psychiatric

symptoms (delusions, violent ideation), and it is highly disruptive. There is consistency with other severe amphetamine induced psychosis case reports in which intense paranoia, agitation, can precipitate dangerous behaviors.[13] This patient's past suicide attempt identifies amphetamine use as a high risk for suicide; and, as a result, the emphasis is on the urgent requirement for effective methods of managing both acute symptoms and underlying substance abuse.[14,15] Persons with stimulant use disorders are at increased risk for suicidal behavior, with evidence that the risk is especially elevated during an acute psychotic episode.[16] Severe psychiatric symptoms in combination with substance induced mood disturbances greatly increase the risk of self-harm. Integrated treatment of this risk includes a combination of pharmacological and psychiatric care along with rehabilitation for substance abuse.[17,18] Treatment of acute amphetamine induced psychosis involving hallucinations, violent ideations, and suicidal behavior requires long term management strategies for both the acute psychosis and prevention of substance abuse which tends to relapse and can precipitate psychiatric symptoms and suicidal behavior.[19,20] The management of amphetamine-induced psychosis, to be effective, is accomplished by a combination of pharmacological and psychiatric treatment as well as substance abuse rehabilitation.[13,21] to address the complex needs of individuals with amphetamine-induced psychosis and to decimate risks of morbidity behaviors. Rehabilitation and psychiatric support services are structured to prevent relapse and promote long term recovery in persons with severe amphetamine disorders.[17,18]

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Submitted: June 3, 2024	*Revised: September 17, 2024*	*Accepted: October 6, 2024*

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CASE REPORT

LEIOMYOSARCOMA OF THE INFERIOR VENA CAVA MASQUERADING AS A DUODENAL STROMAL TUMOUR

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Leiomyosarcomas originating in the inferior vena cava (IVC) are rare vascular tumours characterized by gradual growth and subtle onset. The challenges associated with these tumours stem from their unfavourable prognosis and the absence of established treatment protocols. We present a case of a 52-year-old woman who presented with abdominal pain and was subsequently diagnosed with leiomyosarcoma in the second segment of the IVC. This case highlights the significance of adopting a multidisciplinary approach and emphasizes the necessity for timely identification and intervention in IVC leiomyosarcomas to improve patient outcomes. To our knowledge, this is the first reported case of leiomyosarcoma in the IVC from Pakistan. We believe this case will contribute valuable insights to the existing knowledge on the subject.

Keywords: Leiomyosarcomas; Masquerading; Tumour; Abdominal pain

Citation: Ali F, Bangash A, Butt MA, Aimon S, Saleem R, Atiq M, *et al*. Leiomyosarcoma of the Inferior vena cava masquerading as a duodenal stromal tumour. J Ayub Med Coll Abbottabad 2024;36(4):830–2.

DOI: 10.55519/JAMC-04-13126

INTRODUCTION

Leiomyosarcoma (LM), a malignancy arising from smooth muscle tissue, possesses a complex aetiology and typically carries an unfavourable prognosis. It's recognized as the most common tumour in the venous system and the second most prevalent retroperitoneal neoplasm in the elderly. Emerging in any vein, the inferior vena cava (IVC) is most affected, constituting 5–10% of soft tissue sarcomas.[1,2] LM may display intraluminal growth in 5% of cases, extraluminal growth in 62%, or a combined pattern in 33%. Affecting both genders, it shows a higher incidence in individuals in their fifth and sixth decades of life.[3] The slow growth of leiomyosarcomas often leads to nonspecific symptoms like abdominal pain, weight loss, a palpable abdominal mass, weakness, fever, anorexia, vomiting, and night sweats due to their retroperitoneal location.[4]

CASE

A 52-year-old female with no known comorbidities presented with complaints of abdominal pain and vomiting for 7 days. She was admitted to a local hospital where abdominal imaging revealed a well-defined heterogeneous mass at porta hepatis, displacing the head of the pancreas, infra-hepatic part of the IVC, caudate lobe of the liver, and right renal vein as shown in Figure 1. The baseline workup, including complete blood count, liver function tests, renal function tests, coagulation profile, viral markers, and electrolyte panel was unremarkable. Endoscopic ultrasound showed an ovoid hypo-echoic paraduodenal mass, measuring 6.2×4.2 cm, which was separable from the pancreas. A 22 G ACQUIRE fine needle biopsy was done, exhibiting atypical smooth muscle cells. Immunohistochemistry was performed which was positive for AMSA and desmin stains. Findings were consistent for a spindle cell neoplasm. Intraoperative, the right hepatic lobe was mobilized and a 4 cm mass was noticed arising from the anteromedial wall of the retrohepatic segment of the IVC, which is one of the four segments of the IVC.

The other being suprahepatic, renal and suprarenal. The mass was dissected and separated from the aorta, portal vein, and resected en bloc with the anteromedial wall of the inferior vena cava as shown in Figure 2 (a and d). Subsequently, the anteromedial wall of the IVC was repaired with a Polytetrafluoroethylene (PTFE) 6mm patch as shown in Figure 2 (b and c). An additional margin of the IVC was biopsied, which was negative for malignancy. The resected mass was sent for histopathology, showing a well-circumscribed malignant neoplasm comprising fascicles of spindle cells with patchy areas of necrosis and moderate nuclear pleomorphism (2–3 mitosis/HPF). Cigar-shaped nuclei with areas of multinucleation and Focal hypocellular hyalinized areas were also seen. Staining was positive for ASMA, Desmin, and H-Caldesmon. Post-surgical imaging showed no discrete enhancing masses and nodules.

