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Editorial

Climate Change and its Impact on Health in Pakistan

Uzma Ahsan

For developing countries like Pakistan, climate change is no longer a distant threat; it is a lived reality with profound and far-reaching consequences. Due to its geographical and socio-economic characteristics, Pakistan is among the countries most at risk from climate change, with the health implications of this crisis becoming more apparent.[1]

The Climate Landscape of Pakistan

Pakistan faces a number of climate-related problems such as rising temperatures, unpredictable rainfall patterns, glacier melting, and an increase in the frequency and intensity of natural disasters including droughts and floods. The Global Climate Risk Index ranked Pakistan among the top ten countries most affected by extreme weather events over the past two decades.[2] These climate changes are not only threatening livelihoods and environment but also posing significant risks to health.

Pakistan is a land of divergence and heterogeneity owing to its dry lands and mountain ranges, and its expansive network of rivers, streams, and lakes. All these features make it prone to be affected by the detrimental effects of climate change. Fast paced urban migration and poor infrastructure further contribute to the susceptibility of people to extreme weather changes. The majority of the population residing in rural areas faces the direct brunt of unreliable and inconsistent rainfall and accelerating temperatures that directly affect the produce and sustainable income.[1]

Disease Burden and Health Problems Linked to Climate Change

The healthcare ecosystem in Pakistan has experienced a sharp escalation in various illnesses that are related to climate change in one way or another. For instance, there is a significant rise in diseases related to intense heat waves, like heat stroke and dehydration. In 2015, the intense heat wave in Karachi led to the death of more than 1200 people, highlighting the susceptibility of the population to these life-threatening conditions.[3]

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Additionally, significant spike in vector-borne diseases have also been reported in 2019-2022, primarily due to prolonged monsoon rains and hot humid temperatures, making ideal breeding conditions for mosquitoes and eventually producing a significant surge in patients with dengue fever and malaria. These diseases were particularly on the rise in the areas where previously they were not very common, indicating shift of the disease vectors/mosquito as a result of rapidly changing climate patterns.[4]

Similarly, a rise in water-borne diseases emerging in flood affected areas has been observed. In 2022 flood, cholera, typhoid, and diarrhea became endemic as millions of people were exposed to contaminated water supplies mixed with already existing poor sanitation by the catastrophic floods. All these factors significantly contributed to an upsurge of these deadly water-borne illnesses.[5]

Another byproduct of climate change and accelerated urbanization is increasing air pollution, causing a significant rise in respiratory diseases like asthma and bronchitis. Prolonged droughts and dust storms, particularly in Southern Punjab and Sindh, have increased the susceptibility of people living in these areas to hypersensitivity airway diseases.[6]

This is a significant concern over increasing malnutrition. Climate changes have indirectly affected agricultural productivity, leading to a decline in food availability and inflation. This is reflected as high rates of malnutrition in vulnerable populations like children and pregnant females. This also contributes to weaken their immune system leading to high incidence and susceptibility to infections and diseases.[3]

The Psychological Toll

The impact of climate change on mental and emotional well-being is frequently ignored despite the fact that it causes apprehension, anxiety, and depression in the affected population. The majority of the rural population faces the challenges of reduced production from agricultural land due to extreme variations in environmental factors. This not only adds to their struggle to strive for resources but also puts them in additional financial stress. All of the factors mentioned above contribute to emotional trauma and desperateness, which can cause a rise in suicide rates. This emotional and psychological toll affects the adult and pediatric population equally. Children exposed to repeated climate calamities are likely to suffer from psychosomatic issues, including post-traumatic stress

disorder. Altogether these factors increase the susceptibility of enhanced psychological stress to already marginalized populations who are striving with limited resources.[3]

Tackling the Test

Pakistan must undertake a multi-faceted approach to fight the challenges of global warming related to healthcare.

1. **Enhancing Healthcare Infrastructure:**
   To meet the challenges of climate-induced health crises, an improved infrastructure and human resources are needed in public health. Measures should be taken to improve disease surveillance, fortify the availability of medical supplies along with focus on improving the training of healthcare workers to respond effectively in such disasters. These objectives can be achieved through adequate funding and interdisciplinary collaboration.[1]
2. **Improving Climate Resilience:**
   Once a natural disaster hits a particular population, exposure of the population to extreme weather situations can be reduced by the availability of climate-resilient substructures, such as heat-resistant accommodations and flood defenses. Inhabitants of the areas which are at high risk or prone to floods and other natural disasters must be provided with early warning systems and effective evacuation plans to minimize health risks.[2]
3. **Encouraging Awareness:**
   Public awareness campaigns can sensitize the susceptible communities to take preventive measures against the hazards of natural disasters and climate change. For instance, enhancing awareness about the significance of mosquito control can help restrain the spread of dengue and malaria.[5]
4. **Policy and Advocacy:**
   National health and environment protection policies must incorporate measures to acquire international support for climate protection. Resources and energies must be directed to promote environmental protection and gain access to international climate funds to address the financial burden it faces.[5]
5. **Research and Data Collection:**
   Sustainable measures must be taken to improve the quality of research, particularly in relation to climate change and health hazards in Pakistan. This is crucial for policy-making and targeted interventions. Tailored solutions based on information about geographical susceptibilities and health tendencies will ensure an improved outcome in the masses.[6]

CONCLUSION

Health hazards and disease risks due to climate change pose a continuous threat to the population at risk and require immediate consideration and action. For Pakistan, the stakes are high. In the current era of global warming, the country's ability to safeguard the health and well-being of its citizens depends on coordinated efforts at local, national, and international levels. National participation in support of climate protection measures and public health today will not only save lives but also ensure an improved, more supportable future for generations to come.

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Original Article

Psychometric Assessment of Burnout among Physicians and Nursing Staff Working in the Medicine Department of a Tertiary Care Hospital

Abdul Hameed Soomro, Rizwan Ahmed, Muaz Mubashir, Hassan Atique, Hammad Hussain Sadqi, Ali Hassan

ABSTRACT

Objective: To determine the frequency of burnout among physicians and nursing staff working in the Medicine Department of a public sector tertiary care hospital.

Methodology: This descriptive cross-sectional study was conducted at the Department of Medicine, Federal Postgraduate Polyclinic Hospital, Islamabad from June to December 2022 after ethical approval. After obtaining informed consent, 89 physicians/consultants, residents, and nursing staff working in the Medicine Department were included using non-probability convenient sampling technique. A semi-structured questionnaire consisting of sociodemographic details and the Copenhagen Burnout Inventory (CBI) was distributed. The scale measures burnout based on 3 scales; personal burnout scale (PBS), work-related burnout scale (WRBS), and client-related burnout scale (CRBS). In order to calculate burnout, a mean score >50 was regarded as burnout. The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 25.

Results: The mean age was 32.63±7.50 years. Among 89 participants, 24(27%), 40(44.9%), and 25(28.1%) were consultants, resident doctors, and nurses, respectively. The mean CBI score was 52.10±4.16 and the mean PBS, WRBS, and CRBS scores were 62.17±7.09, 53.97±6.17, and 40.17±8.89, respectively. The frequency of burnout among consultants was 12(50%), while among resident doctors and nurses was 32(80%) and 20(80%), respectively.

Conclusion: A high percentage of healthcare workers are affected by burnout. The frequency of burnout is much higher in resident doctors and nurses as compared to consultants. However, the mean scores of CBI are higher among consultants followed by resident doctors and nurses.

Keywords: *Burnout. Physicians. Nursing Staff. Consultants.*

INTRODUCTION

According to the World Health Organization (WHO), burnout is defined as "a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed". Burnout is labelled as "occupational phenomenon" in the 11th revision of the International Classification of Disease (ICD-11th edition) issued by WHO. Burnout usually targets dedicated and committed individuals resulting in emotional and motivational deterioration.[1] The burnout results not only in mental health problems but also physical exhaustion and ultimately affecting the whole workplace. It consists of physical and mental exhaustion, indifference towards work, and lack of personal accomplishment.[2]

The challenging and demanding nature of medicine acts as a risk factor for burnout among the medical staff. Over the past few years, there has been a huge surge in mental illnesses and suicide rates in the medical community.[3] Shanafelt et al. compared burnout among physicians with other professions having equivalent educational degrees and reported a high prevalence of burnout among physicians.[4] Apart from the clinical duties, education, research, and administrative responsibilities play a pivotal role in the burnout of physicians.[5] Nurses are also not safe from the detrimental effects of burnout. Literature reported an increased burnout-depression among nurses. The potential reasons for burnout among nurses are excessive workload, understaffing, and long shifts.[6,7] Burnout is contagious, affecting the medical staff personally and eventually it impairs the provision of quality of care to the patients even leading to malpractice and medical negligence.[8]

Almost one in three physicians is experiencing burnout these days. In Pakistan, a few studies have been conducted to estimate burnout among physicians and nursing staff, separately. A study conducted in Peshawar reported burnout in 25.39% of the physicians.[9] On the other hand, a study conducted in Lahore estimated a burnout rate of 33% among military doctors only. Contrary to this, Andlib et al., reported a prevalence of 48.6% among nurses.[10] However, there is a lack of studies comparing burnout among physicians and nursing staff working in the same department. Thus, the rationale of this study was to determine the frequency of burnout among physicians and nursing staff working in the Medicine Department of a public sector tertiary care hospital. The study would

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provide valuable insight into the magnitude of burnout among healthcare workers in our local setup so that we can implement training programs to prevent burnout among them.

METHODOLOGY

This descriptive cross-sectional study was conducted among the physicians, residents, and nursing staff working at the Medicine Department of Federal Postgraduate Polyclinic Hospital, Islamabad from June 2022 to December 2022. After getting ethical approval (Letter No. F004/09-2018, 06-06-2022) from the institution, 89 physicians/consultants, residents, and nursing staff working who gave informed consent were included using non-probability convenient sampling technique. However, those on rotations in other departments, vacation, and having employment duration of less than 6 months were excluded. House officers were also not included in this study as they are employed for a fixed term of 3 months only. A semi-structured questionnaire consisting of sociodemographic details and Copenhagen Burnout Inventory (CBI) was distributed among all the included participants. The sociodemographic details included age, gender, designation, marital status, duration of employment, and graduation status (local versus overseas). Copenhagen Burnout Inventory was used to measure the psychometric properties of burnout. It measures burnout based on 3 scales; personal burnout scale (PBS), work-related burnout scale (WRBS), and client-related burnout scale (CRBS). The personal burnout scale assesses the level of burnout in people and comprises six items. The work-related burnout scale assesses the attribution of exhaustion and fatigue experienced due to work and consists of seven items. The client-related burnout scale comprises six items and assesses whether fatigue and exhaustion are attributed to work involving clients, such as patients, students, or similar groups. In order to calculate burnout, a mean score >50 was regarded as burnout.[11]

STATISTICAL ANALYSIS

The data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 25. Categorical data was presented using frequencies and percentages, while continuous variables were described as mean±standard deviation (SD). Mean values for each subscale of CBI were calculated according to the scoring system. One-way analysis of variance (ANOVA) was used to compare CBI and its scales among consultants, resident doctors, and nurses. The post-hoc Tukey's test was applied to determine which groups were significantly different. A p-value of <0.05 was considered statistically significant.

RESULTS

The mean age was 32.63±7.50 years. The majority of the population under study comprised males 49(55.1%). Among the 89 participants, 24(27%), 40(44.9%), and 25(28.1%) were consultants, resident doctors, and nurses, respectively. Forty five (50.6%) subjects were married and 44(49.4%) were single. Eight (9%) of the participants were foreign graduates. The majority 64(71.9%) of the working staff had less than 10 years of experience at the workplace.

According to our analysis, the mean CBI score was 52.10±4.16 and the mean PBS, WRBS, and CRBS scores were 62.17±7.09, 53.97±6.17, and 40.17±8.89, respectively. The frequency of burnout (CBI scores ≥50) among consultants was 12(50%), while among resident doctors and nurses was 32(80%) and 20(80%), respectively (p-value=0.02). There is a significant difference in the mean CBI, PBS, and WRBS scores among consultants, resident doctors, and nurses (p-value=0.008).

Despite the ANOVA indicating a significant overall difference among the groups (p=0.008), the Post-Hoc Tukey's test reveals that none of the pair-wise group comparisons (consultants vs. resident doctors, consultants vs. nurses, resident doctors vs. nurses) was statistically significant which may be due to small sample size.

Table 1: Distribution of Mean Burnout Scores according to CBI

CBI Scores	Consultants	Resident Doctors	Nurses	p-value
Overall CBI (Mean±SD)	52.80±6.01	52.11±3.73	51.42±2.31	0.008*
Personal Burnout (Mean±SD)	54.69±5.67	67.29±4.68	61.17±4.12	0.01*
Work-Related Burnout (Mean±SD)	58.93±6.23	55.71±2.89	46.43±1.80	<0.001*
Client-Related Burnout (Mean±SD)	44.79±8.27	33.33±4.62	46.67±6.80	0.518

**Significant p-value*

DISCUSSION

Burnout has profound impact on mental and physical health. Burnout is a syndrome resulting from poorly managed chronic workplace stress. It is characterized by feelings of exhaustion or depleted energy, increased mental detachment from one's job, negativity or cynicism towards work, and a sense of ineffectiveness or lack of achievement.[12] In our study, the mean age was 32.63±7.50 years with the majority of males 49(55.1%) and married 45(50.6%) participants. In comparison to this, a study conducted at KRL Hospital, Islamabad reported a mean age of 28.07±2.87 years with the majority of females (68.3%).[12] A study conducted in Hong Kong reported similar results with a mean age of 34.1±6.0 years, mostly married (55%) and female population of 43.6%.[13]

In our study, we found that overall CBI mean scores were higher among consultants (52.80±6.01) followed by resident doctors (52.11±3.73) and nurses (51.42±2.31), respectively. Such high burnout scores could be attributed to stressful environments, extreme workload, staff shortages, poor pay scales, poor communication among healthcare professionals, and higher expectations of the patients.[14]

According to our study, 50% of the consultants had burnout. The mean score of CBI among consultants was 52.80±6.01. The mean scores of the personal burnout scale, work-related burnout scale, and client-related burnout scale were 54.69±5.67, 58.93±6.23, and 44.79±8.27, respectively. A study conducted among Lebanese consultants showed 90.1% prevalence of burnout. They also reported higher mean scores of CBI (65.34±17.39), and its subscales i.e. personal burnout scale, work-related burnout scale, and client-related burnout scale of 64.80±17.32, 71.50±16.33, and 58.70±16.14, respectively.[15] On the other hand, a meta-analysis comprising 13 studies estimated a 40% prevalence of burnout in emergency medicine doctors.[16] Another study conducted in Islamabad measured burnout by the Maslach Burnout Inventory scale and reported burnout in 34.6% of the doctors.[12]

A study conducted among resident doctors of various departments using the Oldenburg Burnout Inventory showed a prevalence of 7.2% for disengagement and 51.1% for exhaustion.[17] However, our study showed that 80% of the resident doctors were facing burnout with high personal burnout scale and work-related burnout scale mean scores of 67.29±4.68 and 55.71±2.89, respectively. Comparable results were also found in a study conducted by Majeed et al. using CBI which concluded that more than 50% of the resident doctors had burnout. This study also found high mean scores in the domains of PBS and WRBS.[18] In contrast to our results, a meta-analysis using a pool of 114 studies estimated a global burnout prevalence of 47.3% among resident doctors. However, this meta-analysis has documented limitations in the calculation of burnout prevalence due to significant heterogeneity in the burnout prevalence across different regions of the world.[19] A study was conducted in Kenya to evaluate burnout in 95 postgraduate residents. Forty five (47.3%) residents had a high risk of burnout. The study also reported a high prevalence of burnout in postgraduate residents working in the Pediatrics & Clinical Health Department.[20]

Our results reported burnout in 80% of the nurses. The personal burnout scale, work-related burnout scale, and client-related burnout scale mean scores in the current study were 61.17±4.12, 46.43±1.80, and 46.67±6.80, respectively. On the other hand, a study conducted among nurses working in Jeddah estimated a burnout prevalence of 44.8%. They reported low prevalence due to limitations in approaching the nurses in the COVID-19 era.[21] An Indian study reported an 83% prevalence of burnout in nurses using a self-reported burnout inventory scale, which is comparable to our results.[22] A study conducted in Greece documented personal burnout scale, work-related burnout scale, and client-related burnout scale scores of 50.14±19.63, 52.88±22.07, and 38.49±22.92, respectively in nurses.[23] According to an Egyptian research, 26.8% of nurses and 22.6% of physicians suffered from burnout syndrome. Workload, workplace incivility, and work-life conflicts are the major contributors to burnout syndrome.[24] A cross-sectional study conducted on 200 medical and auxiliary staff showed that the majority of the resident doctors (42%) had high levels of burnout and nurses were least affected (26.5%).[25]

CONCLUSION

Our study concluded that a high percentage of healthcare workers are affected by burnout. The frequency of burnout is much higher in resident doctors and nurses as compared to consultants. However, the mean scores of CBI are higher among consultants followed by resident doctors and nurses.

LIMITATIONS & RECOMMENDATIONS

The sample is small and it is a single-centered study conducted among physicians and nurses of a single department of a tertiary care hospital, so generalization of the results is limited. As the

number of subjects distributed by designation is not the same so, an effective comparative analysis cannot be carried out.

We recommend a multicenter study assessing and comparing burnout across different specialties among physicians and nurses. A lack of interest in the mental health of physicians, residents, and nurses can have detrimental effects on the patients. The hospital administration should run a burnout survey across all the departments to have a generalized idea about burnout among the doctors and nurses. Furthermore, a policy should be made to deal with this issue. Preventive measures such as training programs should also be conducted to prevent burnout.

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Authors' Contributions:
A.H.S: Substantial contributions to study design, acquisition of data, manuscript drafting, and final approval
R.A: Substantial contributions to analysis, and interpretation of data, critical review, and final approval
M.M: Study design, concept, critical review, and manuscript writing
H.A: Study design, concept, critical review, manuscript writing, analysis, and final approval
H.H.S: Data analysis and critical review
A.H: Study design, concept, critical review, and manuscript writing

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Original Article

Diagnostic Accuracy of Unenhanced Focused Abdominal Computed Tomography in Clinically Suspected Cases of Acute Appendicitis with Histopathology as the Gold Standard

Ashok Kumar, Rizwan Ajmal, Jawaid Iqbal, Rabiya Siraj, Quratulain Haroon, Muhammad Junaid Tahir

ABSTRACT

Objective: To evaluate the diagnostic accuracy of unenhanced focused abdominal computed tomography (FACT) in clinically suspected cases of acute appendicitis with histopathology as the gold standard.

