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Letter to the Editor

Three-dimensional printing in medical education: transforming learning and practice!

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Extract

Three-dimensional (3D) printing is revolutionizing medical education, particularly in surgical training, by transforming digital images into tangible models. These models, derived from patient radiological data, allow for enhanced anatomical understanding and hands-on learning. Studies have shown that 3D-printed models significantly improve medical students' comprehension of complex anatomical structures and foster interest in specialized fields such as cardiology. Additionally, 3D printing offers cost-effective solutions for creating both normal and pathological models, which is particularly beneficial in resource-limited settings. While challenges remain, including material limitations and ethical considerations, 3D printing holds tremendous potential in advancing medical education globally.

Keywords

3D printing; Anatomical models; Medical education; Simulation training; Technology

Dear Editor,

Three-dimensional (3D) printing involves the creation of physical objects through geometric representation, utilizing various materials such as polylactic acid, acrylonitrile butadiene styrene, photopolymer resins, titanium, stainless steel, hydroxyapatite, bioglass, and hydrogels such as alginate and gelatin [1,2]. With recent technological advances, 3D printing has become increasingly important in medicine, especially in surgery, as it allows digital renderings to be materialized as physical objects via a printer [3]. As a result, low-cost 3D printers are becoming more accessible. For example, McMenamin et al. highlighted the cost-effectiveness of 3D printing, with upper limb models costing between US$300 and US$350, achieving approximately 97.5% cost savings compared with plastinated models (US$14,000) and approximately 80.6% savings compared with plastic "SOMSO" models (US$1,800) [4].

3D printing holds potential for creating organ models for surgical practice and drug testing. Anatomical models are extensively utilized in teaching medical students with greater precision and detail [5]. In addition to educational settings, 3D printing has the potential to transform global healthcare, particularly in low- and middle-income countries (LMICs), where access to traditional medical training tools and implants is limited.

The introduction of 3D printing technology aims to enhance students' anatomical understanding by providing precise and customized reproductions. These models, derived from patients' actual radiological imaging, are solid tangible objects that allow for free manipulation by the user. By providing precise 3D representations of proportions, orientations, and configurations, such models enable a deeper understanding of complex anatomical arrangements, even if the models cannot be dismantled. For example, a

randomized controlled trial assessed the understanding of congenital heart defects among fifth-year medical students via 3D-printed heart models [6]. The students who used 3D-printed models scored significantly higher on postlecture assessments (16.3 ± 2.6) than did those who used traditional 2D images (14.8 ± 2.8) ($p < 0.001$). Moreover, the 3D model group reported better self-assessed understanding (4.2 ± 0.5) than did the control group (3.8 ± 0.4), highlighting the effectiveness of 3D models in enhancing knowledge [6].

Building on these findings, it is noteworthy to mention a study that integrated 3D printing technology with case-based learning (CBL) and problem-based learning (PBL) to educate clinical medical students about respiratory diseases. The results were similarly promising: students who engaged in 3D printing demonstrated better performance than those taught via traditional methods did, showing improved clinical thinking, increased confidence, better self-study skills, stronger anatomical knowledge, enhanced problem-solving abilities, and greater satisfaction with the teaching method [7].

3D printing's ability to produce on-demand models has revolutionized how training institutes acquire educational tools. Traditionally, the majority of available models depict normal anatomy, whereas pathological models are rarely available. However, by using Digital Imaging and Communications in Medicine (DICOM) files, it is now possible to transform real cases into physical 3D models, enabling educators to create models of rare pathologies and thereby significantly enhancing the educational experience [8]. Educators determine which pathologies to model on the basis of their educational relevance, complexity, and frequency in clinical practice, prioritizing conditions that require a deeper spatial understanding or are challenging to comprehend through traditional 2D images. This capability has opened new possibilities for interdisciplinary collaboration between fields such as bioengineering, materials science, and medicine, further advancing the integration of cutting-edge technology in medical practice [9].

Despite its advantages, 3D printing technology has several limitations. For example, it demands experience in troubleshooting software and fixing equipment. Moreover, extended printing times can result in time-consuming failures, and many types of materials are still unsuitable for 3D printing [10]. Another challenge is the tactile limitation of 3D models compared with real cadavers. Compared with those who learn on plastic models, students who work on real cadavers tend to develop enhanced skills and gain more practical knowledge of anatomy [11]. Additionally, as 3D printing becomes more common in medical education, ethical considerations regarding the accuracy and safety of printed models and implants should be addressed to ensure that the technology is used responsibly and effectively.

The potential of 3D printing in medical education is immense, yet its full capabilities remain to be fully realized. Continued research and investment are crucial to unlocking the broader applications of this technology in medical training and practice. Future studies may focus on improving tactile realism to improve mimicking human tissues, automating the printing process for increased efficiency, and reducing production costs to make the technology more accessible. By addressing its current limitations and exploring new possibilities, particularly in global health contexts, we can ensure that 3D printing reaches its full potential in shaping the future of medical education.