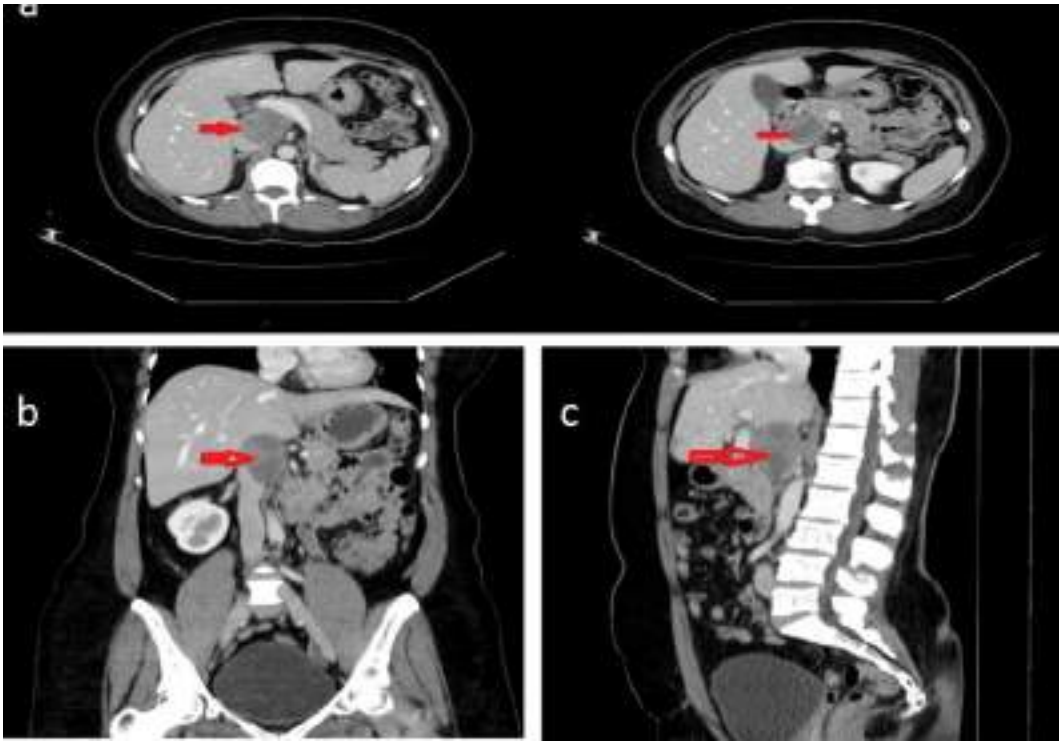

Figure-1:

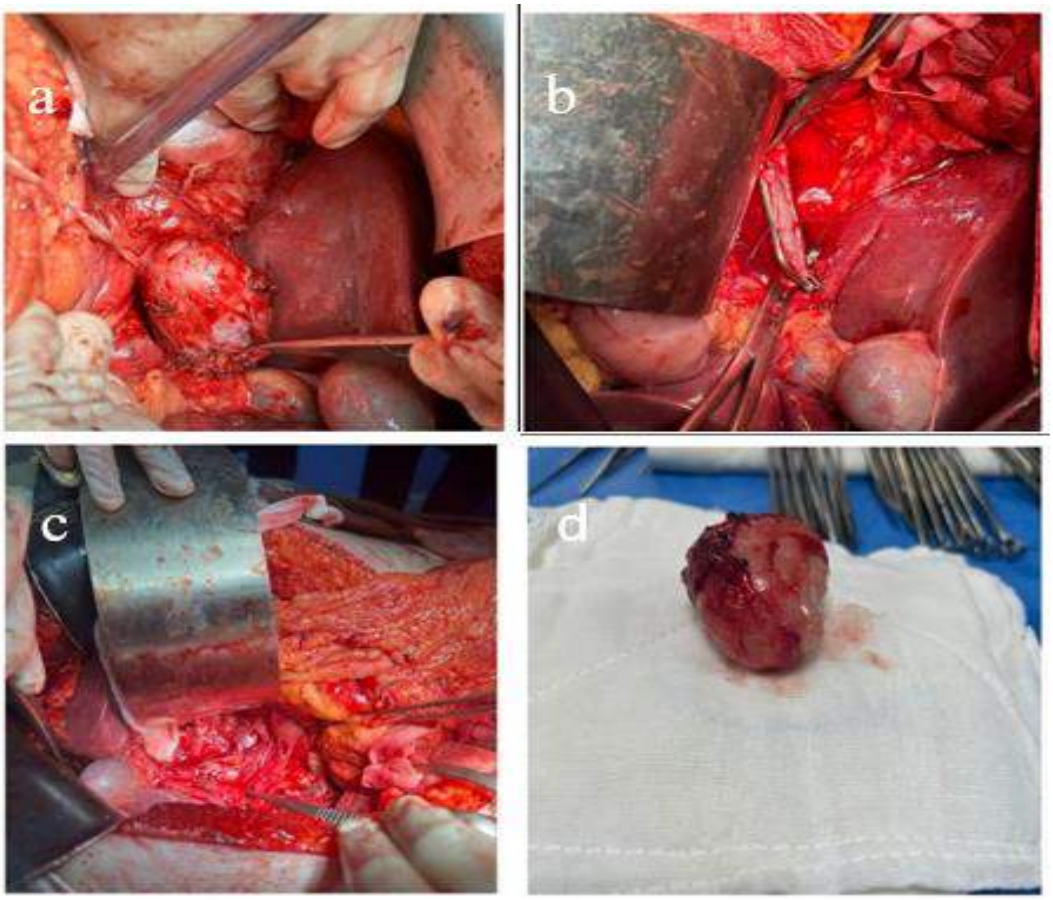

Figure-2:

DISCUSSION

Leiomyosarcoma of the IVC, first described by Perl et al in 1871, is the most common primary tumour of the IVC, with fewer than 600 cases reported worldwide. These tumours of mesenchymal origin typically arise from smooth muscle cells in the tunica media. They account for 0.5% of all adult tissue sarcomas and affect <1/100,000 of all adult malignancies.[5] Surgical resection with clear margins is the definitive treatment, although the prognosis is generally poor. Symptoms are often nonspecific, with abdominal pain being the most common. This case highlights a successfully treated locally advanced LM of the IVC, emphasising the collaborative efforts of gastroenterologists, surgeons, and radiologists in diagnosis and treatment planning.

Leiomyosarcoma predominately arises in females with its incidence peaking in the 5th and 6th decade of life[6]. Notably, our patient also mirrors this demographic profile, being a female in a similar age group. Our patient presented with nonspecific abdominal pain, which is the most common symptom reported in the literature.[7]

Improved survival rates up to a 5-year survival rate of 49.4% are reported with radical tumour dissection compared to those who are managed with medical therapy only.[8] Histopathological analysis of the surgical specimen unveiled negative margins. Hines et al. have documented this outcome as a good prognostic indicator, noting a 5-year survival rate of 68%, in contrast to the zero percent survival observed among patients with positive margins.[9]

Surgical resection is currently the only curable treatment for LM of the IVC, due to the rarity of the disease and lack of data regarding alternative options like chemotherapy, radiotherapy, and chemoradiotherapy. Improved median survival has been reported with adjuvant radiation and chemotherapy as compared to surgical resection alone.[9] While metastasis at the initial presentation is uncommon, instances have been documented where patients present with metastases. The lungs are the most prevalent sites, with subsequent occurrences in the thigh and shoulder muscles, liver, and bones. After achieving complete resection, the likelihood of recurrence at distant sites surpasses that of local recurrence.[10]

Leiomyosarcoma of the IVC remains a significant challenge for timely diagnosis and optimal treatment due to factors like its vague presentation, low incidence, and the absence of established management guidelines. Given these hurdles, we propose that further studies should be conducted to improve patient outcomes and develop evidence-based protocols for the effective management of this condition.