Methodology: This cross-sectional study was carried out at the Radiology Department of Liaquat National Hospital, Karachi from August 2022 to February 2023 after ethical approval. A total of 196 patients presenting to the emergency department with complaints of acute abdominal pain were chosen using a non-probability consecutive sampling method. Alvarado scoring was used to confirm the acute appendicitis clinically. Radiology reports of unenhanced focused abdominal computed tomography were examined for features of appendicitis. The resected samples were dispatched for histopathological examination following appendectomy. The final diagnosis was recorded as a normal appendix or acute appendicitis. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FACT were evaluated using histopathology as a gold standard. Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0.

Results: The mean age of patients was 39.14 ±11.43 years and 110(56.1%) participants were males. The mean duration of signs and symptoms was 1.80±0.76 days and the mean Alvarado scoring was 5.47±0.50. The findings indicated that 77(39.3%) patients were true positive (TP) and 102(52%) patients were true negative (TN). The sensitivity, specificity, PPV, NPV, and diagnostic accuracy of FACT in comparison to histopathology were 89.5%, 92.7%, 90.6%, 91.9%, and 91.3%, respectively.

Conclusion: The FACT possesses considerable sensitivity, specificity, and diagnostic accuracy for diagnosing acute appendicitis. It proves to be a valuable and reliable diagnostic tool, capable of reducing the negative appendectomy rate and facilitating timely and accurate diagnosis, particularly in clinically suspected cases. Furthermore, using non-enhanced FACT scan leads to reduced costs, quicker imaging access, lower radiation exposure, and fewer risks from contrast mediums.

Keywords: *Appendicitis. Appendectomy. Sensitivity & specificity. Radiography. Pathology.*

INTRODUCTION

Acute appendicitis commonly presents as abdominal pain in adult and pediatric populations in the emergency department.[1] Acute appendicitis has an incidence rate of 233 per 100,000 population annually with a risk of 6.7% to 8.6% during a lifetime and similar prevalence rates among males and females. The appendectomy either through open or laparoscopic surgery is the definitive management for acute appendicitis.[2]

The removal of a normal appendix through surgery is a common surgical diagnostic error and is termed as negative appendectomy. It is usually defined as macroscopically or histologically normal appendix with no evidence of pathological inflammation such as infiltration of mucosa by inflammatory cells.[3] A higher negative appendectomy rate (NAR) of 29.5% had been reported in females attributing to a broad spectrum of pathologies presenting with the right iliac fossa (RIF) pain. This is especially true in women of reproductive age with 30.4% NAR. Significant morbidity arises from various complications such as infection of the wound, infertility caused by damage to fimbriae, and a heightened risk of postoperative intra-abdominal adhesions. A negative appendectomy during pregnancy is also a significant hazard to the fetus.[4]

Acute appendicitis requires the most common clinical diagnostic accuracy tool for the diagnosis. Various scoring systems have been proposed such as the Alvarado, deDombal, Lintula, and RIPASA scores.[5] The appropriate history and physical examination had an approximately 80% accuracy for diagnosis of acute appendicitis. Specifically, for males and females, this accuracy ranges from 78% to 92% and 58% to 85%, respectively.[6]

The preoperative diagnosis of acute appendicitis relies on radiological imaging for definitive diagnosis. The increased usage of preoperative ultrasonography and computed tomography (CT) greatly benefits the clinician in establishing an accurate preoperative diagnosis, decreases the NAR, and reduces the number of appendectomies.[7] Computed tomography has a greater sensitivity and NPV in old age for diagnosis of acute appendicitis. It is also associated with less NAR for females of any age group. However, radiological investigations prolong the duration of definitive diagnosis of the patient, expose the patient to radiation, and increase

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the financial cost of the treatment.[8]

Standard abdominal CT scans utilizing intravenous contrast can entail risks associated with the contrast medium and radiation exposure. As a result, there is a pressing need to create alternative scanning protocols that are lower in risk, especially for pediatric patients.[9] Focused abdominal computed tomography is characterized by the limitation of the imaging area extending from the L2 vertebra to the symphysis pubis, presenting various advantages over standard CT imaging. These advantages include a lower radiation dose, greater accessibility, independence from operator skill, relative ease of execution, and straightforward interpretation. Additionally, unenhanced non-contrast CT is particularly beneficial for patients who have compromised renal function or face challenges with intravenous access.[10] Moreover, employing a thin-section CT scan substantially advances the diagnostic accuracy of acute appendicitis through the detection of inflammatory changes in the vicinity of the appendix.[11]

Several studies indicated CT as a significant diagnostic tool for acute appendicitis and should be considered the radiological investigation of choice for suspected cases of acute appendicitis. However, the definitive preoperative investigation for appendectomy is still under investigation to prevent NAR and unnecessary surgical interventions. This research plans to investigate the effect of preoperative computed tomography on the NAR and the prevention of unnecessary surgical interventions and hospitalization. Furthermore, it might help in reducing the treatment and economic burden on the healthcare system. This study aimed to evaluate the diagnostic accuracy of unenhanced focused abdominal CT in cases of clinically suspected acute appendicitis, using the histopathology of postoperative specimens as the gold standard.

METHODOLOGY

This cross-sectional study was carried out at the Department of Radiology, Liaquat National Hospital, Karachi from August 2022 to February 2023. The ethical approval (Letter No. ERC/LNH-39/22, 10-07-2022) of the study was acquired from the institutional ethical review committee. Non-probability consecutive sampling technique was employed for the selection of the participants of any gender, aged between 15 to 60 years having the complaint of pain in the paraumbilical region or RIF and the Alvarado scoring of 5 or higher on clinical examination.[12] The patients with a history of appendectomy, pregnant females, Alvarado scoring of less than 5, and diseases presenting with a symptom of RIF pain as ureteric colic, right ovarian cyst, mesenteric adenitis, pelvic inflammatory disease, and others were confirmed on a thorough history, clinical examination, and relevant investigations before exclusion from the study. The prevalence rate of acute appendicitis is 44.27%.[13] Assuming the sensitivity and specificity of FACT to be 90% and 83.33%, respectively, a sample size of 196 was calculated with the 95% confidence interval and 7% desired precision.[11] The purpose of the study was fully explained before acquiring informed written consent from all the participants.

The demographic information of patients such as age, gender, body mass index (BMI), and duration of symptoms was recorded. Alvarado scoring is a clinical scoring system for the diagnosis of acute appendicitis comprising 8 components [abdominal pain migrating to RIF (score=1), anorexia (score=1), nausea (score=1), tenderness in RIF (score=2), rebound tenderness in RIF (score=1), fever (score=1), leukocytosis >10,000 (score=2), neutrophilia >70% (score=1)] with a total score of 10. A score below 5 excludes acute appendicitis; a score between 5 and 7 suggests a likely diagnosis, while a score above 7 indicates a strong likelihood of acute appendicitis.[12] The Alvarado scoring of each participant was calculated for clinical diagnosis of acute appendicitis. Later on, all patients with a confirmed diagnosis of acute appendicitis on clinical evaluation underwent FACT. The dilated appendix with a distended luminal diameter of more than 6 mm, thickened walls, and inflammation around appendix including stranding of adjacent fat and mesoappendix were labelled as acute appendicitis. All patients underwent open appendectomy through grid iron incision at Mcburnney's point. The resected sample of the appendix was sent for histopathological examination and was classified as a normal appendix or acute appendicitis. The histopathology reporting was ascertained for the final diagnosis. The clinical, histopathological, and radiological variables of each participant were recorded on a predesigned proforma. True positive refers to patients positive on both diagnostic modalities, while true negative refers to those negative on both diagnostic modalities. False positive (FP) indicates patients positive on FACT but negative on histopathology, and false negative (FN) indicates patients positive on histopathology but negative on FACT. The criteria for inclusion and exclusion were strictly followed to remove confounders and bias from this study.

STATISTICAL ANALYSIS

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 23.0. Frequency and percentage were utilized for qualitative variables such as gender and the diagnosis of appendicitis through FACT and histopathology. For the quantitative variables including age, duration of signs and symptoms, and the Alvarado score, mean±standard deviation (SD) was calculated. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FACT were evaluated with histopathology of specimens of the appendix as the gold standard. The stratification of age, gender, body mass index (BMI), duration of signs and symptoms, and Alvarado score was carried out to assess the effect of modifiers on post-stratification sensitivity, specificity, PPV, NPV, and diagnostic accuracy by using the Chi-square test. A p-value of ≤0.05 was considered significant.

RESULTS

The patients had a mean age of 39.14±11.43 years. Out of 196 participants, 110 (56.1%) were male and 86 (43.9%) were female. The mean BMI of the participants was 28.82±5.77 kg/m^2. The mean duration of signs and symptoms was 1.80±0.76 days and the mean Alvarado score was 5.47±0.50 (Table 1).

Eighty-six (43.9%) participants were diagnosed with acute appendicitis on FACT and 85(43.4%) on histopathology. Regarding the comparison of FACT with histopathology for the diagnosis of acute appendicitis, the sensitivity and specificity of FACT were 89.5% and 92.7%, respectively. The PPV of FACT was 90.6% and NPV was 91.9%. Furthermore, the diagnostic accuracy of FACT in comparison to histopathology was 91.3% (Table 2).

Post-stratification, the sensitivity of FACT was higher (91.8%) for ages less than 40 years as compared to individuals with age above 40 years. It was 100% for BMI ≥24.9 kg/m^2 as compared to 73.5% in patients with BMI <24.9 kg/m^2 (Table 3).

DISCUSSION

Acute appendicitis represents the most prevalent surgical emergency encountered globally, requiring prompt diagnosis to avert complications such as gangrene and perforation of appendix. Traditionally, diagnosis of acute appendicitis depends on the clinical examination of the patient, including the history of the patient, physical examination, and findings of investigations.[14] Nonetheless, atypical presentations can cause delays in treatment or result in unnecessary hospitalizations and surgical interventions. It is advisable to consider imaging for patients with atypical presentation, children, women of reproductive age, and older adults, particularly those aged 50 years and above.[1]

Table 1: Demographics of the Participants

Variables		Descriptive Statistics
Gender (Frequency and Percentage)	**Male**	110(56.1%)
	Female	86(43.9%)
Age (Years)	**Mean±SD**	39.14±11.43
BMI (kg/m^2)	**Mean±SD**	28.82±5.77
Duration of Signs & Symptoms (Days)	**Mean±SD**	1.80±0.76
Alvarado Score	**Mean±SD**	5.47±0.50

Table 2: Results of FACT and Histopathology for the Diagnosis of Acute Appendicitis

Diagnosis of Acute Appendicitis	Histopathology			p-value
FACT	**Yes**	**No**	**Total**	
Yes	77(90.6%) (TP)	8(9.4%) (FP)	85	<0.001*****
No	9(8.1%) (FN)	102(91.9%) (TN)	111	
Total	86	110	196	

**Significant p-value*

Table 3: Sensitivity, Specificity, PPV, NPV, and Diagnostic Accuracy of FACT with Demographic Variables

Variables		Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy	p-value
Age (Years)	**<40**	91.8%	85.3%	93.1%	82.9%	89.7%	<0.001*
	≥40	76.9%	96.1%	76.9%	96.1%	93.2%	<0.001*
Gender	**Male**	90.7%	91.1%	90.7%	91.1%	90.9%	<0.001*
	Female	87.5%	94.4%	90.3%	92.7%	91.8%	<0.001*
BMI (kg/m^2)	**<24.9**	73.5%	72.7%	80.6%	64.0%	73.2%	<0.001*
	≥24.9	100.0%	97.7%	96.3%	100.0%	98.5%	<0.001*
Duration of Signs & Symptoms (Days)	**1**	81.6%	100.0%	100.0%	86.0%	91.3%	<0.001*
	2	93.5%	90.7%	87.9%	95.1%	91.3%	<0.001*
	3	100.0%	83.3%	100.0%	81.0%	90.2%	<0.001*
Alvarado Score	**≤5 score**	82.6%	93.0%	90.5%	86.9%	88.3%	<0.001*
	≥6 score	97.0%	92.5%	90.7%	98.0%	94.6%	<0.001*

**Significant p-value*

In our study, FACT had the sensitivity, specificity, PPV, NPV, and diagnostic accuracy of 89.5%, 92.7%, 90.6%, 91.9%, and 91.3%, respectively for the diagnosis of acute appendicitis. Asim et al. observed the low-dose CT scan had sensitivity of 94.65%, specificity of 16.67%, PPV of 16.67%, NPV of 96.5%, and overall diagnostic accuracy of 93.88% with histopathology as a gold standard for diagnosis.[15] Another study by Chan et al. in 2020 revealed sensitivity, specificity, positive predictive value, and negative predictive value of CT scan as 77.8%, 100%, 87.5%, and 100%, respectively. Similarly, NAR was 7.25% with and 22.09% without preoperative CT scan.[16] A study showed that NAR was 6.9% in patients undergoing pre-appendectomy CT scan being lower than the patients without pre-appendectomy CT scan as 19% having a statistically significant difference as p-value=0.04.[17] Butt et al. found the role of FACT in adolescent and adult population as having a sensitivity, specificity, PPV, NPV, and accuracy as 98.6%, 94.3%, 98.9%, 92.6%, and 98%, respectively with the surgical findings as the gold standard in diagnosing acute appendicitis.[8] The findings of these studies correlate well with the current study indicating the diagnostic accuracy of non-contrast-based FACT in acute appendicitis diagnosis.

For comparison of CT scan to other radiological investigations such as ultrasonography, Bahrami et al. observed that for patients having low clinical suspicion of acute appendicitis, the sensitivity and specificity of CT scan were 87.9% and 81.8%, respectively. Similarly, the PPV of CT scan was 94.7% and NPV was 79.3%. However, the sensitivity and specificity of ultrasonography were 74.9% and 63.4%, respectively for patients with clinically low suspicion of acute appendicitis. The PPV and NPV of ultrasonography were also lower than CT scan as 94.3% and 67.6%, respectively. Furthermore, the findings of the CT scan were also consistent with the results of pathology in female patients demonstrating the higher sensitivity and specificity of CT scan than abdominal ultrasonography for diagnosis of acute appendicitis.[18] A study at King Abdulaziz University Hospital also identified the superior role of CT imaging to ultrasonographic imaging for the diagnostic accuracy of acute appendicitis. The sensitivity, specificity, PPV, and NPV of the CT scan were 92%, 75%, 93.8%, and 69.2%, respectively. Ultrasonography was reported to have low sensitivity, specificity, PPV and NPV than CT scan as 85.7%, 50%, 85.7%, and 50%, respectively. Furthermore, the diagnostic accuracy of CT imaging was higher than ultrasonography (88.7% vs. 77.7%).[19]

The effectiveness of low dose CT scan in comparison to the standard CT scan for the diagnosis of acute appendicitis was reported by Sippola et al. They showed the diagnostic accuracy of low dose CT scan was 79% and of the standard CT scan was 80%. The assessment of the severity of acute appendicitis was 79% for both CT scan protocols. Low-dose CT scan had no inferior role than the standard CT scan in the diagnosis of acute appendicitis with the advantage of a significantly lower dose of radiation reducing the risk of radiation hazards.[20]

CONCLUSION

Focused abdominal computed tomography demonstrates a high sensitivity (89.5%) and specificity (92.7%) in diagnosing acute appendicitis with an overall diagnostic accuracy of 91.3% when compared to the gold standard test histopathology. FACT proves to be a valuable and reliable

diagnostic tool, capable of reducing the negative appendectomy rate and facilitating timely and accurate diagnosis, particularly in clinically suspected cases. Furthermore, the utilization of non-enhanced FACT scans is associated with decreased costs, expedited access to imaging, a reduction in radiation exposure, and diminished hazards related to contrast medium.

LIMITATIONS & RECOMMENDATIONS

A small sample size from a single center limits generalizability. The use of non-probability consecutive sampling may introduce selection bias. Further studies are required to evaluate FACT against other diagnostic methods, including ultrasound and contrast-enhanced CT, to guarantee comprehensive assessments while addressing cost-effectiveness and minimizing radiation exposure. The development of standardized diagnostic protocols that include FACT could lead to improved accuracy, reduced morbidity, and better patient outcomes, especially in emergency contexts where timely diagnosis is critical.

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Authors' Contributions:
A.K: Conceive idea, data collection, and manuscript writing
R.A: Conceive idea, data collection, and manuscript writing
J.I: Manuscript writing and editing
R.S: Data analysis and manuscript writing
Q.H: Manuscript editing and review
M.J.T: Manuscript editing and review

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Original Article

Comparison of Outcomes of Induction of Labor with Prostaglandin versus Prostaglandin Plus Intracervical Catheter in Patients with >37 weeks Gestation

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ABSTRACT

Objective: To compare the outcomes of induction of labor with prostaglandin versus prostaglandin plus intracervical catheter in patients with >37 weeks gestation.

Methodology: This quasi-experimental study was conducted at the Department of Obstetrics and Gynecology, Mardan Medical Complex, Mardan from January 2021 to June 2021. After obtaining ethical approval, a total of 80 patients were selected using a non-probability consecutive sampling technique. The patients were categorized into groups A and B with 40 participants in each group. In group A, patients underwent labor induction with prostaglandin alone, while in group B, prostaglandin was combined with the insertion of a size 18 single balloon Foley catheter. The catheter was placed under sterile conditions into the intracervical canal, and the balloon was inflated with 30-60 cm^3 of water. It was left in position for 24 hours unless it became dislodged spontaneously before that period. The Statistical Package for the Social Sciences (SPSS) version 22.0 was used for the analysis of data.

Results: Out of 80 patients, 28(70%) patients in group A had diabetes mellitus compared to group B [25(62.5%)]. In group A, 30(75%) patients had hypertension, while in group B, 12(30%) had hypertension. The outcomes of labor induction showed that 23(57.5%) patients in group A had successful vaginal deliveries while in group B, 31(77.5%) patients had successful vaginal deliveries (p-value=0.05). Regarding body mass index (BMI), patients with BMI >25 kg/m² had a significantly higher success rate (63.2%) in group B as compared to group A (36.8%) (p=0.026).

Conclusion: A combination of prostaglandin and a size 18 single-balloon Foley catheter for labor induction yields better outcomes compared to prostaglandin alone.