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Original Article

Assessment of the nutritional status of tuberculosis patients visiting public sector hospitals in Bhakkar district, Punjab, Pakistan

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Abstract

Nearly 1.7 billion people are exposed to tuberculosis (TB) globally, and low- and middle-income countries (LMICs) are the major contributors to the burden of TB. Malnutrition affects the severity of illness, the effectiveness of treatment regimens, and the recovery process. Moreover, TB is often referred to as a disease of a poor population. Therefore, this descriptive cross-sectional study was conducted at DHQ Hospital in Bhakkar District and tehsil headquarters (THQ) hospitals in Mankera and Kaloor Kot to assess the nutritional status of TB patients. Data were collected from 329 adult TB patients via a purposive sampling technique with a semistructured questionnaire. Patients' nutritional status was assessed via BMI and malnutrition indicators adopted from the Mini Nutritional Assessment (MNA®). The associations between sociodemographic factors and BMI with malnutrition were analyzed via chi-square tests, with the significance level set at $p < 0.05$. Among the 329 respondents, 55.6% were at high risk of malnutrition, and 36.5% were malnourished. A BMI of less than 19 was observed in 5.5% of patients, with a statistically significant association between BMI and malnutrition ($p = 0.001$). However, no significant associations were found between sex or marital status and malnutrition, with p values of 0.194 and 0.339, respectively. The study concluded that malnutrition is prevalent among TB patients, with 36.7% malnourished and 50.46% at risk of malnourishment. The findings revealed no significant associations between malnutrition and sex or marital status, but a significant relationship was observed between malnutrition and BMI, indicating the importance of addressing malnutrition as a critical component of TB management.

Keywords

Tuberculosis; Nutritional status; Treatment adherence; Anti-TB therapy; Malnutrition

1. Introduction

Tuberculosis (TB) is a global health concern owing to its significant contribution to morbidity and mortality [1]. According to the World Health Organization (WHO), nearly one-third of the population is infected with Mycobacterium TB, with 8.8 million cases diagnosed every year, and it is the second-largest cause of death due to infections globally [2,3]. Approximately 45% of the cases are reported in Southeast Asian countries, including Indonesia, India, and China [4]. Early diagnosis and timely treatment of TB are crucial for decreasing the prevalence rate of the disease as well as for preventing complications and drug resistance [5].

In addition to common risk factors for TB, such as HIV infection, diabetes, tobacco use, and substance abuse, malnutrition is one of the major risk factors for this infection and is related to infection severity, poor prognosis, and mortality [6,7]. Malnutrition reduces the absorption capacity of anti-TB medicines in patients, worsening their condition and decreasing their chances of survival [8]. TB treatment modalities further increase the risk of hepatotoxicity. Therefore, nutrition and dietary adequacy are particularly important in preventing and fighting infections, particularly TB [7,9].

Malnutrition is associated with deficiencies in macronutrients; trace elements such as zinc and selenium; and essential vitamins such as vitamin A, vitamin C, and vitamin E [10]. Low intake of micronutrients and vitamins weakens the body's immune system, ultimately leading to severe infections [11]. These essential vitamins are administered as part of the treatment regimen to improve the immunity of TB patients, which is beneficial for reducing the development of recurrent infection, especially in patients with primary TB infection [12]. Notably, including a single dose of 20 micrograms (mcg) of vitamin D for adults in daily supplementation could improve immunity against infection, especially among healthy individuals at risk of or exposed to TB infection [13,14]. Therefore, nutritional inventions for TB patients as a part of their primary course of therapy are effective for curing the infection [15,16].

Given the importance of infections, global health initiatives such as the Sustainable Development Goals (SDGs) have prioritized the reduction and elimination of infections such as TB worldwide [17]. Several programs have been launched to reduce and eliminate the number of TB cases, with a particular focus on Southeast Asia, where malnutrition is one of the key indicators resulting in the highest burden of infection [18]. These programs encompass various aspects of a region's prevention, diagnosis, and treatment of TB infection. However, assessing the nutritional status of infected patients to improve their immunity and support anti-TB treatment remains essential [19]. Although other countries in the same region have developed policies to address TB infection and malnutrition among patients, Pakistan requires baseline data on the nutritional status of TB patients to inform efforts required to address this critical gap [20]. Therefore, this study was conducted with the aim of assessing the nutritional status of TB patients visiting public healthcare facilities.

2. Methodology

2.1. Study design and duration

This descriptive cross-sectional study was conducted over a period of one year, from June 2022 to May 2023.