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Submitted: March 19, 2024	*Revised: May 13, 2024*	*Accepted: June 5, 2024*

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CASE REPORT

PERFORATED JEJUNAL DIVERTICULITIS AS AN UNCOMMON CULPRIT OF ACUTE ABDOMEN: A CASE REPORT AND REVIEW OF LITERATURE

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Small intestinal diverticula are rare compared to colonic diverticula. Jejunal diverticulosis can occur in older men. These diverticula are usually asymptomatic but can present with acute abdomen when symptomatic. Complicated cases can present with perforation, peritonitis, and abscess formation. CT scan is the ideal imaging modality to diagnose perforated jejunal diverticulitis. Complicated cases warrant surgical intervention. A high clinical suspicion is necessary for the timely diagnosis of perforated diverticulitis. We are presenting a case of a 45-year-old who presented with an acute abdomen in a surgical emergency. Perforated jejunal diverticulitis was revealed as the cause of his symptoms during surgery. This case signifies the importance of varied clinical presentations of perforated jejunal diverticulitis and keeping it in the differentials of acute abdomen. Perforated diverticulitis has a high mortality rate, so timely management is of utmost importance.

Keywords: Perforated jejunal diverticulitis; Small bowel diverticula; Surgical management of perforated diverticula

Citation: Maqbool U, Mehmood MF, Maqbool A, Qadeer A, Loon M, Masood S. Perforated jejunal diverticulitis as an uncommon culprit of acute abdomen: A case report and review of literature. J Ayub Med Coll Abbottabad 2024;36(4):833–7.

DOI: 10.55519/JAMC-04-13336

INTRODUCTION

Intestinal diverticula are outpouchings of the intestinal mucosa and submucosa. These are false diverticula, as the outpouching does not involve the entire intestinal wall thickness. These diverticula commonly affect the large intestine. Small intestinal diverticula are rare. Their incidence ranges from 0.06–2.3%.[1] Small intestinal diverticulitis is a rare but important cause of acute abdomen.[2] Among small intestinal diverticula, duodenal diverticula are the most common, followed by diverticula of jejunum or ileum. The annual incidence of jejunal diverticulosis is around 0.3–2.3%.

Small intestinal diverticula are usually found incidentally in the CT scan of the abdomen or during the surgical intervention. These are usually asymptomatic. Only 29% of affected people present with symptoms such as nausea, abdominal pain, and malabsorption.[3] Complications can occur in cases of diverticulitis. These include gastrointestinal bleeding, perforation, peritonitis, adhesions, fistula formation, and localized abscess. These complications are reported in only 10% of cases.[4]

Non-complicated diverticulitis is usually managed conservatively with intravenous fluids, bowel rest, and antibiotics.[5] Complicated diverticulitis invariably requires surgical intervention. Complicated diverticulitis has a high mortality rate if there is a delay in the diagnosis and intervention. Timely diagnosis is of paramount importance for saving a patient's life. We present a case of a middle-aged adult presenting with right iliac fossa pain and tenderness that was clinically diagnosed as perforated appendicitis. During surgery, he was found to have a perforated jejunal diverticulum.

CASE PRESENTATION

A 45-year-old Asian male, a bank clerk by profession, presented to the surgical emergency of Mayo Hospital Lahore on 18th November 2022, complaining of pain in the umbilical region. The patient was brought in by ambulance. He was treated at a local dispensary, where his pain did not settle. He was then referred to Mayo Hospital Lahore. He had an insignificant past medical and surgical history. He was a non-smoker and had no co-morbidities. His family history was also insignificant.

On examination, there was generalized tenderness in the lower abdomen. His pulse was 118/min, and his BP was 90/60 mmHg. There was guarding and rebound tenderness in the right iliac fossa. The Rovsing sign was also positive. Suspecting appendicitis, Alvarado's score was calculated, which came out to be 9/10. The pain started 1 day back. It was sudden in onset and localized to the umbilical region. The pain progressively worsened and became generalized to the lower abdomen. The patient was treated at a local dispensary suspecting constipation. It

was associated with high-grade fever (101℃), anorexia, nausea, and 2 episodes of vomiting. There was no history of abdominal pain, gastritis, constipation, per-rectal bleeding, or diarrhoea. The patient did not complain of any dysuria, urinary urgency, or testicular pain. At his presentation in Mayo Hospital emergency, he was given painkillers after drawing blood samples.

The patient's complete blood counts showed leucocytosis ($15.1\times10^{\wedge3}$ /uL). Abdominal ultrasonography showed mild pelvic ascites. A supine abdominal X-ray showed air in gut loops (Figure-1). An erect chest X-ray showed no air under the diaphragm (Figure-1).

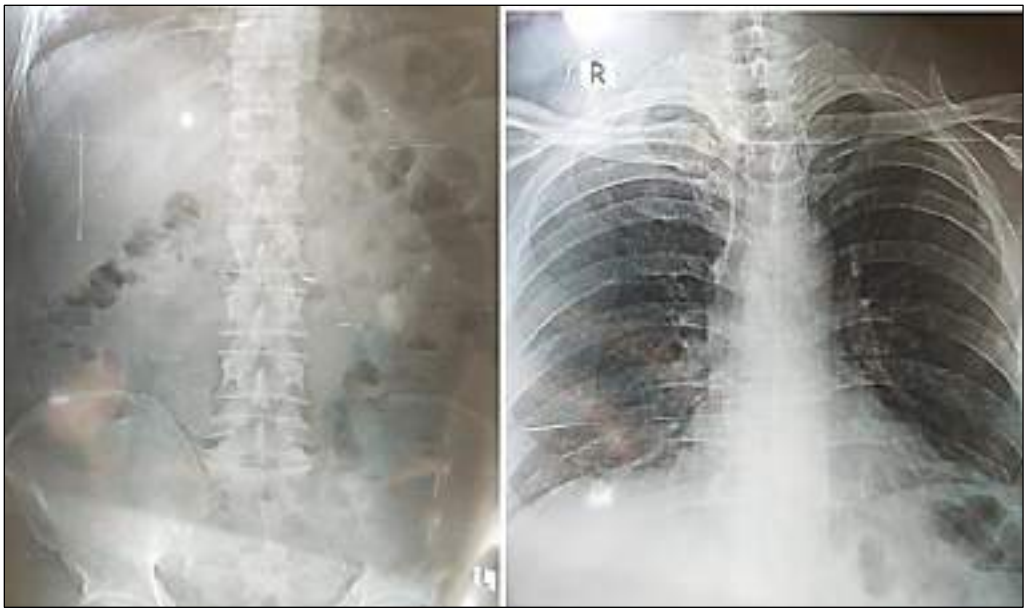

Figure-1- Supine abdominal X-ray showing air in gut loops. An erect chest X-ray shows no air under the diaphragm