Keywords: *Induction of Labor. Prostaglandin. Gestation.*

INTRODUCTION

Prostaglandins and intracervical catheters demonstrate comparable efficacy in cervical ripening and labor induction.[1] Previous studies indicate potentially heightening risks like tachysystole and chorioamnionitis when prostaglandin is used in repeated vaginal doses.[2] However, these drawbacks could be mitigated by administering a single prostaglandin dose alongside the intracervical catheter.[3] Labor induction may be required in certain situations where maternal or fetal well-being necessitates intervention.[4] A favorable cervical state at the start of labor induction is crucial for success. Currently, two strategies, Foley catheters and dinoprostone inserts, are frequently utilized to achieve optimal cervical ripening.[5] The American College of Obstetricians and Gynecologists recommends the use of Foley catheter for induction of labor in a controlled setting with prime focus on monitoring potential complications, especially in patients with previous caesarean section.[6] The utilization of pharmaceutical agents by obstetricians for the initiation of labor prior to the commencement of spontaneous contractions in natural parturition has been a longstanding practice. Numerous agents have been developed and rigorously investigated for their efficacy in stimulating uterine contractions in such scenarios.[7] Induction of labor is a critical procedure often required to ensure safe delivery, particularly in cases where VBAC is desired. Studies show that the success rates of labor induction methods, such as prostaglandin-E2 (PGE2) combined with an intracervical Foley catheter, can significantly impact delivery outcomes.[2,8] One study reported a VBAC success rate of 75% with the combined approach, which contrasts with a 54.17% success rate with PGE2 alone, highlighting the challenges and variability in induction outcomes.[8] The rate of caesarean section was 43% for PGE2 alone, compared to 30.9% with the combined method, emphasizing the importance of optimizing induction techniques to reduce caesarean section rates.[9] Additionally, another study found that adding a Foley catheter to PGE2 during induction increased the success rate of vaginal delivery to 66.6%, compared to 52.7% with the Foley catheter alone.[10] These findings highlight the importance of developing effective strategies to enhance the success of labor induction and minimize the rate of caesarean deliveries.

This study aims to evaluate the effectiveness of labor induction using prostaglandin alone compared to prostaglandin combined with an intracervical

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catheter in women over 37 weeks gestation. By evaluating local data, this study seeks to provide clearer insights into the most optimal management strategies for labor induction in this population, particularly focusing on factors such as maternal characteristics and comorbidities, which have shown varying effects in other settings. The findings would contribute to improving clinical decision-making and guiding healthcare professionals toward evidence-based practices for labor induction in cases requiring intervention.

METHODOLOGY

This quasi-experimental study was conducted at the Department of Obstetrics and Gynecology, Mardan Medical Complex, Mardan from January 2021 to June 2021. The sample size of 80 patients was calculated based on a 49.4% proportion of successful vaginal deliveries in patients treated with prostaglandin alone and a 78.9% success rate in those treated with prostaglandin combined with an intracervical Foley catheter.[9] The calculation was performed using the WHO sample size determination formula, with a test power of 80% and a 95% confidence interval. After obtaining ethical approval (Letter No. 135/BKMC, 13-12-2020) from the institutional review board, a total of 80 patients were selected using a non-probability consecutive sampling technique. Patients aged 18-40 years with gestational age over 37 weeks confirmed by the last menstrual period and of any gravidity and parity were included in the study. Exclusion criteria included women who refused the trial of labor or had co-morbid conditions like chronic kidney or heart disease. Moreover, previous caesarean section or any surgery which breached the uterine cavity was also excluded.

Patients were divided into two groups (40 patients in each group) after informed consent. In group A, women were induced with prostaglandin medication only, whereas prostaglandin was combined with a small balloon catheter placed in the intracervical canal in group B. This catheter was carefully inserted and filled with water, staying in place for a maximum of 24 hours or until it naturally came out. Various parameters including age, height, weight, length of hospital stay, mode of delivery, body mass index (BMI), and outcomes such as success or failure were recorded on a separate proforma for each participant.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 22.0 was used for the analysis of data. Mean±standard deviation (SD) was computed for continuous variables like age, weight, height, and BMI, while frequencies & percentages were calculated for labor induction outcomes. The Chi-square test was applied to compare the induction of labor outcomes among the study groups. Additionally, outcomes were stratified based on factors such as age, BMI, residence, diabetes, and hypertension to identify potential effect modifiers. Post-stratification Chi-square tests were conducted, considering a significance level of $p \leq 0.05$.

RESULTS

In group A, 21(52.5%) participants were aged 18-30 years, and 19(47.5%) were aged 31-40 years. In contrast, group B had a higher proportion [25(62.5%)] in the age range 31-40 years than 18-30 years age range [15(37.5%)]. Participants had a mean age of 29.48±4.74 years with a range from 22 to 39 years in group A. The mean weight was 69.33±2.20 kg (range: 65–76 kg), and the average height was 5.51±0.071 feet. The mean BMI in this group was 25.17±0.895 kg/m^2, ranging from 23-28 kg/m^2. Group B had a mean age of 30.32±4.911 years (range: 21–36 years) with a mean weight of 69.95±2.428 kg (range: 65-76 kg). The height of participants was similar to group A with a mean of 5.51±0.071 feet. The mean BMI for group B was 25.42±0.929 kg/m^2 with a range from 24-27 kg/m^2. Both groups had a predominantly urban population with 60% of group A and 55% of group B residing in urban areas. Diabetes mellitus was more prevalent in the prostaglandin alone group [28(70%)] in comparison to PGE2 with the Foley catheter group [25(62.5%)]. Hypertension was also more common in group A [30(75%)] than in group B [28(70%)]. Twenty three (57.5%) participants of group A experienced successful inductions, while 17(42.5%) cases had unsuccessful outcomes. In comparison, group B had a higher success rate of 77.5%, with only 22.5% reporting unsuccessful inductions (p-value=0.05) (Table 1).

Further analysis of labor induction outcomes by age revealed statistically insignificant difference between the both groups. For patients aged 18-30 years, 11 out of 21 in group A had successful vaginal deliveries, compared to 12 out of 15 in group B. In the 31-40 years age group, 12 out of 19 in group A and 19 out of 25 in group B had successful deliveries. Regarding BMI, there was no significant difference in successful vaginal delivery rates between group A (56.3%) and group B (43.7%) for patients with a BMI ≤25 kg/m² (p=0.912). However, for those with a BMI >25 kg/m², group B had a

significantly higher success rate (63.2%) compared to group A (36.8%) (p=0.026).

The analysis shows that the combined approach of prostaglandin plus intracervical Foley catheter (group B) was more effective in facilitating successful vaginal deliveries among urban residents compared to prostaglandin alone (group A). However, no significant difference was found between both groups in terms of success rates among rural residents (p=0.855).

Among patients with diabetes mellitus, 45.7% in group A and 54.3% in group B had successful vaginal deliveries. Similarly, among patients without diabetes mellitus, 36.8% in group A and 63.2% in group B had successful vaginal deliveries, The difference in success rates of both groups was not statistically significant. For hypertension, 18(45%) participants in group A and 55(22%) in group B had successful vaginal deliveries. Similarly, among patients without hypertension, the success rates were 35.7% in group A and 64.3% in group B (Table 2).

Table 1: Descriptive Statistics and Clinical Characteristics of Study Participants

Variables		Group A (n=40)	Group B (n=40)
		Frequency & Percentage	
Age (Years)	**18-30**	21(52.5%)	15(37.5%)
	31-40	19(47.5%)	25(62.5%)
Residence	**Urban**	24(60%)	22(55%)
	Rural	16(40%)	18(45%)
Diabetes Mellitus	**Yes**	28(70%)	25(62.5%)
	No	12(30%)	15(37.5%)
Hypertension	**Yes**	30(75%)	28(70%)
	No	10(25%)	12(30%)
Outcomes of Induction of Labor	**Successful**	23(57.5%)	31(77.5%)
	Unsuccessful	17(42.5%)	9(22.5%)

Table 2: Stratification of Outcomes of Labor Induction in Comparison to Study Variables

Variables		Groups	Outcomes of Induction of Labor			p-value
			Successful	Unsuccessful	Total	
Age Groups (Years)	**18-30**	**Group A**	11(47.8%)	10(76.9%)	21(58.3%)	0.089
		Group B	12(52.2%)	3(23.1%)	15(41.7%)	
		Total	23(100%)	13(100%)	36(100%)	
	31-40	**Group A**	12(38.7%)	7(53.8%)	19(43.2%)	0.355
		Group B	19(61.3%)	6(46.2%)	25(56.8%)	
		Total	31(100%)	13(100%)	44(100%)	
BMI (kg/m^2)	**≤25**	**Group A**	9(56.3%)	7(58.3%)	16(57.1%)	0.912
		Group B	7(43.7%)	5(41.7%)	12(42.9%)	
		Total	16(100%)	12(100%)	28(100%)	
	>25	**Group A**	14(36.8%)	10(71.4%)	24(46.2%)	0.026*
		Group B	24(63.2%)	4(28.6%)	28(53.8%)	
		Total	38(100%)	14(100%)	52(100%)	
Diabetes	**Yes**	**Group A**	16(45.7%)	12(66.7%)	28(52.8%)	0.142
		Group B	19(54.3%)	6(33.3%)	25(47.2%)	
		Total	35(100%)	18(100%)	53(100%)	
	No	**Group A**	7(36.8%)	5(62.5%)	12(44.4%)	0.221
		Group B	12(63.2%)	3(37.5%)	15(55.6%)	
		Total	19(100%)	8(100%)	27(100%)	
Hypertension	**Yes**	**Group A**	18(45%)	12(66.7%)	30(51.7%)	0.127
		Group B	22(55%)	6(33.3%)	28(48.3%)	
		Total	40(100%)	18(100%)	58(100%)	
	No	**Group A**	5(35.7%)	5(62.5%)	10(45.5%)	0.255
		Group B	9(64.3%)	3(37.5%)	12(54.5%)	
		Total	14(100%)	8(100%)	22(100%)	

**Significant p-value*

DISCUSSION

Prostaglandins and Foley catheters are well-established methods for cervical ripening and labor induction, demonstrating comparable effectiveness in many clinical scenarios. However, combining a single prostaglandin dose with an intracervical Foley catheter can reduce risks associated with prostaglandin overuse, such as uterine

hyperstimulation.[11] Labor induction is often necessitated by maternal or fetal safety concerns, and cervical readiness for ripening and dilation is crucial for successful outcomes.[4]

In this study, group A had a mean age of 29.48±4.739 years and a mean BMI of 25.17±0.895 kg/m^2, while group B had a mean age of 30.32±4.911 years and a mean BMI of 25.42±0.929 kg/m^2. These baseline characteristics align with the findings by Rana et al. They reported a mean age of 27.07±5.628 years and 27.10±5.644 years in the PGE2 and Foley catheter groups, respectively.[12]

In group A, 21(52.5%) patients were in the 18-30 years age group, while 19(47.5%) patients were in the 31-40 years age group, comparable with the findings of the study by Bullough et al.[10] However, results of the study by Croll et al., showed no difference in age groups.[13] In group B, 15(37.5%) patients were in the 18-30 years age group, while 25(62.5%) patients were in the 31-40 years age group. Regarding comorbidities, group A had higher rates of diabetes mellitus (70.0%) and hypertension (75.0%) compared to group B (62.5% and 70.0%, respectively). However, no significant differences in induction outcomes were noted due to these comorbidities.

The success rate of vaginal delivery was significantly higher in group B (77.5%) compared to group A (57.5%). Gilani et al. highlighted that combining prostaglandins with a Foley catheter achieves a vaginal delivery success rate of 75%, which is comparable to our group B outcomes.[8] In another study involving 81 women induced with PGE2 alone, 66.5% achieved vaginal delivery, while out of 127 induced with Foley catheter, about 52.7% had vaginal delivery.[10] Whereas, these findings are in contrast to the current study, 77.5% of patients in the Foley catheter group experienced successful vaginal deliveries. In another study, 229 women met the study criteria with a significant result of 49.4% successful outcomes in the PGE2 alone group and 78.9% in the PGE2 & Foley catheter group (p <0.001).[9] The proportion of successful outcomes in patients subjected to prostaglandin plus intracervical Foley catheter group aligns with the findings of the present study.

Quach et al. evaluated the impact of BMI on labor induction outcomes with Foley catheter or PGE2 alone, reporting that higher BMI was associated with longer labor, fewer vaginal deliveries within 24 hours, and higher caesarean rates. Their findings showed that the Foley catheter was more effective than PGE2 alone with a shorter time to delivery and better outcomes as BMI increased.[14] In contrast, our study demonstrated that combining PGE2 with a Foley catheter resulted in higher vaginal delivery rates and lower caesarean rates, particularly among patients with BMI >25 kg/m², compared to PGE2 alone. Al-Rawaf et al. reported that patients induced with a combination of Foley catheter and prostaglandin had a mean BMI of 28.98±1.91 kg/m², significantly lower (p=0.001) compared to patients induced with prostaglandin alone.[15] This suggests a potential relationship between induction methods and BMI, indicating that combined approaches may be more effective for individuals with lower BMI in contrast to our findings.

Beyrami et al. reported no significant differences in BMI distribution across groups (<25, 25-30, and >30; p=0.88).[16] Our study did not find any significant difference in the induction of labor outcomes between groups with hypertension (HTN) (p=0.127) and diabetes mellitus (DM) (p=0.142). Comparatively, in another study, HTN accounted for 20% of cases in the Foley catheter plus prostaglandin group and 36% in the prostaglandin alone group. Similarly, DM was observed in 8% and 6% of cases in the respective groups.[17] Our study further emphasizes that the combined induction method of prostaglandin and Foley catheter did not yield differing results based on these comorbidities, underlining its uniform effectiveness across these subgroups.

Our study found a predominance of cases in urban areas as compared to rural areas (57.5% vs. 42.5%). Additionally, the study revealed an urban-rural disparity in delivery outcomes. Urban participants in group B had a significantly higher success rate for vaginal delivery (p=0.012), whereas no significant difference was found among rural participants (p-value=0.855). However, this comparison was not done in any study before. A previous study reported a caesarean section rates in Pakistan to be 27.79% and 20.46% among urban and rural pregnant females, respectively. Urban settings often provide better healthcare infrastructure and skilled obstetric care, factors that could improve outcomes.[18]

CONCLUSION

A combination of prostaglandin and a size 18 single-balloon Foley catheter for labor induction yields better outcomes compared to prostaglandin alone. Moreover, the combined approach was found to be particularly effective in facilitating successful vaginal deliveries among patients with BMI >25 kg/m².

LIMITATIONS & RECOMMENDATIONS

This study has several limitations. First, it is a single-centered study, which may limit the generalization of the findings to other healthcare settings with different demographics or resource availability. Additionally, the relatively small sample size may restrict the statistical power to detect subtle differences between groups. The study also did not account for confounding factors such as socioeconomic status, education level, and prior obstetric history, which may influence delivery outcomes.

Future research should consider multi-center studies with larger sample sizes to validate and generalize the findings. Efforts should also focus on understanding the impact of socioeconomic and educational disparities on induction outcomes, particularly in rural settings. Policymakers should address resource disparities between urban and rural healthcare systems to ensure equitable access to quality obstetric care.

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Authors' Contributions:

N.J: Substantial contributions to study design, acquisition of data, manuscript drafting, and final approval
H: Substantial contributions to the acquisition of data, manuscript drafting, and final approval
N.U.K: Substantial contributions to analysis, and interpretation of data, critical review, and final approval
D.S: Substantial contributions to the concept, study design, critical review, and final approval
A.I: Study design, concept, critical review, and manuscript writing
H.Q: Study design, concept, critical review, manuscript writing, analysis, and final approval

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Original Article

Efficacy of Sodium-Glucose Cotransporter 2 Inhibitors versus Angiotensin-Converting Enzyme Inhibitors for Reducing Proteinuria in Diabetic Kidney Disease

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ABSTRACT

Objective: To evaluate the mean reduction in proteinuria in diabetic kidney disease (DKD) patients by empagliflozin (SGLT2 inhibitor) in comparison to enalapril (ACE inhibitor).

Methodology: This comparative descriptive study was conducted at the Department of Nephrology, Allied Hospital, Faisalabad from June 2023 to December 2023 after ethical approval. A total of 60 participants aged 20 to 70 years with the diagnosis of diabetic nephropathy were included using non-probability consecutive sampling and were distributed into groups A & B. Each group comprised 30 participants. After taking informed consent, group A patients received empagliflozin 25 mg/day and group B received enalapril 10 mg/day for 12 weeks. The urinary samples of all patients were collected to estimate the urinary albumin to creatinine ratio (UACR) before and after 12 weeks of intervention. The Statistical Package for the Social Sciences (SPSS) version 25 was used for the data analysis.

Results: Out of 60 participants**,** 25(41.67%) were females and 35(58.33%) were males. The mean ages of participants in groups A and B were 39.77±11.75 years and 40.43±12.20 years, respectively. The UACR change after 12 weeks in group A was -42.33±2.54% and it was -30.33±2.40% in group B (p-value=0.0001).

Conclusion: Empagliflozin has a more reno-protective effect in diabetic kidney disease than enalapril and is more effective in reducing proteinuria and the progression of DKD.

Keywords: *Sodium-glucose cotransporter 2 inhibitor. Angiotensin-converting enzyme inhibitors. Diabetic kidney disease.*

INTRODUCTION

Chronic kidney disease (CKD) poses a significant risk to public health, having a 13.4% prevalence worldwide.[1] The critical risk factors for CKD are diabetes mellitus and hypertension.[2] Diabetes mellitus and other associated comorbidities, such as hypertension, obesity, and atherosclerosis have an essential role in the pathogenesis of CKD, cardiovascular diseases, and overall mortality.[3] Renal function deteriorates over time in diabetic patients. About 20-30% of diabetic patients develop nephropathy, ultimately resulting in end-stage renal disease (ESRD), progressing to renal replacement therapy, such as hemodialysis or kidney transplantation.[4] The progression of ESRD in diabetic patients could be prevented by control of serum glucose levels and blood pressure and suppression of the renin-angiotensin-aldosterone system (RAAS).[5] The incidence of DKD is rising, and by 2040, it is expected to affect 200 million individuals globally.[3] Proteinuria is linked to cardiovascular death, renal failure, acute kidney injury, and CKD progression. It is a critical risk factor and a treatment target in diabetes care with a solid link to both renal and cardiovascular outcomes.[6] The effective management of proteinuria reduction and progression in DKD is vital in reducing morbidity and mortality. Reducing proteinuria helps slowing the deterioration of the glomerular filtration rate (GFR). Antihypertensive drugs such as angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers have a reno-protective effect due to their antihypertensive and antiproteinuric actions.[7] Angiotensin-converting enzyme inhibitors exert their effect by activating the RAAS and have a role in the management of renal disease. They have been utilized to prevent neuro-humoral activation and intraglomerular hypertension as well as to prevent the increase in serum creatinine and progression to ESRD.[5]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors are anti-diabetics with proven benefit of glycemic control. They also influence weight loss, control blood pressure, prevent cardiovascular events, and progression of CKD.[8] Sodium-glucose cotransporter 2 inhibitors have a direct effect on kidney hemostasis by reducing the GFR through the net production of adenosine and vasoconstriction of afferent arterioles through tubuloglomerular feedback.[9] Empagliflozin, an SGLT2 inhibitor, has a reno-protective effect mediated by reduced glomerular hyperfiltration and intraglomerular pressure, preventing barotraumas, and proteinuria. Reduction in intraglomerular pressure is typically associated with an immediate hemodynamic drop in

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GFR and long-term proteinuria reductions by lowering the urinary albumin to creatinine ratio (UACR).[10]

Angiotensin-converting enzyme inhibitors and SGLT2 inhibitors both reduce proteinuria and inhibit the progression of CKD to ESRD. Literature elaborating on the combination therapy of SGLT2 inhibitors and ACE inhibitors is available, however, the studies comparing SGLT2 inhibitors and ACE inhibitors for the reduction of proteinuria and their effect on UACR are deficient both locally & internationally and require further evaluation. This study was designed to assess the mean reduction of proteinuria in DKD patients by empagliflozin (an SGLT2 inhibitor) compared to enalapril (an ACE inhibitor).

METHODOLOGY

This comparative descriptive study was conducted at the Department of Nephrology, Allied Hospital, Faisalabad from June 2023 to December 2023. The ethical approval (Letter No. 601/2022, 15-06-2022) was acquired from the ethical review board of Punjab Medical College, Faisalabad. The non-probability consecutive sampling technique was used to recruit 60 patients undergoing treatment through the outpatient department after informed consent. Patients of both genders, aged between 20-70 years and diagnosed with DKD having eGFR >30 mL/min/1.73 m^2 at presentation and UACR >300 mg/g were included after taking informed consent. All the patients with a history of hypertension, allergy to the drugs under study, human immunodeficiency virus (HIV) infection, hyperkalemia (serum potassium level >5.0 mmol/L), malignancy, systemic diseases affecting the cardiovascular, cerebrovascular, pulmonary or hepatobiliary system, and pregnant or nursing mothers were excluded. The participants could withdraw from this study at any moment, and their personal information was kept anonymous to exclude bias. All the patients were divided into two groups, i.e. group A and group B. The participants in group A and group B received empagliflozin (SGLT2 inhibitor) 25 mg per day and enalapril (ACE inhibitor) 10 mg per day for 12 weeks, respectively. The age, gender, duration of disease, stage of CKD as per Kidney Disease: Improving Global Outcomes Guidelines[11] and blood pressure of participants were recorded. Before initiating drug intervention in each group, the 24-hour urinary sample of each participant was collected by wasting the first sample and then collecting urine for 24 hours, including the first urine sample of the next day. The chemical pathologists assessed the albumin and creatinine levels in the urine. Urinary albumin to creatinine ratio was calculated for each participant. All the participants then underwent prescribed treatment as empagliflozin 25 mg per day in group A and enalapril 10 mg per day in group B. Each participant was followed till the completion of the study, i.e. 12 weeks. Similarly, the 24-hour urinary sample of each participant was collected & analyzed at 12 weeks, and UACR was calculated.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 25 was used for the data analysis. Mean±standard deviation (SD) was calculated for numerical variables. The categorical variables, such as age, gender, and disease duration were expressed as frequencies and percentages. An independent sample t-test was used for comparison of mean percentage change in UACR among both groups. The effect modifiers, such as age and stage of CKD were stratified, and a post-stratification independent sample t-test was applied. The p-value <0.05 was considered statistically significant.

RESULTS

The mean age of study participants was 39.94±11.91 years with a mean age of 39.77±11.75 years in group A and 40.43±12.20 years in group B. Out of 60 participants, 25(41.67%) were females and 35(58.33%) were males with a female-to-male ratio of 1:1.4. The mean duration of diabetes mellitus was 6.31±3.89 years and it was 6.50±3.99 years in group A and 6.13±4.13 years in group B. The mean systolic blood pressure in groups A and B was 133±15 mmHg and 131±14.2 mmHg, respectively. After 12 weeks of treatment, the mean change in UACR in group A was -42.33±2.54% and in group B was -30.33±2.40% (p-value=0.0001) (Table 1).

Post-stratification, a substantial difference was observed between the two groups regarding the mean percentage change in UACR across all age groups, having statistical significance (p=0.0001). Similarly, a statistically significant difference between both drugs was found across all stages of CKD with a p-value of 0.0001 (Table 2).

Table 1: Demographic Variables of Study Groups (n=60)

Variables	Group A Mean±SD	Group B Mean±SD
Age (Years)	39.77±11.75	40.43±12.20
Diabetes Mellitus Duration (Years)	6.50±3.99	6.13±4.13
Systolic Blood Pressure (mmHg)	133±15	131±14.2
Percentage change in UACR	-42.33± 2.54	-30.33±2.40

Table 2: Stratification of Percentage Change in UACR with respect to Study Variables

Variables		Group A UACR Change (%) Mean±SD	Group B UACR Change (%) Mean±SD	p-value
Age (Years)	**20-45**	-42.56±2.36	-30.71±2.47	0.0001*
	46-70	-42.50±2.42	-29.85±2.30	0.0001*
Stage of CKD	**I (eGFR ≥ 90 mL/min)**	-42.75±2.06	-29.0±2.0	0.0001*
	II (eGFR 60-89 mL/min)	-42.54±2.22	-30.54±2.57	0.0001*
	III (eGFR 30-59 mL/min)	-42.45±2.73	-30.43±2.38	0.0001*

**Significant p-value*

DISCUSSION

The SGLT2 inhibitors are the most recent family of oral antihyperglycemics for the management of diabetes, and significant improvements have been reported in their effectiveness and safety. Diabetes mellitus type 2 raises significant risk of cardiovascular and renal complications, leading to an increase in morbidity and treatment failure. The management of hyperglycemia, hypertension, and albuminuria could reduce the risk of developing cardiovascular and renal complications.[12]

After 12 weeks treatment, the mean UACR change was -42.33±2.54% in patients receiving empagliflozin, higher than the mean UACR change of -30.33±2.40% in patients receiving enalapril (p-value=0.0001). Empagliflozin was more effective in preventing albuminuria than the ACE inhibitors.

Kadowaki et al. showed rapid improvement in mean change in UACR with the use of empagliflozin in all groups of proteinuria as compared to placebo, significantly in the groups of patients with microalbuminuria (-40 mg/g vs. -19 mg/g) and macroalbuminuria (-50 mg/g vs. - 26 mg/g) at 12 weeks. Proteinuria has a significant role in the progression of CKD, and reduction of proteinuria could ultimately decelerate this progression.[13] Waijer et al. reported an 18% reduction in UACR by empagliflozin at 12 weeks as compared to placebo and its use raises the chance of reduction in UACR by >30% (p <0.001). Furthermore, each 30% decrease in UACR showed significant reduction in major cardiovascular events, cardiovascular deaths/hospitalizations for heart failure, and outcomes of kidney.[14] Tian et al. reported that the 12-week treatment with SGLT2 inhibitors helped in UACR reduction in both the microalbuminuria and macroalbuminuria groups. The decrease in UACR was from 87 to 75 mg/g (p-value=0.003) in the microalbuminuria group and from 861 to 738 mg/g (p-value=0.037) in the macroalbuminuria group.[15]

We found that empagliflozin had a higher reno-protective role in all stages of CKD than enalapril (p=0.0001). A study on type 2 diabetes patients reported that the reno-protective and cardioprotective roles of SGLT2 inhibitors were comparable to those of ACE inhibitors. However, the duration and amount of data reported for SGLT2 inhibitors versus ACE inhibitors were insufficient to consider SGLT2 inhibitors as first-line therapy for the treatment of CKD patients with diabetes.[16]

Regarding the renal effect of SGLT2 inhibitors in comparison to other hypoglycemic drugs, Nagasu et al. reported that after treatment, the change in the mean annual rate of eGFR was -0.47 mL/min/1.73 m^2 per year and -1.22 mL/min/1.73 m^2 per year in the SGLT2 inhibitor and other hypoglycemic drugs groups, respectively. The difference of decline in the eGFR rate between the groups was 0.75 mL/min/1.73 m^2 per year, indicating a significant advantage for SGLT2 inhibitors (p <0.001).[17] Similarly, Kitaoka et al. compared SGLT2 inhibitors with other glucose-lowering drugs in halting eGFR reduction among patients ≥75 years with DKD. They

found the mean annual rate of eGFR change in the SGLT2 inhibitors group of -0.80 mL/min/1.73 m^2 per year while it was -1.78 mL/min/1.73 m^2 per year in other glucose-lowering drugs group. When complications such as eGFR reduction up to 40% or progression to ESRD were compared, the SGLT2 inhibitors group showed lesser prevalence as compared to the other group.[18] Tsai et al. highlighted the improved treatment effect with SGLT2 inhibitors as they decreased the risk of renal disease progression by reducing eGFR decline up to ≥50%, ESRD or deaths due to renal disease. These drugs also delay the eGFR decline by 0.99 mL/min/1.73 m^2 annually and reduce the risk of adverse outcomes such as acute kidney failure. This benefit of SGLT2 inhibitors supports the use before initiation of renal replacement therapy as maintenance hemodialysis or kidney transplant.[19] Similarly, Klen et al. also stated that the use of SGLT2 inhibitors reduces the need of kidney transplant therapy by over 40%.[20] Liu et al. found that SGLT2 inhibitors significantly reduce the progression of CKD with a hazard ratio of 0.60. Furthermore, the risk of developing ESRD was also reduced.[21]

CONCLUSION

The 12-week study comparing empagliflozin and enalapril in DKD patients demonstrated that empagliflozin had an effective role in reducing proteinuria than enalapril. This reduction in proteinuria is crucial in slowing the progression of CKD and delaying the onset of ESRD. The study adds to the evidence supporting the reno-protective effects of SGLT2 inhibitors in DKD.

LIMITATIONS & RECOMMENDATIONS

This was a single-center study and was conducted for only 12 weeks. Furthermore, no adverse effects were documented during the study. A more comprehensive evaluation of the potential adverse effects of empagliflozin and enalapril could have been beneficial. The study also lacked long-term outcomes and did not comprehensively evaluate other treatment modalities for DKD. Finally, there might be unaccounted confounding variables that could have influenced the outcomes. However, further research with longer duration, large sample size, and blinded design is recommended to validate these findings and investigate possible adverse effects comprehensively.

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Authors' Contributions:
M.A: Conceive idea, data collection, and literature review
M.S: Conceive idea, data collection, and literature review
A.R: Data collection, literature review, and manuscript writing
T.R: Literature review and manuscript writing
Z.H: Manuscript review and editing
W.T: Manuscript review and editing

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Original Article

Effect of Sociodemographic Factors on Prevalence of Obsessive-Compulsive Disorder among Medical and Non-Medical Students

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ABSTRACT

Objective: To determine the effect of sociodemographic factors on the prevalence of obsessive-compulsive disorder (OCD) among medical and non-medical students of Lahore.

Methodology: This cross-sectional study was conducted at CMH Lahore Medical College & Institute of Dentistry, Lahore from April 2024 to June 2024 after ethical approval. Three hundred and thirty students in medical and non-medical fields were recruited by non-probability convenient sampling after obtaining informed consent. Measurement tools included Obsessive-Compulsive Inventory-Revised (OCI-R) scale. Sociodemographic data (age, gender, area of living, field of study) and data related to OCD were also collected. The analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26.

Results: A higher prevalence of OCD was found in non-medical students (71.5%) as compared to medical students (57%) (p-0.006). The prevalence of OCD was greater in males (76%) as compared to females (58.8%) (p=0.004). Obsessive-compulsive disorder was more common in day scholars (67.3%) and urban students (74%) as compared to hostelites (59.7%) and rural students (59.5%), respectively.

Conclusion: OCD was more prevalent in non-medical students than in medical students. Moreover, the prevalence of OCD has a significant association with gender and geographical location.

Keywords: *Obsessive-compulsive disorder. Medical students. Mental health.*

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a common psychological disorder which occurs before adolescence begins and it becomes significant in the early twenties.[1] Obsessions and compulsions are two different entities. Obsessions are thoughts which repeatedly come into someone's mind and affect the individual, causing distress, while compulsions are actions which a person does to feel relaxed and to divert his/her attention from these thoughts.[1] Obsessive-compulsive disorder has six different types. Contamination/washing OCD is characterized by constant stress about germs and dirt, leading to avoidance of touching objects and a continuous feeling of not being clean enough, resulting in repeated hand-washing or extended bathing sessions without reaching a sense of cleanliness. Checking OCD involves an ongoing fear that any tragedy may occur, resulting in repeated checks of locks to ensure the safety of doors & electric appliances and confirm they are switched off. Excessive collection of things, even those deemed useless, leading to difficulty in discarding items is included in Hoarding OCD. Obsessive OCD manifests as severe remorse associated with intrusive thoughts, resulting in self-perception as a bad individual. Compelling actions to restore the specific order when surroundings are not arranged according to a desired pattern is a characteristic feature of symmetry & ordering OCD. Counting and repeating OCD arises when a person engages in repetitive activities, such as counting or repeating actions until a sense of being “just right” is achieved.[2] The International Classification of Diseases (11th revision) states that for an OCD diagnosis, individuals must display repetitive obsessions, compulsions, or a combination of both. These obsessions and compulsions must lead to considerable distress and should consume more than one hour daily for at least two weeks.[3] The mechanism through which OCD occurs is still unknown but research suggests that it is genetically linked as it has been seen to run in families.[2,4] The reason why OCD is underdiagnosed can be attributed to the prevailing stigma of mental health. People hesitate to seek help or disclose their symptoms due to fear of judgment which leads to underreported cases and lack of awareness.[5] According to research, 2 to 3% of the world’s population is affected by it. In the United States, more than 1 in every 50 persons is affected by this disorder. However, it is diagnosed in less than half of the affected population and less than half of the diagnosed population receives appropriate treatment that includes cognitive behavioral therapy and selective serotonin reuptake inhibitors.[6] According to a study conducted in Saudi Arabia, 26% of medical students had probable OCD, while it was found in 43% of medical students in a study conducted in

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Iraq.[2,7] Literature review showed that no study has been conducted on the effect of sociodemographic factors on the prevalence of OCD. Also, no comparison has been done between medical and non-medical students in Pakistan. Consequently, the current study was conducted to evaluate the influence of sociodemographic factors on the prevalence of OCD among medical and non-medical students in Lahore.

METHODOLOGY

This descriptive cross-sectional study was carried out from April 2024 to June 2024 to assess the prevalence of OCD among medical and non-medical students of different universities in Lahore. The study was conducted at CMH Lahore Medical College & Institute of Dentistry, Lahore after ethical approval (Letter No. 12/ERC/CMHLMC, 21-01-2024) from the ethical review board of the institution. The sample size was calculated to be 330 based on a 95% confidence interval and a 5% margin of error using 26% prevalence of OCD among medical students and expected 10% dropout rate with the WHO sample size calculator.[2] Non-probability convenient sampling technique was used to recruit the students from medical colleges in Lahore and non-medical students from various universities of Lahore. Inclusion criteria specified individuals aged 17 years and above. The students already diagnosed with OCD were also included. The students who did not give consent were excluded.

The data was collected from medical and non-medical students through a validated Obsessive-Compulsive Inventory-Revised (OCI-R) Scale. The OCI-R scale has 18 questions, divided into 6 subscales (hoarding, obsessing, washing, neutralizing, checking, and ordering). Likert scale which coded from 0-4 (not at all, a little, moderately, a lot, and extremely) with a maximum total score of 72 was used for the answers to the questions. The cut-off range was 27. A score more than 27 was considered probable obsessive-compulsive disorder.[5] Sociodemographic data (age, gender, area of living, field of study) and data related to OCD were also collected. Informed written consent was acquired from the students and the information obtained was kept confidential.

STATISTICAL ANALYSIS

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive analysis, including mean±standard deviation (SD), was applied to numerical data, while frequencies and percentages were used for categorical data. The Chi-square test was applied to assess relationships among variables, with a p-value of ≤0.05 considered statistically significant.

RESULTS

The study comprised 330 students in total, with 165 (50%) medical students and 165 (50%) non-medical students. The sociodemographic characteristics of the participants are presented in Table 1. Table 2 displays the frequency distribution of responses from medical and non-medical students related to the OCI-R score. Regarding the items related to symptoms of hoarding, a strong significant difference was observed between medical and non-medical fields in the items ‘I avoid throwing things away because I am afraid, I might need them later’ and ‘I have saved up so many things that they get in the way’ with p-values of 0.02 and 0.05, respectively. A significant difference was observed in the item 'I get upset if others change the way I have arranged the things' under the subscale of ordering (p-value=0.04). Of the items representing neutralizing subscale, the items ‘I feel I must repeat certain numbers’ and ‘I feel there are good and bad numbers’ had significant difference among medical and non-medical students having p-values of 0.012 and 0.001, respectively. According to the checking subscale, medical and non-medical students showed a significant difference in the item 'I repeatedly check gas, and water taps and light switches after turning them off’ with a p-value of 0.02. Regarding items under the obsessing subscale, we found a significant difference between both groups in the item ‘I frequently get nasty thoughts and find difficulty in getting rid of them’ (p- value=0.038). In the washing subscale, a significant difference was noted between the groups. In the items 'I find it difficult to touch an object when I know it has been touched by strangers or certain people' and 'I wash my hands more often and longer than necessary' with p-values of 0.014 and 0.001, respectively.