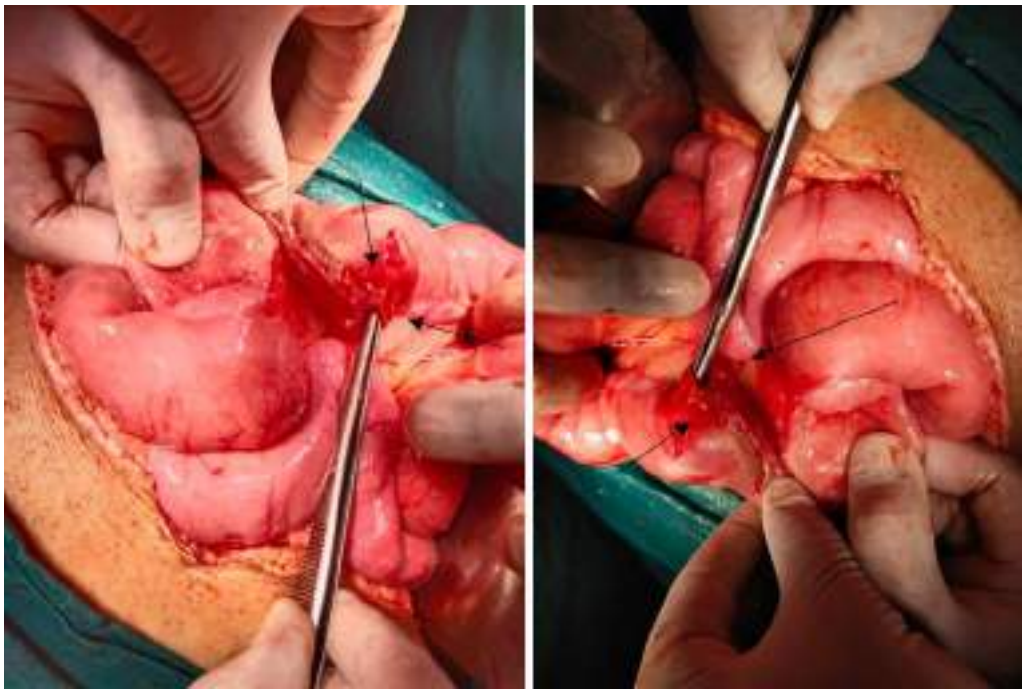

Figure-2- Intraoperative images showing perforated jejunal diverticulum 1.5 feet distal to the duodenojejunal junction and extraluminal inflammation of the jejunum

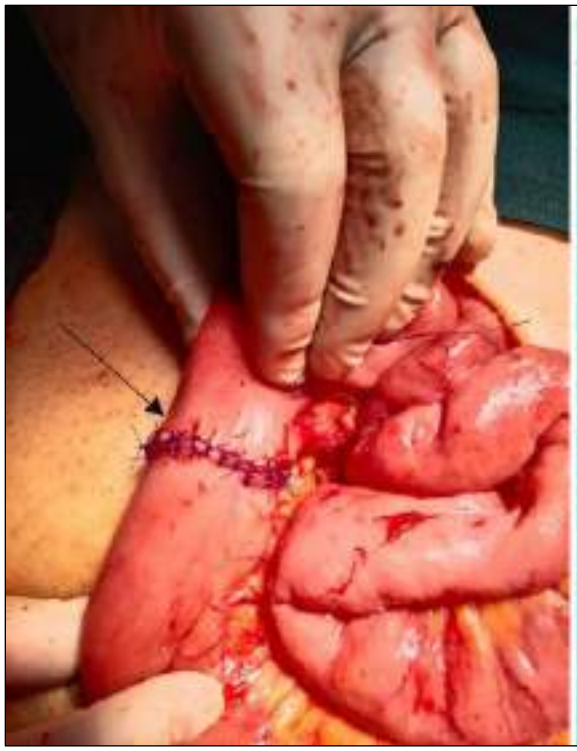

Figure-3: End-to-end anastomosis of the jejunum

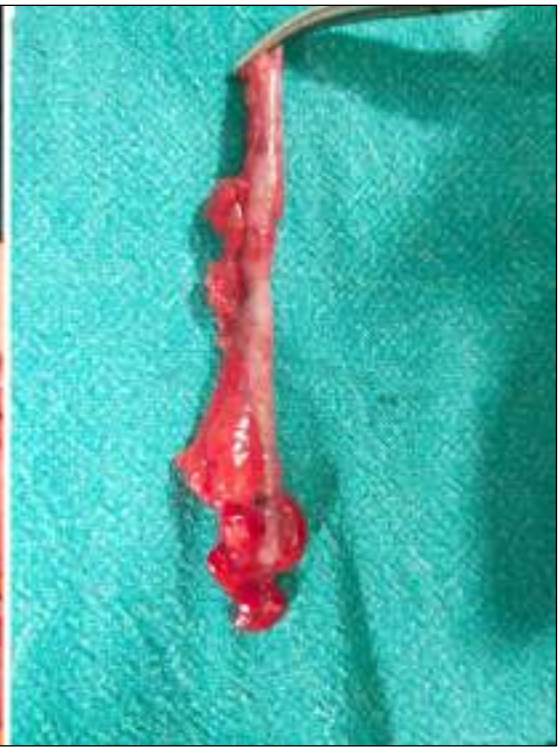

Figure-4: Resected jejunal segment

Based on these investigations, a clinical diagnosis of perforated appendicitis was made. Other differentials considered were urinary tract infection, gastroenteritis, subacute intestinal obstruction, and caecal mass. The history, examination findings, and investigations pointed toward perforated appendicitis and excluded other causes. So, a surgical treatment of appendicitis was decided.