Table 3 shows variations in OCD prevalence in various sociodemographic categories. Based on the field of study, students not in medical fields showed a greater frequency of OCD compared to medical students (p=0.006). Males exhibited higher OCD prevalence compared to females (p=0.004). People residing in urban areas demonstrated a higher prevalence than people living in rural areas (p=0.009). Day scholars showed a higher OCD prevalence compared to hostelites but this difference was statistically insignificant. These findings indicated that there is a potential influence of sociodemographic factors on the prevalence of OCD.

Table 1: Sociodemographic Characteristics of the Study Participants

Sociodemographic Variables		Frequency & Percentage
Age (Years)	**17-20**	164(49.7%)
	21-24	166(50.3%)
Gender	**Male**	104(31.5%)
	Female	226(68.5%)
Geographical Location	**Urban**	108(32.73%)
	Rural	222(67.27%)
Field of study	**Medical**	165(50%)
	Non-Medical	165(50%)
Students' Accommodation Status	**Hostelites**	134(40.6%)
	Day Scholars	196(59.4%)

Table 2: Frequency distribution of OCD Score between Medical and Non-Medical Students

Q. No.	Questionnaire	Field of Study	Frequency and Percentage					p-value
			Not at all	A little	Moderately	A lot	Extremely	
1	I have saved up so many things that they get in the way.	Medical	37(22.4%)	40(24.2%)	59(35.8%)	19(11.5%)	10(6.1%)	0.05*
		Non-Medical	60(36.4%)	35(21.2%)	42(25.5%)	15(9.1%)	13(7.8%)	
2	I check things more often than necessary.	Medical	36(21.8%)	30(18.2%)	51(30.9%)	33(20%)	15(9.1%)	0.35
		Non-Medical	29(17.6%)	43(26%)	55(33.3%)	27(16.4%)	11(6.7%)	
3	I get upset if objects are not arranged properly.	Medical	24(14.5%)	42(25.5%)	42(25.5%)	38(23%)	19(11.5%)	0.81
		Non-Medical	20(12.1%)	44(26.7%)	48(29.1%)	39(23.7%)	14(8.5%)	
4	I feel compelled to count while I am doing things.	Medical	38(23%)	45(27.3%)	48(29.1%)	25(15.2%)	9(5.4%)	0.17
		Non-Medical	23(13.9%)	59(35.8%)	52(31.5%)	25(15.2%)	6(3.6%)	
5	I find it difficult to touch an object when I know it has been touched by strangers or certain people.	Medical	52(31.5%)	44(26.7%)	28(16.9%)	31(18.8%)	10(6.1%)	0.014*
		Non-Medical	31(18.8%)	52(31.5%)	48(29.1%)	23(13.9%)	11(6.7%)	
6	I find it difficult to control my thoughts.	Medical	28(16.9%)	37(22.4%)	26(15.8%)	44(26.7%)	30(18.2%)	0.24
		Non-Medical	21(12.8%)	41(24.8%)	38(23%)	45(27.3%)	20(12.1%)	
7	I collect things I don't need.	Medical	49(29.7%)	43(26%)	42(25.5%)	25(15.2%)	6(3.6%)	0.49
		Non-Medical	39(23.7%)	40(24.2%)	43(26%)	33(20%)	10(6.1%)	
8	I repeatedly check doors, windows, drawers, etc.	Medical	55(33.3%)	40(24.2%)	40(24.2%)	18(10.9%)	12(7.4%)	0.36
		Non-Medical	40(24.2%)	39(23.7%)	52(31.5%)	19(11.5%)	15(9.1%)	
9	I get upset if others change the way I have arranged the thing.	Medical	30(18.2%)	35(21.2%)	34(20.6%)	36(21.8%)	30(18.2%)	0.04*
		Non-Medical	42(25.5%)	34(20.6%)	31(18.8%)	18(10.9%)	40(24.2%)	
10	I feel I must repeat certain numbers	Medical	66(40%)	30(18.2%)	41(24.8%)	26(15.8%)	2(1.2%)	0.012*
		Non-Medical	43(26%)	30(18.2%)	43(26%)	39(23.7%)	10(6.1%)	
11	I sometimes have to wash or clean myself simply because I feel contaminated.	Medical	37(22.4%)	45(27.3%)	41(24.8%)	31(18.8%)	11(6.7%)	0.46
		Non-Medical	26(15.8%)	51(30.9%)	49(29.7%)	26(15.8%)	13(7.8%)	
12	I am upset by unpleasant thoughts that come into my mind against my will.	Medical	26(15.8%)	41(24.8%)	35(21.2%)	41(24.8%)	22(13.4%)	0.57
		Non-Medical	23(13.9%)	37(22.4%)	47(28.5%)	34(20.6%)	24(14.5%)	
13	I avoid throwing things away because I am afraid, I might need them later.	Medical	27(16.4%)	32(19.4%)	39(23.7%)	44(26.7%)	23(13.9%)	0.02*
		Non-Medical	30(18.2%)	50(30.3%)	43(26%)	24(14.5%)	18(10.9%)	
14	I repeatedly check gas and water taps and light switches after turning them off.	Medical	60(36.4%)	40(24.2%)	33(20%)	19(11.5%)	13(7.8%)	0.02*
		Non-Medical	33(20%)	50(30.3%)	42(25.5%)	24(14.5%)	16(9.7%)	
15	I need things to be arranged in a particular way.	Medical	16(9.7%)	51(30.9%)	42(25.5%)	32(19.4%)	24(14.5%)	0.23
		Non-Medical	22(13.4%)	44(26.7%)	55(33.3%)	21(12.8%)	23(13.9%)	
16	I feel there are good and bad numbers.	Medical	78(47.3%)	31(18.8%)	29(17.6%)	23(13.9%)	4(2.4%)	0.001*
		Non-Medical	49(29.7%)	32(19.4%)	41(24.8%)	25(15.2%)	18(10.9%)	
17	I wash my hands more often and longer than necessary.	Medical	61(37%)	25(15.2%)	37(22.2%)	30(18.2%)	12(7.4%)	0.001*
		Non-Medical	44(26.7%)	42(25.5%)	50(30.3%)	8(4.7%)	21(12.8%)	
18	I frequently get nasty thoughts and find difficulty in getting rid of them.	Medical	49(29.7%)	37(22.4%)	35(21.2%)	31(18.8%)	13(7.8%)	0.038*
		Non-Medical	27(16.4%)	43(26%)	48(29.1%)	28(16.9%)	19(11.5%)	

**Significant p-value*

Table 3: Comparison of OCD on the basis of Sociodemographic Variables

Sociodemographic Variables		OCD Free	Probable OCD	Total	p-value
Field of study	**Medical**	71(43%)	94(57%)	165	0.006*
	Non-Medical	47(28.5%)	118(71.5%)	165	
Gender	**Male**	25(24%)	79(76%)	104	0.004*
	Female	93(41.2%)	133(58.8%)	226	
Geographical Location	**Urban**	28(26%)	80(74%)	108	0.009*
	Rural	90(40.5%)	132(59.5%)	222	
Students' Accommodation Status	**Day Scholars**	64(32.7%)	132(67.3%)	196	0.198
	Hostelites	54(40.3%)	80(59.7%)	134	

**Significant p-value*

DISCUSSION

Our results showed a high prevalence of OCD in both medical (57%) and non-medical (71.5%) students. A study conducted in Jordan showed a high prevalence (58.53%) of OCD in university students.[8] Another study at Taibah University, Saudi Arabia, found the OCD prevalence among medical students to be 26%.[2] Similarly, research on Iraqi medical students carried out during the COVID-19 pandemic showed that the prevalence of OCD was 43%.[7] Quek et al. reported a significant prevalence of anxiety and depressive symptoms among medical students, which often coexist with OCD.[9] So, it was already proved by research that medical students have more OCD.[2,7] Contrary to the above, a comparison between medical and non-medical students in our study showed OCD being more common in non-medical students. This finding is somewhat unexpected, as previous literature has often reported higher levels of stress-related disorders among medical students due to the demanding nature of their education.[10] However, our findings suggest that non-medical students might face stressors that significantly contribute to the development of OCD, such as different academic pressures, lifestyle factors, social pressures, or possibly less access to structured mental health support, or perhaps the structure of non-medical programs that may not provide as much structured support as medical programs. This finding may be explained by the medical students' awareness of mental health disorders and fear of being labelled with a potentially stigmatizing condition.[11] In another study that assessed the comparison of psychiatric issues among medical and non-medical students, anxiety levels were found to be higher in non-medical students.[12]

Our study found that males had a higher prevalence of OCD (76%) compared to females (58.8%). In contrast to our findings, Pampaloni et al. found that females are more likely to develop OCD and other anxiety disorders.[13] Another study showed that the onset of OCD is early in males and late in females so males may dominate in OCD cases in the teenagers but in the adult population, females tend to have higher OCD. The gender difference in OCD prevalence might be due to various factors, including biological susceptibility, social and cultural pressures, and differences in help-seeking behavior.[14]

Urban students had a higher prevalence of OCD (74%) compared to rural students (59.5%) with a significant p-value of 0.009. Contrary to this, research conducted in the United States indicated that one-fifth of the rural population has mental illness and due to inadequate medical facilities and less specialized healthcare providers, they receive treatment less frequently.[15] In contrast another study showed opposite results suggesting that urban environments, with their higher levels of pollution, faster pace of life, higher population density, and greater exposure to environmental stressors, noise, and social stressors, can contribute to the higher prevalence of mental health disorders, including OCD.[13]

Day scholars had a higher prevalence of OCD (67.3%) compared to hostelites (59.7%) with a p-value of 0.198, which was not statistically significant. Similarly, another recent research conducted in Lahore in 2024 showed overall poor health status in day scholars as compared to hostelites.[16] Research confirms that physical and mental health are closely interconnected, with poor physical health contributing to poor mental health, and vice versa.[17] In contrast, another study showed opposite results suggesting that living on campus can provide a buffer against academic stress due to closer proximity to support services.[18] However, the non-significant p-value indicates that the difference might not be substantial and warrants further investigation.

The study identified specific OCD-related behaviors that were significantly more prevalent among non-medics. Non-medical students showed higher instance of repetitive behaviors and checking compulsions, which might reflect the high levels of detail and perfectionism required in their training.[19] These behaviors are consistent with symptoms described in studies where OCD manifests through compulsions aimed at mitigating anxiety related to performance and responsibilities.[20,21]

The study was designed to determine OCD prevalence among students, so no psychological support was provided due to limited resources. However, the students were encouraged to seek help if needed.

CONCLUSION

Non-medical students exhibited a higher prevalence of OCD than their medical counterparts. This result suggests that the stressors faced by non-medical students may be more conducive to the development of OCD. Moreover, the prevalence of OCD was found to have a statistically significant association with gender and geographical location.

LIMITATIONS & RECOMMENDATIONS

Generalization of results is limited due to the small sample size. The nature of the study is cross-sectional and it allows us to look at data from a single point in time.

The higher prevalence of OCD among non-medical students highlights the importance of mental health interventions that address the unique stressors experienced by this group. Universities should consider implementing mental health support services tailored to the specific needs of students from medical and non-medical backgrounds. For medical students, interventions such as stress management workshops, mindfulness training, and regular mental health check-ups could be beneficial. Non-medical students might benefit from counseling services, career guidance, and social support networks to help them navigate their unique challenges.

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Authors' Contributions:
R.M: Concept design, initial write-up, and final approval
E.F: Concept design, initial write-up, and final approval
F.I: Drafting, critical revision, and final approval
H.S: Data collection/analysis
M.I: Drafting, critical revision, and final approval
T.R: Data collection/analysis
R.K.A: Drafting, critical revision, and final approval

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Original Article

Spectrum of Therapeutic Plasma Exchange - Experience at a Tertiary Care Hospital

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ABSTRACT

Objective: To assess the most frequent indications of therapeutic plasma exchange (TPE) along with their outcomes at a tertiary care hospital in Pakistan.

Methodology: This cross-sectional study was carried out for a period of 6 months from July 2021 to December 2021 in Pak Emirates Military Hospital, Rawalpindi after ethical approval. A total of 81 patients were enrolled using non-probability consecutive sampling technique after obtaining their informed consent. Demographic information, plasma exchange indications, and clinical outcomes were noted. Therapeutic indications were subcategorized and classified according to the American Society for Apheresis (ASFA) guidelines. Data was analyzed using the Statistical Package for the Social Sciences version 23.

Results: Out of 81 patients, 60(74.1%) were males and 21(25.9%) were females with age range from 11-90 years and highest number of patients observed in the 31-50 years age group. Among 17 TPE indications, neurological disorders were the most frequent accounting for 76.5% of total cases followed by 11.1% cases of hematological diseases, while renal (3.7%) & rheumatic disorders (4.9%) and others (3.7%) were less prevalent. Most of the TPE indications fall in ASFA category I (63%) followed by category II (13.6%), category III (4.9%), and category IV (1.2%). However, 14(17.3%) patients did not have any classified cause. Forty nine (60.5%) patients responded positively to treatment, 21(26%) patients did not show any improvement after TPE, whereas, deaths were reported in 11(13.5%) patients.

Conclusion: Neurological diseases are the most common indications of therapeutic plasma exchange. Patient improvement was seen in more than half of the study population and deaths were reported in a few patients. In addition, unclassified TPE indications have also been observed which warrants further evaluation.

Keywords: *Neurological disorders. Plasmapheresis. Hematological diseases.*

INTRODUCTION

Apheresis is an extracorporeal process which involves the separation of the desired component from whole blood of the patient, performed by an automated device, and re-infusion of the remaining ones with or without physiological fluid.[1] The infusion of replacement fluid such as a colloid solution or mixture of colloid/crystalloid solution confers therapeutic effect in certain conditions notably thrombotic thrombocytopenic purpura (TTP).[2] The rationale for therapeutic plasma exchange is the removal of deleterious substances such as autoantibodies, immune complexes, cryoglobulins, myeloma light chains, toxins or lipids from the plasma of the patient and in-turn providing non-pathogenic immunological soluble factors.[3] The methods employed for the separation of blood components include centrifugation or membrane filtration which separates blood products on the basis of density or size, using membrane with porosity of 0.2-0.5 microns.[4]

Therapeutic plasma exchange is a paramount treatment modality for many systemic diseases particularly of autoimmune etiology according to the guidelines established by the American Society for Apheresis (ASFA). It classifies conditions and diseases into four categories. Category I indications utilize apheresis as a first-line treatment either stand-alone or in conjunction with other treatment modalities. Category II includes indications where apheresis is employed as a second-line treatment when first-line therapies are not available or contraindicated. Indecisive TPE indications fall in category III and apheresis decision should be individualized. Performance of apheresis procedure for category IV indications could be ineffective or harmful thus not to be performed.[5] Numerous studies illustrated the TPE procedure as an effective treatment option for more than one-third of immune-mediated neurological disorders owing to its rapid onset of action. Moreover, other TPE indications include hematological, renal & rheumatic disorders, and solid organ transplantation.[6] In Pakistan, there is limited information available about the continuous revisions and updates in the spectrum of indications for TPE. Hence, the current study was conducted to obtain the evidence-based frequency of indications in order to assist clinicians in carrying out the TPE procedure as an efficacious treatment modality.

METHODOLOGY

This cross-sectional study was conducted at the Plasma Exchange Unit of Pak Emirates Military Hospital, Rawalpindi from July to December 2021.

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After obtaining approval (Letter No. AFIT-ERC-20-012, 17-03-2020) from the institutional review board, a total of 81 patients were included using non-probability consecutive sampling technique. Sample size was calculated using OpenEpi software with confidence interval of 95%, margin of error of 7%, and anticipated frequency of TPE for vasculitis as 11.4%.[7] Patients who presented with indication of therapeutic plasma exchange were included after obtaining informed written consent. Patients who were unwilling to participate, undiagnosed at the time of the study, and undergoing apheresis for any cellular blood component were excluded.

All patients were also informed about the outcomes and associated risks following the TPE procedure. Data regarding demographics such as age and gender, total TPE procedures, clinical response, and fatal events were recorded through questionnaire. Plasma exchange was carried out using centrifugation-based instrument (Fresenius, Germany) under the supervision of physician and transfusion medicine specialist. In each session, a total of 3-4 liters of whole blood was processed and about 1.5-2 liter plasma was exchanged with albumin and fresh frozen plasma as a replacement fluid depending on the patient's condition. The most common indications of therapeutic plasma exchange along with their frequencies were noted according to the ASFA Classification categories (I, II, III, and IV).[5] The clinical outcomes of patients were recorded.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 23.0 was used to analyze data. Descriptive statistics were applied to summarize demographics, TPE indications, and clinical outcomes as frequencies and percentages.

RESULTS

A total of 81 patients meeting the eligibility criteria were recruited during 6 months study period and underwent 405 TPE procedures. On an average, the range of treatment sessions in each category was 4-5 cycles. Out of 81, 60(74.1%) were males and 21(25.9%) were females with a male-to-female ratio of 2.8:1. Patients were stratified into various age groups and most of the patients were in a range of 31-50 years (Figure 1).

A total of 17 TPE indications were noted and categorized into various subcategories including neurological, hematological, renal & rheumatic disorders, and others. In 67(82.7%) cases, TPE was performed as per ASFA guidelines. Neurological conditions (76.5%) were the predominant TPE indications followed by hematological disorders (11.1%), while renal (3.7%), rheumatic disorders (4.9%), and others (3.7%) were less prevalent.

According to ASFA guidelines, most of the indications fall in category I which was observed in 51(63%) cases. Out of total, 11(13.6%), 4(4.9%), and 1(1.2%) patient were in category II, category III, and category IV, respectively. However, 14(17.3%) patients who underwent TPE did not have any classified cause according to ASFA guidelines. Out of total, 49(60.5%) patients responded positively to treatment, 21(26%) patients did not show any improvement after TPE, whereas death was reported in 11(13.5%) patients (Table 1).