The patient was started on IV fluids, IV antibiotics, and IV analgesics. His BP was optimized. Surgical management was decided as perforated appendicitis was suspected. He was shifted to the emergency operation theatre. Lanz incision was given, and the abdominal wall was opened layer by layer. Purulent fluid appeared on opening the peritoneum. The appendix was identified at the junction of the taenia coli. There was frank pus around it but it was not inflamed, the appendiceal base was healthy, and there was no perforation. About 200 ml of purulent fluid was removed by suction. Mesoappendix was ligated, and appendectomy was done. Suspecting a different cause of abdominal pain as there was no perforated appendix, a pelvic drain was placed. Purulent fluid began to appear in the drain a few minutes later. The Lanz incision was extended to the midline to have better access to the pelvis. Gauze pieces were placed in the pelvis and were found to be soaked in pus. Now, gauze pieces were pushed upwards to the small gut and were found to be stained with pus. At this time, it was decided to do an exploratory laparotomy to determine the cause of the pelvic abscess. A midline laparotomy incision was given, and the abdominal wall was opened layer by layer. The duodenum was examined at first to rule out duodenal perforation. The small intestine was examined throughout its length, starting from the duodenum. Multiple jejunal diverticula were found 1.5 feet distal to the duodenojejunal junction. A perforated, inflamed jejunal diverticulum was found with a streak of pus going down the length of the intestine (Figure-2).

The abdominal cavity was washed thoroughly with warm saline. The gut segment containing the perforated diverticulum was resected, and end-to-end anastomosis of the two ends of the jejunum was performed with a Prolene 3.0 round body suture (Figure-3,4). Hemostasis was secured, a drain was placed, and the abdominal cavity was closed layer by layer. The procedure was performed by the consultant general surgeon of the surgical team.

A nasogastric tube was passed, and the patient was shifted to the ward. He was kept NPO for 5 days. Injectable antibiotics (ceftriaxone and metronidazole) were started. The patient was mobilized the next day. His drain showed no output after 3 days and was subsequently removed. Incentive spirometry was encouraged. Oral intake was started 5

days later with a liquid diet. The patient tolerated the oral diet and showed good post-operative recovery.

He was discharged after 8 days and followed up in OPD at 2 weeks and 4 weeks post-op. He had normal bowel function, and there were no post-operative complaints. Histopathological examination of the resected specimen showed intestinal mucosa. There was no evidence of a parasitic infestation, inflammatory bowel disease, or malignancy. He had no post-operative complications or adverse events.

DISCUSSION

Jejunal diverticulosis is a rare condition affecting only 0.3–2.3% of the population. These diverticula are formed by the outpouchings of the mucosa and submucosa through the muscularis propria of the small intestinal wall at areas where vasa recta pierce the muscular wall. These are potentially weak areas in the muscular propria. Where the aetiology involving colonic diverticula includes constipation, decreased dietary fiber in the diet, and old age; the small gut diverticula are formed due to intestinal dyskinesias, abnormal peristalsis, and high intraluminal pressures.[6] Jejunal diverticulosis predominantly affects men in their advanced age. The initial imaging modality is an erect chest X-ray which shows air under the diaphragm in case of perforation. However, X-rays have a limited significance in diagnosing jejunal diverticulitis, where most patients present with acute abdominal pain. The gold standard imaging modality is the abdomen CT scan, which can accurately diagnose the jejunal diverticula and its complications. On CT scan, jejunal diverticula look like round structures outside a small gut lumen containing air and debris.[7] The management strategies depend upon the presenting case. There are no definite treatment guidelines for jejunal diverticulitis. Non-complicated cases where a patient presents with acute abdominal pain are usually managed conservatively with IV fluids, bowel rest, and antibiotics. Most cases of diverticulitis resolve with conservative management, and surgical intervention is unnecessary. Complicated cases where intestinal perforation and peritonitis occur require surgical intervention.[8]

This case was typically interesting as the affected patient was 45 years old, and his clinical features mimicked perforated appendicitis. The patient usually has upper abdominal pain or signs of generalized peritonitis. Our patient presented with right iliac fossa pain and localized tenderness, leading to a clinical diagnosis of perforated appendicitis. This case signifies the importance of keeping perforated diverticulitis as an important differential in the acute abdomen, the varied clinical presentations of this pathology, and employing a CT scan to reach an accurate diagnosis preoperatively. This case represents an atypical and rare clinical presentation of perforated jejunal diverticulitis. Our case had a pelvic abscess secondary to perforation. There is a reported case of an abdominal wall abscess secondary to perforated jejunal diverticulitis.[9] The perforated diverticulum had penetrated the abdominal wall leading to an abdominal mass. The perforated diverticulum can also be the source of bacterial thromboembolism. A case reports the death of an adult female with an infected right atrial thrombus and pulmonary emboli secondary to a perforated jejunal diverticulum.[10] The diverticulitis in a patient with jejunal diverticulosis can occur secondary to enterolith.[11] It can obstruct the lumen predisposing to inflammation. Jejunal diverticulosis is also reported to form secondary to a gastrointestinal stromal tumor.[12] Histopathological examination of the resected specimen is necessary to rule out any malignancy. There is a case reporting jejunal diverticulosis in a patient with systemic lupus erythematosus. There is no evidence linking SLE with the underlying aetiology of jejunal diverticulosis, and further research is necessary.[13] Although jejunal diverticulosis typically presents in older adults, complicated cases have been reported in a 37-year-old female and an 11-year-old child.[14,15] Our case further reiterates the importance of keeping perforated jejunal diverticulitis in mind while assessing middle-aged patients presenting with acute abdomen.

CONCLUSION

Perforated jejunal diverticulitis is a rare disease with varied clinical presentations and a high mortality rate. The disease can present in relatively young patients and can mimic perforated appendicitis. High clinical suspicion and employment of CT scan modality are necessary to reach an accurate diagnosis. Complicated cases should be managed with timely surgical intervention. Histopathological examination of resected specimens should be done to rule out any malignancy.

Consent and funding statement:
Informed consent was taken from the patient for this publication. The authors report no conflict of interest or funding source for this manuscript.

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Submitted: May 4, 2024	*Revised: June 8, 2024*	*Accepted: June 12, 2024*

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CASE REPORT

PYLORIC ATRESIA ASSOCIATED WITH EPIDERMOLYSIS BULLOSA- A CASE REPORT

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Pyloric atresia is a rare congenital condition marked by obstruction of the gastric outflow because the pylorus is absent or severely narrowed. Blistering and fragility of the skin and mucous membranes are symptoms of the hereditary condition epidermolysis bullosa (EB). It is highly uncommon for pyloric atresia and epidermolysis bullosa to co-occur, and this presents substantial diagnostic and treatment difficulties. We describe a case of a newborn who was born with pyloric atresia and epidermolysis bullosa, focusing on the clinical presentation, the diagnostic procedure, and the surgical therapy. The complex interactions between these two dissimilar illnesses highlight the value of a multidisciplinary approach combining neonatologists, dermatologists, and paediatric surgeons for precise diagnosis and thorough care. By sharing this case report, we hope to add to the limited literature on this particular set of congenital defects and highlight the importance of increased clinical awareness and team-based treatment approaches when dealing with cases this complicated.

Keywords: Pyloric atresia; Epidermolysis bullosa; Carmi syndrome; Heineke-Mikulicz pyloroplasty

Citation: Saleem A, Khan AM, Ahmed M. Pyloric atresia associated with epidermolysis bullosa- a case report. J Ayub Med Coll Abbottabad 2024;36(4):838–40.

DOI: 10.55519/JAMC-04-13593

INTRODUCTION

The inherited, variable group of uncommon genetic dermatoses known as epidermolysis bullosa (EB) is characterised by mucocutaneous fragility and blister development and is frequently brought on by minor trauma. Traditionally divided into EB simplex (EBS), junctional EB (JEB), Kindler EB, and dystrophic EB (DEB) according to the degree of basement membrane zone separation.[1] The narrowing of the pylorus and skin blistering are the predominant symptoms of Pyloric Atresia Associated with Junctional Epidermolysis Bullosa (PA-JEB), which is often severe and sometimes fatal in the neonatal era.[2] Only 91 cases of Epidermolysis Bullosa with Pyloric Atresia were reported up until 2012, the first case being reported in 1968.[3,4] Congenital localised absence of skin (aplasia cutis congenita) affecting the extremities and/or head, milia, nail dystrophy, scarring alopecia, hypotrichosis, and corneal abnormalities are additional characteristics shared by Epidermolysis Bullosa with Pyloric Atresia and the other primary forms of epidermolysis bullosa[5]. Surgery for pyloric atresia is only successful for short-term survival. The long-term prognosis of pyloric atresia associated with epidermolysis bullosa is nearly always poor, and the majority of patients die from epidermolysis bullosa related complications.[4] This paper's goal is to describe a severe case of pyloric atresia linked to epidermolysis bullosa.

CASE PRESENTATION

A three-day old baby girl was brought to the paediatric unit with multiple skin lesions (shown in figure-1) and difficulty with respiration for the last 24 hours. Antenatal history revealed that mother had polyhydramnios and gestational diabetes prenatally and emergency caesarean section at 37 weeks of pregnancy done due to foetal distress. Baby was doing well after delivery and was discharged to mother care. No skin lesions noted by parents or doctor at that time.

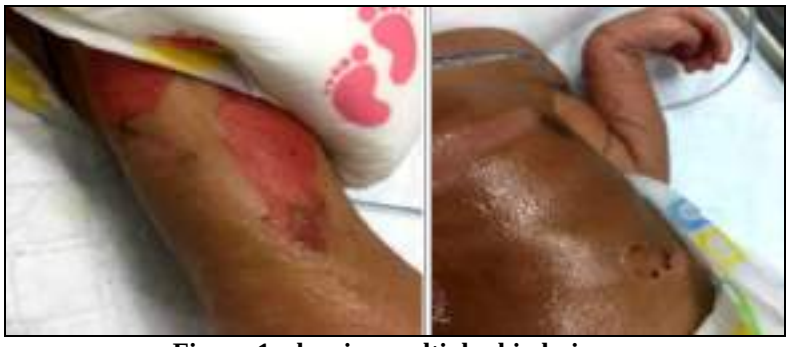

Figure-1: showing multiple skin lesions

On examination, the infant appeared sick, subcostal and suprasternal recessions were noted, bilateral creps with predominance to the right side noted. There were four blistering lesions on the lower limbs, one on the nose tip, and two on the scalp. It did not affect the oral mucosa. The dermis beneath was red, but there was no bleeding or discharge. The Nikolsky sign was positive with blistering in areas of friction. Lesions on the scalp and lower limbs were more prevalent, measuring 2-3 cm in diameter and blistering. The remainder of the exam was unremarkable. Her anthropometric data fell below the 10th percentile, with weight of 2.5 kg, FOC of 13.3 inches and length of 47 cm.

Initial management started with baby kept nil per oral, NG tube passed, oxygen support was given, intravenous maintenance fluids started and labs and chest x-ray ordered. Antibiotics started on injectable Cefotaxime and Amikacin as per local NICU initial protocol. Labs were grossly normal, but the chest x-ray revealed multiple bilateral infiltrates with marked right upper zone involvement. Baby also noted to have a large single gas bubble in the stomach area with no gas shadow distally. (Figure-2)

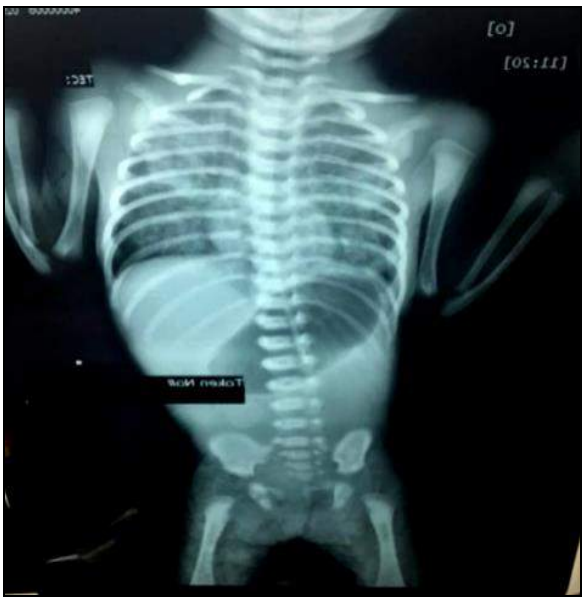

Figure-3: A large single gas bubble in epigastric region

Opinion from Paediatric Surgery and dermatology department sorted. Dermatology opinion was in favour of Epidermolysis Bullosa Junctional Variety and advised skin biopsy once child is stable, local application of fucidin cream and daily dressing. A paediatric surgeon's opinion was in favour of pyloric atresia. Antibiotic regime changed to IV Cefotaxime, Vancomycin and Metronidazole. Surgery for pyloric atresia planned.