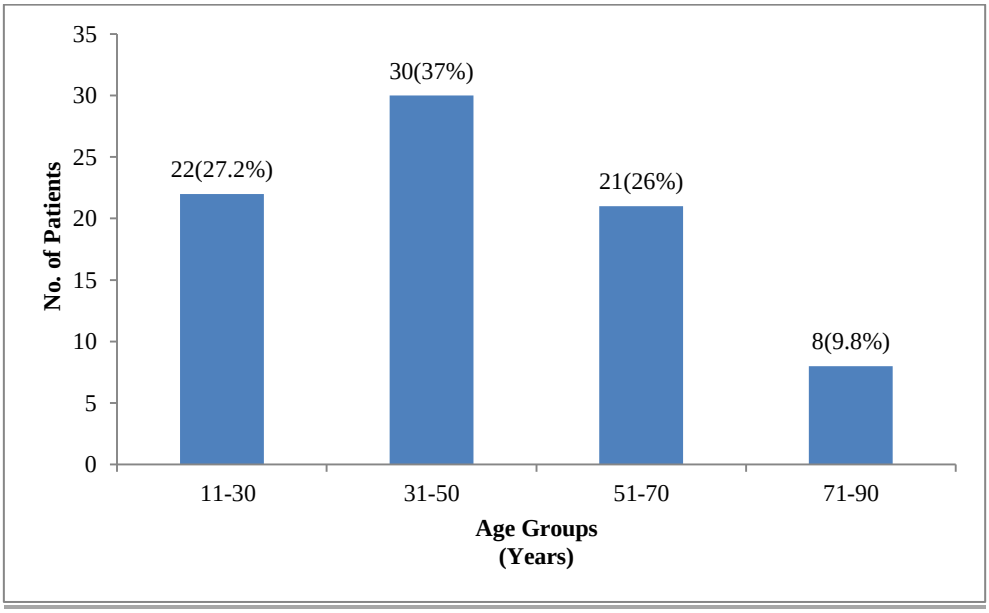

Figure 1: Distribution of Patients by Various Age Groups

Table 1: Clinical Response in Patients who underwent Therapeutic Plasma Exchange at Tertiary Care Hospital

TPE Indication		Number of Patients	ASFA Category 2019	Patients with Improvement n(%)	Patients with no Improvement n(%)	Expired Patients n(%)
Neurological Disorders	**Guillain-Barre Syndrome**	28(34.6%)	I	21(75%)	4(14.3%)	3(10.7%)
	Chronic Inflammatory Demyelinating Polyradiculoneuropathy	12(14.8%)	I	7(58.3%)	3(25%)	2(16.7%)
	Myasthenia Gravis	8(9.9%)	II	5(62.5%)	1(12.5%)	2(25%)
	Transverse Myelitis	10(12.3%)	Un-classified	4(40%)	6(60%)	-
	Neuromyelitis Optica Spectrum Disorder	3(3.7%)	II	2(66.7%)	1(33.3%)	-
	Subarachnoid Hemorrhage	1(1.2%)	Un-classified	-	1(100%)	-
	Total	62(76.5%)	-	39(62.9%)	16(25.8%)	7(11.3%)
Hematological Disorders	**Thrombotic Thrombocytopenic Purpura**	6(7.4%)	I	3(50%)	1(16.7%)	2(33.3%)
	Hemolytic Uremic Syndrome	1(1.2%)	I	-	-	1(100%)
	Multiple Myeloma	2(2.5%)	III	2(100%)	-	-
	Total	9(11.1%)	-	5(55.6%)	1(11.1%)	3(33.3%)
Renal Disorders	**Chronic Glomerulonephritis**	2(2.5%)	III	-	2(100%)	-
	Renal Transplant	1(1.2%)	I	1(100%)	-	-
	Total	3(3.7%)	-	1(33.3%)	2(66.7%)	-
Rheumatic Disorders	**Rheumatoid Arthritis**	1(1.2%)	IV	1(100%)	-	-
	Lower Limb Vasculitis	2(2.5%)	I	1(50%)	1(50%)	-
	Vasculitis	1(1.2%)	I	1(100%)	-	-
	Total	4(4.9%)	-	3(75%)	1(25%)	-
Others	**Dermatoses**	1(1.2%)	Un-classified	1(100%)	-	-
	Chronic Obstructive Pulmonary Disease	1(1.2%)	Un-classified	-	-	1(100%)
	Sertoli Cell Only Syndrome	1(1.2%)	Un-classified	-	1(100%)	-
	Total	3(3.7%)	-	1(33.3%)	1(33.3%)	1(33.3%)

DISCUSSION

Therapeutic plasma exchange is employed in treatment of many autoimmune disorders which is based on the removal of disease-causing substances from patient blood.[3] Majority of the participants in our study were males. A study by Solanki et al. also reported male predominance, whereas in contrast female predominance was observed by Chegini et al.[8,9] Another study conducted in Rawalpindi, Pakistan also showed majority of male population.[10] Therapeutic apheresis is not commonly performed for patients at extremes of ages because fragile vascular systems of children and comorbidities/polymedication in elderly patients are likely causes of consequent complications.[11] In our study, a small proportion of elderly patients underwent TPE after necessary precautions under close supervision of the expert staff.

In this study, neurological disorders constituted a major portion in TPE indications as observed in 62(76.5%) cases. The most frequent indication was Guillain-Barre syndrome (GBS) followed by chronic inflammatory demyelinating polyradiculoneuropathy and myasthenia gravis (MG). Current findings are in contrast with a survey conducted by Korkmaz et al. which demonstrated MG as the most common TPE indication among neurological disorders.[12] Guillain-Barre syndrome and MG were less frequent TPE indications reported in a study from the Neuroscience Centre of the United Kingdom.[13] A study from Egypt reported GBS as the main indication which is consistent with our findings.[14] The total number of patients improved after TPE in our study was 49(60.5%) while 21(26%) patients did not show any improvement after TPE. A study conducted in Switzerland reported an overall survival rate of 88.6% in patients after TPE.[7] In another study, 76.2% of total patients experienced symptom regression after TPE whereas in patients diagnosed with GBS, 57.1% showed improvement.[15] In our study, we found improvement in 75% of GBS patients. However, a study conducted by Seyhanli et al. showed that a large number of patients with neurological diseases failed to respond to TPE, having allergic reactions and hypotension.[16]

Hematological conditions accounted for 11.1% of TPE indications. The most prevalent was TTP which is a life-threatening disorder and procedure should be initiated within 4-6 hours. This emergent indication is associated with significant mortality if TPE is not performed timely.[3] Our study showed that TPE was being performed majorly for good

evidence indications (category I/II) which is in accordance with the study carried out by Ranganathan et al.[17] Only one patient in our study who underwent TPE was a diagnosed case of rheumatoid arthritis (RA). Rheumatoid arthritis is classified as category IV and the application of TPE into the treatment of RA is not recommended according to ASFA guidelines. However, rational therapeutic choice could be considered when the substance to be removed is toxic and the half-life is longer than the duration of the process itself.[18] According to a study, the majority of these patients had a high titer of autoantibodies or hyperglobulinemia and had a poor response to conventional treatments, but showed a good response to TPE.[19] Therapeutic plasma exchange was also performed on 10 cases of transverse myelitis which have not been incorporated in ASFA guidelines. According to Ring et al., one-third of the indications in their study were also graded as unclassified as per ASFA guidelines.[7]

Our study also showed a death rate of 13.5%, which is quite low as compared to a Brazilian study where mortality rate after TPE was found to be 24%.[20] Another study reported 21% mortality rate among thrombotic thrombocytopenic purpura patients undergoing TPE.[21]

Less supporting data was found in the literature regarding the employment of TPE in other unclassified disorders. This highlights the need of rationale approach by the physicians for considering TPE as a treatment option in such cases. As these conditions hold low evidence, thus further evaluation is warranted, for the role of TPE.

CONCLUSION

Neurological diseases are the most common indications of therapeutic plasma exchange. Patient improvement was seen in more than half of the study population and deaths were reported in a few patients.

In addition, unclassified TPE indications have also been observed which warrants further evaluation.

LIMITATIONS & RECOMMENDATIONS

It was a single-centered study with a small sample size. Prospective multicenter surveillance systems are needed for monitoring TPE and its effects on various autoimmune diseases. In developing countries like Pakistan, healthcare facilities especially plasma exchange facility is inaccessible to people living in remote and rural areas due to which delayed presentation of patients may worsen their existing condition and get no benefit despite prompt management by TPE. Further research is recommended to gain a deeper understanding of the efficacy and safety of TPE in different neurodegenerative diseases in our population.

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Authors' Contributions:
M.A.R: Study design/concept, study planning, data collection, experimentation/study conduction, manuscript writing, analysis/interpretation, and discussion writing
M.K: Study planning, data collection, experimentation/study conduction, and facilitation for study analysis
A.J.A: Analysis/interpretation, discussion, and statistical analysis
M.A.R: Study planning, data collection, experimentation/study conduction, and facilitation for study analysis
W.H: Analysis/interpretation, discussion, and writing critical review
M.K: Data analysis and critical review
I.Q.J.H: Data analysis and critical review

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Original Article

Diagnostic Accuracy of Ultrasound in Differentiating Benign and Malignant Thyroid Nodules taking Fine Needle Aspiration Cytology as Gold Standard

Sara Waheed, Muhammad Saleem Akhter

ABSTRACT

Objective: To assess the diagnostic accuracy of ultrasound in differentiating benign and malignant thyroid nodules taking fine needle aspiration cytology as gold standard.

Methodology: This descriptive cross-sectional study was carried out in the Department of Radiology, Sahiwal Teaching Hospital, Sahiwal from April 2022 to October 2022. Two hundred and eleven patients of both genders with an age range of 16-65 years having thyroid nodules were included in the study. The subjects with proven thyroid malignancy, receiving any treatment, or with recurrent nodules were excluded. Selected patients underwent ultrasound to label thyroid nodules as benign (negative) or malignant (positive). Afterwards, nodules were confirmed as benign (negative) or malignant (positive) on fine needle aspiration cytology (FNAC). Data was interpreted using the Statistical Package for the Social Sciences (SPSS) version 25. We estimated the sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of ultrasonography taking FNAC as the gold standard.

Results: The mean age of patients in this study was 46.11±9.85 years. Out of 211 patients, 138 (65.4%) were females and 73 (34.6%) were males. Ultrasonography identified malignant thyroid nodules in 103(48.8%) patients, demonstrating sensitivity and specificity of 83.33% and 91.75%, respectively. The diagnostic accuracy of ultrasonography in differentiating benign and malignant thyroid nodules was 87.2% keeping FNAC as the gold standard.

Conclusion: Ultrasound is an exceptionally sensitive and accurate method used to distinguish between malignant and benign thyroid nodules, which is helpful in timely diagnosis and suitable management planning.

Keywords: *Thyroid nodule. Fine needle aspiration. Ultrasonography.*

INTRODUCTION

Thyroid nodule is a swelling that arises in the thyroid gland. It is a distinct lesion separated from rest of the thyroid parenchyma.[1] The overall worldwide prevalence of thyroid nodules is 24.83%, which has increased over the successive years.[2] Females are reported to be more prone to develop thyroid nodules than males (36.51% versus 23.47%). In Pakistan, 78% of thyroid nodules are found to be benign, whereas 22% of the cases are labelled as malignant.[3]

Various risk factors contribute to the development of malignant thyroid lesions including increased radiation exposure, especially to the head and neck, genetic mutations, decreased iodine intake, underlying autoimmune conditions, high estrogen levels, increased exposure to environmental pollutants, and high body mass index.[4] Benign thyroid nodules commonly present without any symptoms. The main goal of assessing thyroid nodules is to timely and accurately identify the malignant lesions and also avoid unnecessary intervention and over-treatment.[5]

Imaging remains a main tool for the assessment of thyroid nodules. It also aids in developing a management plan for these nodules. Different imaging modalities are widely in use to assess thyroid lesions like sonography, computed tomography (CT), and magnetic resonance imaging (MRI). These imaging methods are valuable for planning surgery and postoperative monitoring.[6]

Among various imaging modalities, ultrasonography can detect thyroid nodules in approximately 68% of cases.[7] Ultrasound examination helps to assess various characteristics of thyroid lesions including size, margins, calcifications, and cervical lymph node enlargement.[8]

Although imaging modalities are beneficial in the initial analysis of thyroid swellings, FNAC further aids in assessing these lesions. Fine needle aspiration cytology helps clinicians to identify malignant cases and it also aids in avoiding non-essential surgical procedures. Fine needle aspiration cytology is an invasive procedure.[9]

The rationale of our research was to ascertain the diagnostic accuracy of ultrasound in differentiating benign and malignant thyroid enlargement, using FNAC as gold standard. As ultrasound is being widely used as a non-invasive imaging modality to evaluate thyroid nodules, its reliability in differentiating benign from malignant lesions has not been extensively validated in the local population. To date, published data from our region is lacking regarding the effectiveness of ultrasound in this context, creating a gap in evidence-based practice. This study aims to fill this gap by offering essential insights into the diagnostic utility of ultrasound, thus enhancing the prompt diagnosis and effective management of thyroid nodules.

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METHODOLOGY

This descriptive cross-sectional study was carried out at the Radiology Department of Sahiwal Teaching Hospital, Sahiwal from April 2022 to October 2022. Sample size of 211 was calculated at 95% confidence level and margin of error as 5%, taking the prevalence of thyroid nodules as 26.0%, sensitivity of ultrasonography at 93.15%, specificity at 89.86%, and desired precision level at 0.10.[10,11] After obtaining ethical approval (Letter No. 93/SLMC/SWL, 19-06-2021) from the ethical review committee, patients were selected using non-probability consecutive sampling technique. Two hundred and eleven patients of both genders with an age range of 16-65 years having thyroid swelling were included. Subjects with proven thyroid malignancy, recurrent nodules, or receiving any treatment were excluded. Informed consent was obtained from the patients. Ultrasonography was carried out by a consultant radiologist on Esaote MyLab Twice ultrasound machine having 3.5-5 MHz Curvilinear and 7.5-15 MHz Linear probe. Reports were assessed and the presence of benign or malignant thyroid nodule was noted following standard thyroid imaging reporting and data system (TI-RADS) criteria. Nodules showing features of cystic lesions, hyperechoic, smooth regular margins, without microcalcifications, and shape wider than taller were considered benign and labelled as negative. Nodules exhibiting features of solid lesions, hypoechoic, irregular margins, exhibiting microcalcifications, and shape taller than wider were diagnosed as malignant and positive.[12] Afterwards, patients were sent for FNAC. All samples were obtained under local anesthesia. Samples were taken and sent for cytology. Samples exhibiting features of being less cellular, cystic with colloid cells, and distinct margins were labelled as negative (benign). Microscopic examination of malignant or positive lesions showed features of increased cellularity, sheets of cells, absent or scant colloid, and indistinct margins.[12]

The lesions that were positive or negative on both modalities were defined as True positive (TP) or True negative (TN), respectively. False positive (FP) was defined as those lesions which were positive on ultrasound but negative on FNAC, while false negative (FN) was defined as those lesions which were positive on FNAC but negative on ultrasound.

STATISTICAL ANALYSIS

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 25. Quantitative data were reported as mean±standard deviation (SD), while qualitative variables were represented as frequency and percentage. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of ultrasound were determined using FNAC as a gold standard test. To compare the effectiveness of ultrasonography, the paired sample t-test was used, considering a p-value of ≤ 0.05 as significant.

RESULTS

The current study evaluated 211 participants aged between 16 and 65, with mean age of 46.11 ± 9.85 years. One hundred and forty three (68%) subjects were between 41-65 years, while 68(32%) fell between 16-40 years of age.

Majority of the patients [138(65.4%)] were females, whereas 73(34.6%) were males and a female-to-male ratio of 1.9:1. Ultrasound was carried out on all subjects enrolled in the study, showing malignant thyroid nodules in 103(48.8%) patients. Afterwards, FNAC, regarded as the gold standard, confirmed malignant thyroid nodules in 114(54%) cases (Table 1). This difference in detection rate between both modalities shows that FNAC identified a few more cases that were missed on ultrasound. The effectiveness of ultrasonography was then assessed as opposed to FNAC results. The sensitivity of ultrasonography was shown to be 83.33%. This showed that among all subjects having thyroid nodules, 83.33% were shown malignant by ultrasonography. Specificity of ultrasonography was 91.75%. This high specificity is suggestive of the effectiveness of ultrasonography in ruling out patients who do not have malignant thyroid nodules, thus reducing the probability of false positives. The PPV of ultrasonography i.e. probability of ultrasound to assess malignant thyroid nodules truly among all positive results was found to be 92.23%, highlighting that there was a high probability that the malignant nodule was present. Conversely, NPV was 82.41%, manifesting that when the lesion was not detected by ultrasonography, there was an 82.41% chance that the subject indeed did not have a malignant thyroid nodule. Overall, the diagnostic accuracy of ultrasonography was calculated to be 87.20%. It demonstrated statistically significant accuracy in diagnosing malignant thyroid nodules, with a p-value of 0.0001.

Table 1: Diagnostic Accuracy of Ultrasonography and FNAC for Detection of Thyroid Nodules

Diagnosis of Thyroid Nodules	Positive Result on FNAC	Negative Result on FNAC	p-value
Positive on Ultrasound	95(TP)	08(FP)	0.0001*
Negative on Ultrasound	19(FN)	89(TN)	

**Significant p-value*

Table 2: Parameters of Diagnostic Accuracy of Ultrasonography

Diagnostic Parameters	Ultrasonography
Sensitivity	83.33%
Specificity	91.75%
Positive Predictive Value	92.23%
Negative Predictive Value	82.41%
Diagnostic Accuracy	87.20%

DISCUSSION

The increasing prevalence of thyroid nodules especially among females, emphasizes the importance of precise and early diagnosis for timely clinical management.[13] Our study supports this imaging tool as reliable in differentiating benign from malignant thyroid nodules.

The mean age of participants in our study was 46.11±9.85 years and most of the patients [143(68%)] belonged to the 41–65 years age group, aligning with the existing literature that indicates that the probability of thyroid nodules increases with age. Ospina et al. reported similar findings that the probability of developing thyroid nodules increases with advanced age, emphasizing age as an important cause for concern in the growth of thyroid nodules.[14] This highlighted age as a predisposing factor in thyroid nodules growth and leads to the understanding that changes related to aging in the thyroid gland contribute to the formation of nodules.

Consistent with the previous research, our study observed a higher prevalence of thyroid nodules among females and a female-to-male ratio of 1.9:1. Comparable results were noted in a research study carried out in China by Li et al., which reported that females tend to have a higher incidence of thyroid nodules (44.7% versus 29.9% in males), which might be due to hormonal influence.[15] A high female-to-male ratio (7.7:1) was also found in another study.[16] This gender disparity is often attributed to hormonal influences, particularly the effects of estrogen and other sex hormones, which may contribute to thyroid cell growth and function. A higher prevalence of thyroid nodules in females emphasizes the need for targeted screening and early diagnostic strategies in this population, particularly for women in middle age and beyond, when the risk appears to be the highest.[17]

In the present study, ultrasonography detected thyroid nodules in 103(49%) patients. This detection rate is comparable to that reported by Rothberger et al. They identified thyroid lesions in 34% of the patients using ultrasonography.[18] This consistency highlights the reliability of ultrasonography in identifying thyroid nodules across diverse patient populations and clinical settings.