Surgery done on day 10 of admission. During the procedure pyloric atresia-web type was noted with an underutilised small bowel; as a result, Web excision and pyloroplasty were performed on the baby. She was released from the hospital seven days after the surgery with an uneventful postoperative course. Parents were called for the follow up but there was no response from them. However, they came to the dermatology OPD post-surgery with complaints of multiple skin lesions. She was admitted in ICU with sepsis but unfortunately, she expired during her stay at the hospital. Skin biopsy was a part of the plan but it was never done.

DISCUSSION

Swinburne and Kohler provided the first description of Pyloric atresia and Epidermolysis Bullosa coexistence in 1968. Since Carmi proposed the pathophysiology of the condition, it is also known as "Carmi syndrome".[6] Histopathologic analyses and observation of recognisable clinical signs are used to make the diagnosis of Epidermolysis Bullosa. It is possible to use ultrasonography to diagnose pyloric atresia in utero. Starting at week fourteen of pregnancy, anatomical stomach traits can be investigated. The connection of polyhydramnios with stomach expansion is usually used to make the diagnosis. Our patient also experienced polyhydramnios during pregnancy. Additionally, patient with this condition also presents with clinical signs such as non-bilious vomiting, respiratory distress, dehydration, and abdominal distension.[7]

Patients with Epidermolysis Bullosa associated with Pyloric Atresia may also experience gastrointestinal, urinary, lung, ocular, and kidney difficulties (dysplastic/multicystic kidney, hydronephrosis/hydroureter, ureterocele, duplicated renal collecting system, missing bladder),[4–8] while our patient presented with pyloric atresia only. The junctional group is where Pyloric Atresia is most typically connected to the bulk of CEB types. Despite surgical treatment, this relationship is a diverse disease with significant fatality rates that approach 100%,[9] that, despite surgical repair, can cause mortality within a few months of birth.[7]

A literature search turned up just one case report in Pakistan describing the connection between Pyloric atresia and Epidermolysis Bullosa. (The Aga Khan University's Surgery Department)[10] A history of gestational diabetes is reported in many case reports, as well as in our patient, but its importance is unknown[11]. There have been a number of familial examples of pyloric atresia recorded, however our patient has no known substantial family history of the condition.[12] Epidermolysis Bullosa with pyloric atresia is an autosomal recessive trait and our patient

was a product of consanguineous marriage too. ITGA6, ITGB4, and PLEC gene mutations are among the potential causes of this. These genes give instructions on how to produce proteins that are essential for the skin and digestive system. About 80% of instances of this condition are caused by mutations in the ITGB4 gene, while only 5% of cases are caused by mutations in the ITGA6 gene.[13]

The management of EB with pyloric atresia lacks established treatment options. The therapies are primarily symptomatic and include conservative measures including the use of the proper dressing, infection prevention, and dietary supplements. Steroids used topically may be used to treat localised inflammation.[14] Treatment for pyloric atresia includes correcting dehydration and biological irregularities, followed by a pyloroplasty procedure that removes the diaphragm. The most widely utilised procedure is the Heineke-Mikulicz pyloroplasty.[15] The prognosis of this condition is poor despite surgical therapy for concurrent pyloric atresia due to nutritional disruption, absorption disruption, and in many cases, the advancement of sepsis. As a result, aggressive surgical treatment is frequently postponed in EB patients who also have pyloric atresia. According to a recent study, however, four out of every five patients who presented with stable vital signs tolerated treatment well following surgery.[14]

Without timely and appropriate treatment, pyloric atresia (PA) and EB are a fatal combination, often leading to death. Severe skin denudation can cause complications such as septicaemia, electrolyte imbalance, protein loss, and dehydration, which contribute significantly to poor outcomes. Even with treatment, the prognosis remains guarded due to the risk of complications, including urologic issues like ureterovesical blockage, underscoring the importance of routine follow-up.[4]

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Submitted: July 14, 2024	*Revised: November 18, 2024*	*Accepted: November 20, 2024*

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SPECIAL COMMUNICATION

BUILDING CAPACITY AND ENHANCING KNOWLEDGE OF THE HEALTHCARE PROVIDERS REGARDING HEALTHCARE FINANCING IN PAKISTAN

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Background: The Office of Research, Innovation, And Commercialization (ORIC) of the Health Services Academy in Collaboration with the Punjab Employees Social Security Institution (PESSI) and the German Corporation for International Cooperation (GIZ) organized and conducted a 2-day training workshop on "Healthcare Financing". This was intended to learn about healthcare finance by analyzing government regulations, private companies, and international collaboration. Explore various funding sources for healthcare, observe how healthcare operates around the world, and devise effective money management strategies so that healthcare can expand and benefit everyone. **Aims:** This paper reports on the training program, which aims to train healthcare providers on the concepts of healthcare financing and build their understanding and knowledge of healthcare systems, models, and implementation of intelligent financing strategies for sustainable financial growth and organizational success. **Methods:** A team of experts developed the curriculum and its accompanying material. Initial training was given to the healthcare providers of all participating institutions. Staff from public and private hospitals enrolled in the training and other frontline healthcare workers were invited. Four types of educational material were produced and used; a guidance booklet, a training video, and a set of PowerPoint presentations to explain the HCF and its importance. **Results:** A 2-day training workshop was conducted in which the pre- and post-knowledge regarding the HCF of all the participants was assessed. All the participants belonged to public health fields and all of the participants were public health experts. **Conclusion:** With limited resources and in a short period, the ORIC with the collaboration of PESSI and GIZ trained a good amount of healthcare workers to address the complex challenges and opportunities within the industry and key aspects of healthcare financing, from the evolving payment mechanisms and emerging trends to the global perspective on funding health initiatives

Keywords: Healthcare; Trainings; Workers; Health

Citation: Naeem N, Aslam R, Kumar N, Raza I, Naeem K, Kumar R. Building capacity and enhancing knowledge of the healthcare providers regarding healthcare financing in Pakistan. J Ayub Med Coll Abbottabad 2024;36(4):841–3.