Alexander et al. documented sonography as a useful modality for serial monitoring of nodules.[19] This role is particularly significant in case management of benign thyroid nodules or those under active surveillance for nodules with indeterminate cytology. Serial ultrasound evaluations allow clinicians to track changes in nodule size, shape, and echogenicity over time, which may provide critical information about the progression or stability of the lesions.[20]

The high sensitivity (83.33%) and specificity (91.75%) of ultrasonography observed in our study further corroborate its use in clinical settings. These findings reflect the results of a study carried out by Ren et al. in 2019 highlighting sonography's role in distinguishing benign from malignant thyroid nodules.[21] The consistency of our findings with previously published data emphasizes the robustness of ultrasonography as a non-invasive, accurate, and efficient modality for evaluating thyroid nodules, thereby reinforcing its importance in routine diagnostic workflow.

The positive predictive value of thyroid ultrasonography was 92.23%, and the negative predictive value was 82.41%. These values show that ultrasonography is not only effective in diagnosing thyroid nodules but also in excluding patients without nodules and reducing the probability of unessential interventions. The diagnostic accuracy of 87.20% observed in our study was statistically significant with a p-value=0.0001 and encourages the use of ultrasonography as a first-line diagnostic modality for thyroid nodules. Similar results were reported by Tareen et al. The diagnostic accuracy of ultrasonography was 91.55% in this study.[11] Another study reported a comparable accuracy of 89.33%, further strengthening the utility of ultrasonography in clinical settings.[22]

A study conducted in Yemen in 2019 documented ultrasonography as an excellent tool to assess thyroid nodules based on certain specific features such as shape, nature of margins, echogenicity, and calcifications. These features were utilized as critical criteria for differentiating between benign and potentially malignant nodules. They found the sensitivity and specificity of ultrasound in diagnosing benign nodules of the thyroid to be 98.38% and 71.42%, respectively, indicating that ultrasonography is highly effective in correctly identifying benign thyroid nodules.[23]

Fine needle aspiration cytology remains the gold standard for determining the nature of thyroid nodules, especially in cases where ultrasonography alone may

be insufficient to detect malignancy. Naveen et al. recommended to correlate ultrasound findings with FNAC results for optimal diagnosis and management. This integrated approach minimizes the risk of misdiagnosis, allows for early detection of malignant lesions, and aids in planning an effective management plan for such patients.[24]

Another study demonstrated the sensitivity, specificity, and positive predictive value of ultrasound in evaluating thyroid nodules to be 92.31%, 97.30%, and 92.31%, respectively recommending ultrasound as high yield tool to differentiate benign lesions from malignant.[25]

CONCLUSION

Ultrasonography is a highly sensitive, accurate, non-invasive, and cost-effective modality to differentiate malignant and benign nodules of the thyroid gland. This will aid in improving patient care by timely diagnosis, appropriate treatment, and avoiding unessential biopsies with consequent reduction in patient morbidity and mortality.

LIMITATIONS & RECOMMENDATIONS

The small sample size was one of the limitations of the study. Furthermore, most of the nodules in our findings turned out to be benign limiting the interpretation. Therefore, future studies recruiting a substantial number of subjects are suggested in the future.

Conflict of interest: None.
Source of funding: None.

Authors' Contributions:
S.W: Concept of the study, drafting, collection of data, and statistical analysis
M.S.A: Concept of the study, drafting, statistical analysis, and final approval

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Original Article

Efficacy and Safety of Dapagliflozin in Patients of Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Objective: To find the efficacy and safety of dapagliflozin in patients of heart failure with reduced ejection fraction (HFrEF).

Methodology: This quasi-experimental study was conducted at the Punjab Institute of Cardiology, Lahore from July 2023 to August 2024 after obtaining ethical approval. This study included 220 patients diagnosed with heart failure with left ventricular ejection fraction (LVEF) below 40% and in a stable clinical condition through non-probability consecutive sampling technique. Participants were segregated into two distinct groups. Each group included 110 patients. Group I received dapagliflozin, whereas group II was administered a placebo. The Statistical Package for the Social Sciences (SPSS) version 29 was used for the analysis of data.

Results: The mean age of the participants in group I was 58.09±10.1 years, while it was 57.61±11.2 years in group II. Patients in both groups were taking comparable medication and no significant difference was found. Cardiovascular death took place in 50(22.7%) of dapagliflozin group, compared to 17(31.8%) in placebo group (p=0.15). In the dapagliflozin group, 18.2% of patients experienced hospitalization for heart failure compared to 31.8% in the placebo group, yielding hazard ratio of 0.57 (95% CI: 0.33–0.96; p=0.03). The difference in both groups was insignificant for the rate of volume depletion (8% vs. 5%, p=0.41) and renal dysfunction (5% vs. 7%, p=0.56). The dapagliflozin group depicted a profound improvement in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score (10 points vs. 4 points, p=0.01) and a mean difference of +6 in KCCQ score compared to placebo (p=0.02).

Conclusion: Dapagliflozin enhances the quality of life of heart failure with reduced ejection fraction enormously lowers the likelihood of worsening heart failure, and decreases cardiovascular deaths.

Keywords: *Sodium-glucose transporter 2. Heart failure. Cardiovascular death.*

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) represents a major clinical issue marked by the heart's reduced capacity to pump blood effectively, resulting in a series of severe symptoms and a higher risk of death. The management of HFrEF has traditionally relied on a combination of lifestyle modifications, pharmacological interventions, and, in some cases, device therapies.[1] Despite these treatment options, morbidity and fatality rates remain high, necessitating the exploration of new therapeutic options. Congestive cardiac failure, especially heart failure with normal left ventricular ejection fraction, is seen more frequently among individuals with type 2 diabetes compared to the general population.[2] Diabetes and heart failure with reduced ejection fraction are associated with multiple comorbidities, such as obesity, insulin resistance, hypertension, and coronary artery diseases.[3] The hospitalized HFrEF population with and without diabetes mellitus had poorer outcomes than the general population.[4] Patients with diabetes had worse outcomes compared to those without diabetes.[5] Dapagliflozin acts as a competitive sodium-glucose transporter 2 (SGLT2) antagonist. The type 2 sodium-glucose transporters are found on the epithelial cells in the proximal end of the convoluted tubule segment S1 of the kidney. Functionally, 90% of glucose reabsorption is accomplished by these transporters in the kidneys.[6] Dapagliflozin inhibits glucose reabsorption by blocking SGLT2.[7] Dapagliflozin was initially utilized in the management of type 2 diabetes mellitus but now it has emerged as a promising agent in cardiovascular disease.[8] It has cardiovascular protective effects. It acts as diuretics and decreases ventricular load. It reduces cardiovascular death and worsening of heart failure.[9] Notably, clinical trials have indicated that dapagliflozin can lower hospitalization risk for heart failure and cardiovascular mortality in patients diagnosed with HFrEF, irrespective of their diabetic status.[10] Literature on the efficacy of dapagliflozin is lacking. So, this study was planned to find the efficacy and safety of dapagliflozin in patients of heart failure with reduced ejection fraction.

METHODOLOGY

This quasi-experimental study was conducted at the Punjab Institute of Cardiology, Lahore for a duration of more than one year from July 2023 to August 2024. A sample size of 155 was calculated using the prevalence of heart failure in Pakistan, estimated to be approximately 10% at 95% confidence level and a 5% margin of error.[11] However, 220 participants were included to ensure adequate statistical power and balance across the quasi-randomized groups.

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After obtaining ethical approval (Letter No. Research/ERC/Cardiology/153, 28-06-2023), this study included patients with diagnosed heart failure through non-probability consecutive sampling technique after informed consent. The stable patients of heart failure with LVEF <40% were enrolled. Patients having a history of renal impairment, i.e. estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m², insulin-dependent diabetes mellitus, myocardial infarction or cerebrovascular disease in the past 3 months were excluded. Participants were segregated into two distinct groups. Each group included 110 patients. Group I received treatment with dapagliflozin, while group II was administered a placebo. Patients in both groups continued to receive standard care for HFrEF, including angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, beta-blockers, mineralocorticoid receptor antagonists, diuretics, and statins according to guidelines. Patients in group I received 10 mg of dapagliflozin once daily, while group II patients received a matching placebo for blinding of patients. The primary efficacy endpoints were cardiovascular death, hospitalization, and emergency visits. Safety endpoints encompassed the incidence of volume depletion, decline in eGFR, renal dysfunction, and hypoglycemia. The Kansas City Cardiomyopathy Questionnaire was employed to assess the quality of life (QOL), functional status, and symptom burden. Scores were recorded at baseline, and changes were assessed at 6 months to evaluate primary endpoints, safety, and treatment efficacy.

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 29 was used for the analysis of data. Mean±standard deviation (SD) was calculated for continuous variables and frequencies and percentages for categorical variables. The primary efficacy endpoint, cardiovascular death, hospitalization rates, and emergency visits were assessed by Cox Proportional Hazard Ratios with 95% confidence intervals. Statistical differences of numerical variables such as mean difference in KCCQ score, and days of hospitalization were analyzed by independent t-test. The Chi-square test was applied to compare volume depletion, renal dysfunction, and hypoglycemia. A p-value of ≤0.05 was taken as significant.

RESULTS

The mean age of the participants in group I was 58.09±10.1 years, while it was 57.61±11.2 years in group II. Table 1 presents the demographic and clinical data for both groups. The patients in each group were on similar medications with no significant difference noted (Table 2).

In group I, cardiovascular death occurred in 50(22.7%) patients compared to 70(31.8%) patients in the placebo group, showing a hazard ratio of 0.70 (95% CI: 0.43-1.14; p=0.15), indicating a potential decrease, although it lacked statistical significance.

In the dapagliflozin group, 18.2% of patients experienced hospitalization for heart failure compared to 31.8% in the placebo group, yielding hazard ratio of 0.57 (95% CI: 0.33-0.96; p=0.03), indicating a significant decline. Similarly, emergency visits were lesser in the dapagliflozin group (13.6% vs. 25.5%) with hazard ratio of 0.53 (95% CI: 0.29-0.95; p=0.03), demonstrating a significant decrease (Table 3). Regarding hospitalization, the mean hospital stay was 5.5±2.5 days in group I and it was 8.0±3.0 days in group II. A statistically significant difference was found between two groups regarding hospitalization (p=0.01).

The difference in both groups was insignificant for the rate of volume depletion (8% vs. 5%, p=0.41) and renal dysfunction (5% vs. 7%, p=0.56). Severe hypoglycemia was not reported in both groups. Reduction in eGFR was -1.5 mL/min/1.73 m² in dapagliflozin group, whereas in placebo group, it was -3.0 mL/min/1.73 m² (p-value=0.03). Patients receiving dapagliflozin showed 10 points mean improvement in the KCCQ score compared to 4 points in the placebo group (p=0.01), signifying enhanced quality of life. Additionally, the mean difference in KCCQ score was +6 in the dapagliflozin group compared to placebo (p=0.02), indicating a significant improvement (Table 4).

DISCUSSION

Our results showed that in patients treated with dapagliflozin, cardiovascular death occurred in 50(22.7%) patients as compared to 70(31.8%) patients in the placebo group. In the dapagliflozin group, 18.2% of patients required hospitalization due to heart failure, compared to 31.8% in the placebo group. Another study concluded that in patients with HFrEF, the use of dapagliflozin significantly decreased cardiovascular death and hospitalization because of heart failure worsening.[12] A randomized trial was carried out to assess the efficacy of dapagliflozin in patients of heart failure with reduced ejection fraction as compared to placebo. This trial showed 9.6% cardiovascular deaths in the dapagliflozin group as compared to 11.5% in the

placebo group with a p-value of 0.001. Furthermore, 10.0% and 13.7% of patients experienced heart failure in the dapagliflozin and placebo groups, respectively.[5]

The renal dysfunction was decreased in the dapagliflozin group as compared to the placebo group (5% vs. 7%). In both groups, there is a small reduction in the estimated glomerular filtration rate but the lesser reduction in the dapagliflozin group is pointing to a renal protective effect. Another study observed that the risk of deterioration of eGFR was high in the placebo group when compared with the dapagliflozin group.[13] Jhund et al. conducted a study to evaluate the efficacy of dapagliflozin in HFrEF patients. They concluded that dapagliflozin slowed the decline rate of eGFR.[8] A randomized controlled trial was conducted on 6263 patients to assess the effectiveness of dapagliflozin in improving QOL of heart failure patients with normal or slightly decreased ejection fraction. They concluded that dapagliflozin lowers the likelihood of events of worsening heart failure, cardiovascular death, and renal failure. It also slowed the rate of kidney dysfunction.[14] The reduction in the number of patients with heart failure and those admitted to the hospital, as well as emergency visits, exemplified the drug's efficacy. These reductions in hospitalization and emergency visits result in; cost savings and change in healthcare burden hence dapagliflozin demonstrated the potency to positively affect healthcare utilization in HFrEF patients. A randomized trial reported that dapagliflozin reduces the decline in eGFR, renal failure, cardiovascular mortality, and hospitalization due to heart failure.[15] A meta-analysis concluded that dapagliflozin significantly reduces cardiovascular deaths, hospitalization due to heart failure, hospital visits, and all-cause mortality.[16]

Table 1: Demographic and Clinical Data of Patients

Demographic Characteristic		Dapagliflozin Group (n=110)	Placebo Group (n=110)
Age (Years)	**Mean± SD**	58.09±10.1	57.61±11.2
Gender (Frequency and Percentage)	**Male**	60(54.5%)	67(61%)
	Female	50(45.5%)	43(39%)
BMI (kg/m^2)	**Mean± SD**	28±5	29±6
Smoking Status (Frequency and Percentage)	**Current Smoker**	27(24.5%)	30(27.3%)
	Former Smoker	50(45.5%)	45(40.9%)
	Non-Smoker	33(30)	35(31.8%)
Comorbidities (Frequency and Percentage)	**Hypertension**	80(72.7%)	78(71%)
	Diabetes Mellitus	40(36.4%)	42(38.2%)
	Chronic Kidney Disease	15(13.6%)	17(15.5%)

Table 2: Medication Usage of Study Participants of Both Groups

Medication Usage	Dapagliflozin Group (n=110)	Placebo Group (n=110)	p-value
	Frequency and Percentage		
Angiotensin-Converting Enzyme Inhibitors	60(55%)	62(56%)	0.88
Angiotensin II Receptor Blockers	34(31%)	33(30%)	0.89
Beta-Blockers	99(90%)	98(89%)	0.88
Diuretics	82(75%)	83(76%)	0.87
Mineralocorticoid Receptor Antagonists	45(41%)	46(42%)	0.87
Statins	70(64%)	68(62%)	0.77

Table 3: Efficacy Outcomes of Study Groups

Efficacy Outcomes	Hazard Ratio	95% Confidence Interval	p-value
Cardiovascular Death	0.70	0.43-1.14	0.15
Hospitalization Rate	0.57	0.33-0.96	0.03*
Emergency Visits	0.53	0.29-0.95	0.03*

**Significant p-value*

Table 4: Quality of Life Scores of Study Groups

KCCQ Score	Dapagliflozin Group (n=110)	Placebo Group (n=110)	p-value
Improvement in KCCQ Score (mean points)	+10	+4	0.01*
Quality of Life (mean KCCQ difference, at baseline and 6 months)	+6	+2	0.02*

**Significant p-value*

Our results showed that dapagliflozin improves KCCQ score and quality of life. Important components associated with symptoms, the highest level of function, and health-related quality of life all showed significant improvements, as depicted by the KCCQ scores in our study. In our study, the patients in the dapagliflozin group showed a mean improvement of 10 points compared to patients in the placebo group who demonstrated a mean improvement of 4 points at 6 months. This indicates not only a decrease in clinical events but also improvement in patient quality of life by dapagliflozin. Another study was conducted to analyze the efficacy of dapagliflozin on health status outcomes in patients with heart failure through KCCQ. Patients were evaluated at 4 & 8 months and it was reported that patients treated with dapagliflozin had more improvement in mean KCCQ score at 8 months follow-up in comparison to placebo (p-value <0.0001). The study concluded that dapagliflozin reduced the worsening of heart failure and cardiovascular mortality. Moreover, it also improved QOL and health status of included patients.[17]

A study conducted by Kosiborod et al. reported that dapagliflozin improves all domains of baseline KCCQ score and QOL of patients. It also reduces the worsening of heart failure and cardiovascular death as compared to placebo in patients of heart failure with reduced ejection fraction.[18]

CONCLUSION

Dapagliflozin significantly lowers the risk of worsening heart failure, cardiovascular mortality and improves the QOL in patients of heart failure with reduced ejection fraction.

LIMITATIONS & RECOMMENDATIONS

This was a single-centered study, limiting the generalizability of our findings. Future multi-centered studies in diverse geographical locations including patients with comorbidities, such as insulin dependent diabetes, advanced chronic kidney disease, and other cardiovascular conditions are recommended to enhance the external validity of these results.

Conflict of interest: None.
Source of funding: None.

Authors' Contributions:

K.Z: Data collection, analyzing data, interpretation of data, and supervision
S.M.H: Writing - review & editing and final approval
A.M: Methodology and design of work
M.I: Statistical analysis
A.M: Drafting the manuscript & revision and other related works
B.R.M: Data curation and practical work

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Original Article

Association of Knowledge of Upper Respiratory Tract Infections and Demographic Factors with Knowledge, Attitudes, and Practices regarding Antibiotic Use and Resistance in General Population of Punjab, Pakistan: A Cross-Sectional Study

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ABSTRACT

Objective: To assess the association of knowledge of upper respiratory tract infections (URTIs) and demographic factors with knowledge, attitudes, and practices (KAP) regarding antibiotic use and resistance in general population of Punjab, Pakistan.

Methodology: This descriptive cross-sectional study was conducted from August 2024 to November 2024 after obtaining ethical approval from the institution. Four hundred and thirty five participants from various regions of Punjab were included using non-probability convenience sampling. Individuals aged 18 years or above who were willing to participate and able to read & write with at least a high school degree were included. Individuals with a medical background, including healthcare professionals, medical students, paramedical, and allied health professionals were excluded. Data for demographics, knowledge about URTIs, and KAP regarding antibiotic use and resistance was collected and analyzed via descriptive statistics and Chi-square test of association. Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.0.

Results: The study included 435 participants with a mean age of 26.3±9.73 years. Among the respondents 177(40.69%) were males and 345(79.31%) had education above high school. Almost 78% of the participants showed poor knowledge about URTIs. Three hundred and twenty seven (75.2%) participants showed good knowledge about antibiotics with age, education, and urban residence being significantly associated with it. Out of 435, 195(44.8%) participants demonstrated appropriate attitudes, significantly associated with higher education and urban residence. Only 38.3% of participants demonstrated appropriate practices with age, gender, education, and residence showing a significant association. Having good knowledge about URTIs significantly raised the odds of having good knowledge and appropriate attitudes and practices regarding antibiotic use and resistance.

Conclusion: The participants have a satisfactory understanding regarding antibiotic use and resistance. However, they are still lacking adequate attitudes and practices regarding their use and resistance. There is a significant association between knowledge of URTIs, education level & residence and KAP regarding antibiotic use and resistance. Age has a significant relation with knowledge and practices regarding antibiotic use and resistance.

Keywords: *Respiratory tract infections. Anti-bacterial agents. Health knowledge, attitudes, practice.*

INTRODUCTION

Antimicrobial resistance (AMR) poses a significant global health threat, jeopardizing the efficacy of antibiotics essential for treating bacterial infections. In 2019 alone, it was estimated that bacterial AMR directly contributed to 1.27 million deaths worldwide.[1] Beyond diminishing clinical effectiveness, AMR also places a substantial burden on healthcare economics, thereby compromising the overall quality of healthcare. To address this challenge, the World Health Organization initiated the Global Antimicrobial Resistance and Use Surveillance System (GLASS), aimed at standardizing global AMR surveillance.[2] According to the 2022 GLASS report, data collected from 76 countries revealed that over 50% resistance among bacteria was observed against 18.1% of the analyzed antimicrobial combinations.[2] Pakistan ranks 29th globally in terms of age-standardized mortality rates associated with AMR, especially concerning bloodstream and lower respiratory tract infections.[3]

This highlights the urgent need to identify the precise factors driving AMR, specifically in lower-income countries, such as Pakistan. Among these factors, the most significant is the misuse and overuse of antimicrobials, often due to a lack of comprehensive understanding of AMR.[4] This misuse encompasses practices, such as self-medication with antibiotics, especially for viral infections where they are ineffective, leading to the accelerated emergence of drug-resistant pathogens.[4] Moreover, not following prescribed guidelines from healthcare professionals and failing to complete antibiotic courses further exacerbate this problem.[5] The inadequate understanding of AMR in Pakistan can be attributed to various factors, including low levels of health literacy, insufficient healthcare resources, patient overload in government hospitals, and deficient healthcare infrastructure in rural areas.[6] Additionally, the dispensing of non-prescribed antibiotics contributes significantly to the issue.[7]

The most common outpatient infections in Pakistan are URTIs with an observed increase in incidence

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rates of approximately 8.59% from 1990 to 2019.[8] Due to their widespread occurrence, URTIs are often linked with the improper use of antibiotics and self-medication.[9] This is problematic because URTIs are usually caused by viruses, against which antibiotics are ineffective. Consequently, the over-prescription and misuse of antibiotics for treating URTIs stand out as a critical concern in the fight against AMR.[10]

A previous study has revealed less than satisfactory level of knowledge about antibiotic use among the general population of Pakistan.[11] Therefore, it is imperative to develop awareness regarding highly resistant pathogens and implement antibiotic stewardship programs. Pakistan's National Action Plan on Antimicrobial Resistance 2017 outlines five primary objectives aimed at controlling AMR with a significant emphasis placed on educating and raising awareness among the population.[12]

Hence, evaluating the knowledge levels and associated factors among the general population regarding common infectious diseases, such as URTIs, becomes crucial. Such assessments can help target specific populations and address their educational needs. So, the rationale of this study was to evaluate the association of knowledge of URTIs and demographic factors with knowledge, attitude, and practices (KAP) regarding antibiotic use & resistance.

METHODOLOGY

This descriptive cross-sectional study was conducted at King Edward Medical University, Lahore from August 2024 to November 2024. The study was approved (Letter No. 447/RC/KEMU, 13-07-2024) by the ethical review board of the institution. A sample size of 369 participants was calculated using 40% prevalence of appropriate attitudes regarding antibiotic use at 95% confidence interval (CI) and 5% margin of error.[10] However, 435 participants met the eligibility criteria and were included in the study. A non-probability convenience sampling technique was used to select participants. Individuals aged 18 years or above who were willing to participate and able to read & write with at least a matriculation certificate were included. Individuals with a medical background, including healthcare professionals, medical students, paramedical, and allied health professionals were excluded. An online questionnaire, reaching data was collected through a validated questionnaire shared via Google Forms.[10] The online questionnaire was shared with individuals from various regions of Punjab including urban and rural areas, to ensure the representation of diverse population groups through various online platforms and social media channels. Eligible participants who met the inclusion criteria were asked to complete the questionnaire online. It assessed knowledge of URTIs and knowledge, attitudes, and practices regarding antibiotic use and resistance. For each KAP question, correct or appropriate responses were assigned a score of one point, while incorrect or inappropriate responses received a score of zero. The total score ranges for knowledge, attitude, and practice parts were 0-4 each. A cutoff of 2 points was used to classify participants into categories of good (>2) or poor (≤2) knowledge, appropriate (>2) or inappropriate (≤2) attitude, and appropriate (>2) or inappropriate (≤2) practices.

STATISTICAL ANALYSIS

Data was analyzed using the Statistical Package for the Social Sciences (SPSS) version 27.0. Descriptive statistics were used, including frequencies & percentages for categorical variables, and mean±standard deviation (SD) for continuous variables. The Chi-square test was utilized to find associations of KAP regarding antibiotic use and resistance with various sociodemographic characteristics and knowledge about URTIs.

RESULTS

The mean age of the participants was 26.3±9.73 years with the majority (82.76%) falling between 18-30 years. Among the respondents, 177(40.69%) were male and 345(79.31%) had education above high school. Table 1 shows the sociodemographic information of the study population.

Knowledge about URTIs:

Out of 435 participants, 318(73.1%) reported a history of URTI among which, 68.2% had received antibiotics for their last episode, and 73.8% of respondents believed antibiotics were necessary for treating URTIs. Also, 42.7% believed they contracted the infection from the environment, while 20% attributed it to a family member. Questions about URTI symptoms received the highest percentage (83%) of incorrect responses with only 17% of participants correctly identifying typical URTI symptoms. Overall, poor knowledge was observed in about 78% of the participants.

Knowledge about Antibiotic Use and Resistance:

Overall, 75.2% of respondents demonstrated good knowledge regarding antibiotic use and resistance with 40.7% out of total correctly answering all four questions. This suggests a satisfactory prevalence of adequate knowledge in the study population. Further analysis identified important demographic associations with the knowledge level. Participants

aged 18-30 years showed good knowledge in 72.5% of cases compared to 85.7% among those aged 31-50 years. The Chi-square test (p-value=0.011) indicated a significant association between age and antibiotic knowledge. Good knowledge was reported in 198(76.7%) females and 129(72.9%) males with no significant association between gender and antibiotic knowledge. Participants with education above high school demonstrated higher frequency (82.6%) of good knowledge compared to those with only high school education (46.7%), showing a significant association (p-value <0.001). Urban residents displayed better knowledge (79.7%) compared to rural residents (50%), indicating a significant association (p-value <0.001) between urban residents and antibiotic knowledge. Regarding knowledge about URTIs, participants with good knowledge about URTIs exhibited higher good knowledge rates about antibiotics (90.6%) compared to those with poor URTI knowledge (70.8%), showing a significant association (p-value <0.001).

Attitudes toward Antibiotic Use and Resistance:

Out of 435 participants, 44.8% of participants demonstrated appropriate attitudes. Regarding demographic factors, age did not show a significant association with attitude, as 44.2% of those aged 18-30 years, 47.6% aged 31-50 years, and 50% aged above 50 years exhibited appropriate attitudes. Similarly, gender did not significantly influence attitudes with 46.5% of females and 42.4% of males displaying appropriate attitudes. However, education level showed a significant association with 53% of participants with education above high school demonstrating appropriate attitudes compared to 13.3% with only high school education (p-value <0.001). Additionally, participants with good knowledge about URTIs displayed more appropriate attitudes (68.8%) than those with poor knowledge (38.1%), showing a significant association (p-value <0.001). Urban residents exhibited a higher proportion of appropriate attitudes (47.9%) compared to rural residents (27.3%) with a statistically significant association (p-value=0.002).

Practices regarding Antibiotic Use and Resistance:

Only 38.3% of participants showed appropriate practices, a lower prevalence compared to appropriate knowledge and attitudes regarding antibiotics as mentioned earlier. Regarding demographic factors, age showed a significant association with practices, with 75% of those aged above 50 years, 39.2% aged 18-30 years, and 28.6% aged 31-50 years exhibiting appropriate practices (p-value=0.009). Gender significantly influenced practices, as 46.5% of females compared to 27.1% of males demonstrated appropriate practices (p-value=0.001). Education level showed a significant association with practices. Participants with education above high school had higher rates of appropriate practices (41.8%) compared to those with only high school education (26.7%) (p-value=0.009). Participants with good knowledge about URTIs showed a significant trend towards higher rates of appropriate practices (53.1%) compared to those with poor knowledge (34.5%) (p-value <0.001). Similarly, urban residents displayed a trend towards more appropriate practices (41.5%) compared to rural residents (22.7%), (p-value=0.004).

Table 1: Sociodemographic Characteristics of Study Population

Parameter	Category	Frequency & Percentage
Age (Years)	**18-30**	360(82.76%)
	31-50	63(14.48%)
	>50	12(2.76%)
Gender	**Male**	177(40.69%)
	Female	258(59.31%)
Residence	**Urban**	369(84.83%)
	Rural	66(15.17%)
Type of Family	**Nuclear Family**	288(66.21%)
	Extended Family	147(33.79%)
Education Level	**High School**	90(20.69%)
	Above High School	345(79.31%)
Occupation	**Student**	276(63.45%)
	Private Job	78(17.93%)
	Housewife	36(8.27%)
	Business	30(6.9%)
	Government Job	15(3.45%)

Table 2: Comparison of Study Variables with Knowledge about Antibiotics Use and Resistance

Characteristic		Knowledge about Antibiotics		p-value
		Good	Poor	
Age (Years)	**18-30**	261(72.5%)	99(27.5%)	0.011*
	31-50	54(85.7%)	9(14.3%)	
	>50	12(100%)	0(0%)	
Gender	**Female**	198(76.7%)	60(23.3%)	0.360
	Male	129(72.9%)	48(27.1%)	
Education Level	**High school**	42(46.7%)	48(53.3%)	<0.001*
	Above high school	285(82.6%)	60(17.4%)	
Knowledge about URTIs	**Good**	87(90.6%)	9(9.4%)	<0.001*
	Poor	240(70.8%)	99(29.2%)	
Residence	**Urban**	294(79.7%)	75(20.3%)	<0.001*
	Rural	33(50%)	33(50%)	

**Significant p-value*

Table 3: Comparison of Study Variables with Attitudes towards Antibiotic Use and Resistance

Characteristic		Attitude towards Antibiotic Use and Resistance		p-value
		Appropriate	Inappropriate	
Age (Years)	**18-30**	159(44.2%)	201(55.8%)	0.822
	31-50	30(47.6%)	33(52.4%)	
	>50	6(50%)	6(50%)	
Gender	**Female**	120(46.5%)	138(53.5%)	0.394
	Male	75(42.4%)	102(57.6%)	
Education level	**High school**	12(13.3%)	78(86.7%)	<0.001*
	Above high school	183(53%)	162(47%)	
Knowledge about URTIs	**Good**	66(68.8%)	30(31.3%)	<0.001*
	Poor	129(38.1%)	210(61.9%)	
Residence	**Urban**	177(47.9%)	192(52.1%)	0.002*
	Rural	18(27.3%)	48(72.7%)	

**Significant p-value*

Table 4: Comparison of Study Variables with Practices regarding Antibiotic Use and Resistance

Characteristic		Practice regarding Antibiotic Use		p-value
		Appropriate	Inappropriate	
Age (Years)	**18-30**	141(39.2%)	219(60.8%)	0.009*
	31-50	18(28.6%)	45(71.4%)	
	>50	9(75%)	3(25%)	
Gender	**Female**	120(46.5%)	138(53.5%)	<0.001*
	Male	48(27.1%)	129(72.9%)	
Education level	**High school**	24(26.7%)	66(73.3%)	0.009*
	Above high school	144(41.8%)	201(58.2%)	
Knowledge about URTIs	**Good**	51(53.1%)	45(46.9%)	<0.001*
	Poor	117(34.5%)	222(65.5%)	
Residence	**Urban**	153(41.5%)	216(58.5%)	0.004*
	Rural	15(22.7%)	51(77.3%)	

**Significant p-value*

DISCUSSION

Knowledge, attitudes, and practices regarding antibiotic use have been extensively researched across various populations globally.[13] Large systematic reviews, including multinational studies have revealed low levels of knowledge about antibiotic resistance, leading to poor attitudes and practices in antibiotic use for treating infections.[13,14] Specifically, there is a common misconception in the larger global general population about antibiotics being effective against viral infections.[14] This issue is particularly important for common seasonal URTIs, which are typically caused by viruses.[9]

The results of our study revealed a significant association between knowledge of URTIs and knowledge, attitudes & practices regarding antibiotic use and resistance. Only 37% of participants were able to correctly identify the causative organisms of URTIs as bacteria & viruses and nearly all of them showed good knowledge and appropriate attitudes

regarding antibiotics. A survey conducted in India concluded that KAP regarding antibiotic use and resistance was poor in the general population. However, similar to our results, individuals with good knowledge regarding URTIs had high odds of good KAP.[10]

Some demographic variables also affect the KAP related to antibiotics. Our results revealed a significant association between education level and knowledge, attitudes & practices. A cross-sectional study conducted on the Malaysian population depicts that 67.5% of the included sample had inadequate knowledge regarding antibiotic use and resistance and people with high education level achieved better knowledge scores.[15] The reason seems to be that more educated individuals are better informed on the etiology of their illness and the concept of AMR, leading to more appropriate use of antibiotics.[16] Additionally, it has been shown that more educated people are likely to rely on physicians for medical advice.[17,18] Surveys conducted on educated parents have shown that over 90% follow their pediatricians' recommendations regarding antibiotic use for their children.[17,19] This trend is particularly common among educated mothers, who tend to be more health-conscious and actively seek knowledge about treatments for their children.[20] This, perhaps, could also shed light on why women had higher odds of having good knowledge and appropriate attitudes regarding antibiotics, though these associations were not statistically significant which could be a consequence of a small sample size. Residence also influenced knowledge, attitudes & practices about antibiotics use with urban residents having higher rates of good knowledge compared to rural residents (79.7% vs. 50%). This difference is likely due to the greater availability of health facilities and educational opportunities in urban areas.[21] Lastly, gender was significantly associated with practices regarding antibiotics with females having higher odds than males. As previously mentioned, this is probably because women are more actively involved in health-related activities.[22] A survey conducted on the Romanian population showed that 46.7%, 69.4%, and 80.1% of the study population had adequate knowledge, appropriate attitudes, and practices regarding antibiotic use and resistance, respectively. Moreover, they found a significant association of age, gender, and educational status with KAP related to antibiotic use and resistance.[23]

In our study, it was found that even if people had adequate knowledge about antibiotics, their practices regarding antibiotic use were less than satisfactory as 66.4% of respondents admitted to use antibiotics without a physician's prescription. Most of them believed that even if they visited a physician, they would be prescribed the same antibiotic they had taken themselves. Similar trends regarding self-medication have been observed in previous research.[24,25] The problem is that even if patients correctly identify the appropriate treatment for their condition, they might overlook the risks of overdosing, underdosing, or premature cessation of the antibiotic course.[24] This significantly contributes to antibiotic resistance. In our study, approximately 30% of participants reported stopping their antibiotics once their condition improved. This rate is slightly lower than that reported in a previous study (over 70%)[24], but it could be attributed to the small sample size of our study, which may not have captured the true prevalence of premature cessation.

CONCLUSION

The participants have a satisfactory understanding regarding antibiotic use and resistance. However, they are still lacking adequate attitudes and practices regarding their use and resistance. There is a significant association between knowledge of URTIs, education level & residence and knowledge, attitudes & practices regarding antibiotic use and resistance. Age has a significant relation with knowledge and practices regarding antibiotic use and resistance. This association suggests that having accurate knowledge about these diseases influences appropriate attitudes toward their treatment. Despite this correlation, the practice of antibiotic use remains problematic due to high rates of self-administration and premature cessation of antibiotics in our population. To address these challenges, social marketing emerges as a suitable strategy for altering individual behaviors regarding antibiotic use.

LIMITATIONS & RECOMMENDATIONS

This study had a small sample size, making the findings preliminary. To accurately assess the association between knowledge about URTIs and KAP regarding antibiotics, longitudinal data would be required, where participants' infections are properly evaluated and their practices observed over time. Due to the cross-sectional nature of this study, a comprehensive evaluation was not possible.

Awareness of AMR is crucial due to its growing importance as a global issue. However, merely conducting awareness programs and education-driven interventions may not effectively change the general population's attitudes and beliefs regarding antibiotic use and resistance. There is a need for a

shift in the behavior of the masses, which can be achieved through targeted social campaigns. For instance, instead of focusing broadly on educating people about the dangers of AMR, campaigns could specifically emphasize the importance of completing prescribed antibiotic courses and highlight the benefits of doing so. By concentrating on such specific changes, appropriate behaviors can be fostered more effectively within society. Regulatory authorities also play a critical role in enhancing surveillance efforts related to AMR.

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Authors' Contributions:
M.Z.R: Conception, visualization, data curation, data analysis, and manuscript writing
S.B: Conception, visualization, data curation, data analysis, and manuscript writing
A.K: Conception, visualization, manuscript writing, and supervision
M.M: Conception, visualization, data curation, data analysis, and manuscript writing
H.M.E.A: Conception, visualization, data curation, data analysis, and manuscript writing
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