DOI: 10.55519/JAMC-04-13995

INTRODUCTION

Health financing is concerned with the generation, allocation, and utilization of financial resources in healthcare systems. One of the key changes confronting the national health system is the scarcity of funds to deliver health services. Pakistan's total per capita expenditure in 2013 was US$ 37, with the government spending 37% (US$ 13.7), the remainder being out-of-pocket payments by individuals and households (55%), and those from external sources (7%). Total health expenditures as a percentage of gross domestic product are 2.8%.[1,2]

Implementing national health insurance plans is supposed to minimize individuals' and households' out-of-pocket expenses and protect against catastrophic costs. Furthermore, the various models of Public-Private Partnerships will play a role in increasing the efficiency of system operations, which are likely to be reproduced and mainstreamed in many service delivery sectors.[3]

The focus of WHO assistance is to promote and advocate for increased resource allocation and mobilization toward UHC attainment through advocacy, national health finance policy formulation, and promotion of PPP schemes. National and provincial advocacy efforts to boost resource allocations, assistance to national health insurance plans, Examine and encouraging the replication of public-private

partnership projects, and creating a national health finance policy are some of the examples.[4]

Challenges in global health financing include the difficulty in procuring funds for global public goods, health systems strengthening, and long-term investments in global health.[5] However, when structured well, these types of investments can have robust and sustainable returns. There is also a need to address issues of volatility, fragmentation, and fungibility in health aid. Despite progress, global health financing faces numerous challenges.[6]

To understand these concepts and overcome the financial burden on health systems, the Office of Research, Innovation, And Commercialization (ORIC) in collaboration with Punjab Employees Social Security Institution (PESSI) and the German Corporation for International Cooperation (GIZ) arranged and disseminated a two-day training on the healthcare financing. This training aimed at developing a profound understanding of the key principles of healthcare financing, the influence of government policies, private sector involvement, and international collaborations on healthcare financial landscapes, and advanced financial management techniques and implementation of intelligent financing strategies for sustainable financial growth.

METHODS

Training program: The purpose of this training was to train the healthcare workers on healthcare financing techniques and how these techniques can be used to generate and manage funds for the betterment of healthcare systems and communities that they serve.

Program design: The ORIC of Health Services Academy, an established national in-service training, research, and academic institution attached to the Ministry of National Health Services, Regulation, and Coordination, in collaboration with PESSI and GIZ, undertook this training program. It called the participants belonging to various fields of medicine and healthcare and from different healthcare institutions such as NIH etc. A team of experts in designing and delivering healthcare training developed the curriculum and its accompanying material. The Health Services Academy maintained a list of registered participants and those who completed the training, and supported activities throughout

Training material: Three educational materials were produced: a curriculum booklet, documentary videos, and PowerPoint presentations to explain the HCF and its importance. The guidance booklet was a reference document for each participant and contained details of HCF that can be practiced according to the type of expenditure, funding, or any financial activity. The training videos were short documentaries on the history and trends of HCF. The PowerPoint presentation slides had a detailed description and in-depth knowledge about Healthcare Systems and Models, government and private sector financing, healthcare payment mechanisms, global health financing, smart financing strategies, and emerging trends and innovations.

RESULTS

The training was given to the healthcare workers and public health practitioners. The training lasted for 2 days. A pre and post-test was conducted to evaluate their knowledge before they took the training and after the training. Before the onset of the training, a pre-test was conducted on all the participants (Figure-1). Then the training on different modules of HCF was disseminated to them. The knowledge of the participants was built and on day 2 the participants were given a post-test (Figure-2).

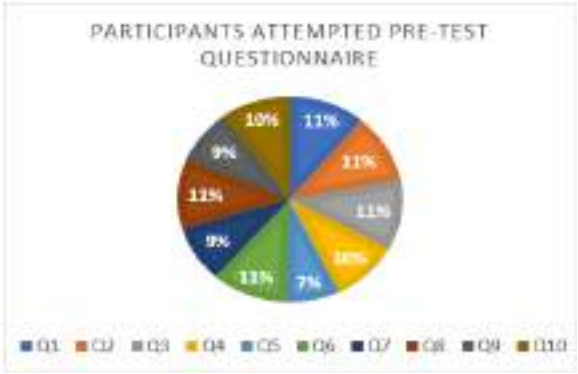

Figure-1

Figure-2

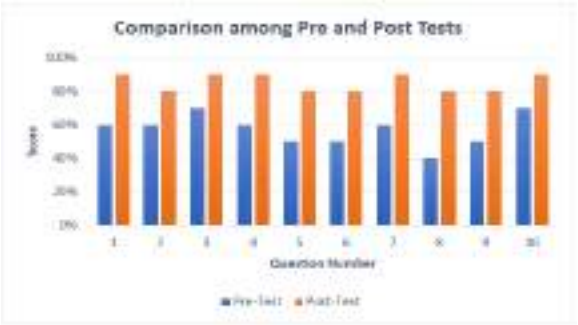

Figure-3

The success of this practice is reflected in the Figure-3. This shows that the knowledge of the participants on HCF before the training was very low which enhanced to an exemplary level after the session. This recommends that if such training sessions are arranged and disseminated, we can produce more knowledgeable healthcare professionals concerning HCF strategies and decision-making.

DISCUSSION

Healthcare staff must be knowledgeable about healthcare financing to allocate resources effectively and make sound decisions. However, research reveals that financial literacy among healthcare workers might be inadequate, emphasizing the necessity for adding finance management into the curriculum of healthcare-linked courses.[7] This is especially crucial for physician leaders, who face specific financial strains in the healthcare system, particularly in the context of budgetary problems caused by COVID-19.[8] Improving financial health literacy and knowing the costs of healthcare are also necessary for shared decision-making and patient engagement.[9] Nurses, in particular, are encouraged to enhance their knowledge of healthcare finance to better grasp its relationship to patient care and organizational financial health.[10] Effective financial management in healthcare is critical for managing the industry's rising complexity and navigating difficulties such as regulatory compliance, cost reduction, and asset management.

This training session aimed at enhancing the knowledge of the healthcare providers regarding the HCF and catastrophic spending and purchasing. Through the 2-day training, using the HCF curriculum, PowerPoint slides, and documentaries, the knowledge of the HCPs was enhanced and that was evident from the results. The knowledge of the participants was enhanced after training.

CONCLUSION

From the literature and practices, it can be seen that how the funding in the healthcare is complicated. Expert insights give light on critical aspects of healthcare financing, such as evolving payment methods, emerging trends, and a global perspective on funding health programs. Policymakers and stakeholders must understand various healthcare models, funding mechanisms, and the influence of social variables on health outcomes. Smart financing solutions, such as innovative investments and fair healthcare funding, are critical for maximizing resources for long-term and favourable health outcomes. These debates illustrate continuous efforts to strike a balance between economic principles, cost-effectiveness, and the ethical imperative for equitable access to healthcare. In short, navigating the evolving terrain of healthcare funding necessitates collaboration, adaptation, and a complete understanding of how economic forces, social considerations, and ethics work together to produce a healthier and more equitable world.

ACKNOWLEDGMENT:

We extend gratitude to all of the training facilitators who contributed to the sessions.

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Submitted: October 30, 2024	*Revised: November 18, 2024*	*Accepted: November 21, 2024*

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