2.2. Study settings

The study was conducted at the 360 bedded district headquarters (DHQ) hospital situated in Bhakkar, which has various operational clinical, administrative, diagnostic, and supporting departments, along with other services such as a blood bank, patient transfer services (1122), a hepatitis clinic, and a thalassemia center. Furthermore, the study also included tehsil headquarters (THQ) hospitals in Mankera and Kaloor Kot.

2.3. Participant selection

The study included all TB patients who were diagnosed via laboratory testing, had TB infection for more than three months and were above the age of 18 years. The three-month timeframe was chosen after the confirmed diagnosis of TB to ensure that only patients with visible infection were recruited, as it typically takes nine months for pa-

tients to fully recover. Moreover, this period also provides sufficient time for TB to start affecting the nutritional status of patients [21]. However, the study did not include pregnant women with TB or patients who had any other comorbidities, including diabetes mellitus (DM), thyroid gland functional issues, cancers, and chronic heart and kidney diseases. All patients provided written informed consent before inclusion in the study.

2.4. Sample size

The sample size of 323 TB patients was calculated via the online OpenEpi sample size calculator (version 3.01) while maintaining a 95% confidence level, a 5% margin of error, and a 70% incidence of TB in Pakistan, which was slightly increased to 329 to account for potential dropouts [22].

2.5. Sampling technique

A nonprobability purposive sampling method was employed for the selection of adult TB patients visiting the targeted outdoor departments of the DHQ and THQ hospitals.

2.6. Study tool development

A structured questionnaire with few open-ended questions was adopted to gather self-reported information about the TB patients [23]. The patients were asked to provide sociodemographic information such as age, education, sex, marital status, area of residence, employment status, average monthly income and family system and details regarding nutritional history, including declining food intake owing to the loss of appetite, weight loss, body mass index (BMI) (calculated using the standard formula, with height and weight measured during the interview) and medical history, by asking whether they took more than 3 prescription drugs per day [23]. Furthermore, the participants were asked about their daily intake of meals (1 meal, 2 meals, 3 meals), protein intake, fruit or vegetable intake, fluid intake, mode of feeding, perception of their own health status, health status compared with other TB patients, mid-arm circumference, and calf circumference (measured by the principal investigator using standard techniques for mid-arm and calf circumference). Finally, the Mini Nutritional Assessment (MNA®) tool was used to determine the malnutrition status of the participants. Patients were asked to respond to the questions on the basis of their experiences from the past three months to reduce probable recall bias in patient responses.

2.7. Study measures

The study adopted the MNA® tool, which has two parts, a screening section (with six questions and a maximum of 14 points) and an assessment section (with 12 questions and a maximum of 16 points) with an overall score of 30 [23]. Patients with points ranging from 24 to 30 were considered normal, whereas patients with scores ranging from 17 to 23.5 were considered at risk of malnutrition, and those scoring below 17 were classified as malnourished.

2.8. Data collection

Face–to-face interviews were conducted with TB patients visiting the outpatient departments of the selected hospitals and who provided consent to participate in the study.

2.9. Ethical approval

The study was approved by the Institutional Review Board of Allama Iqbal Open University (No. AIOU-NSED-23-215). Prior permission was obtained from the concerned authorities of the hospitals before data collection.

2.10. Data analysis

The collected data were entered into SPSS 25.00 for analysis and interpretation in line with the study objectives. Descriptive statistics, e.g., frequency, percentage, mean, and standard deviation, were calculated for the quantitative and qualitative variables. The associations between sociodemographic indicators (i.e., sex and marital status) and BMI and the malnutrition status indicator were calculated via a chi-square test.

3. Results

Table 1 shows the sociodemographic profile and nutritional history of the TB patients. The study participants had a mean age of 44.56 ± 17.30 years, with an average of 8.06 ± 5.09 years of education. Most of the patients were females (63.22%), married (79.94%), or urban residents (56.23%). Approximately two-thirds of the patients were employed (71.73%), followed by self-employed (22.19%) and unemployed (6.08%). The majority of the TB patients (41.46%) had average monthly incomes between Pakistani Rupees (PKRs) of 60,000 and 100,000.

Table 1. Sociodemographic profile of the TB patients (n = 329).

Variables		Frequency (%)	Mean ± SD
Age (in years)		-	44.56 ± 17.30
Education (in years)		-	8.06 ± 5.09
Gender	Male	212 (36.78)	-
	Female	208 (63.22)	-
Marital status	Single	66 (20.06)	-
	Married	263 (79.94)	-
Area of residence	Rural	144 (43.77)	-
	Urban	185 (56.23)	-
Employment status	Employed	236 (71.73)	-
	Self-employed	73 (22.19)	-
	Unemployed	20 (6.08)	-
Average monthly income	< 20,000	13 (3.95)	-
	20,000 – 60,000	66 (20.06)	-
	60,000 – 100,000	137 (41.64)	-
	> 100,000	113 (34.35)	-
Family system	Nuclear	214 (65.05)	-
	Joint	115 (34.95)	-

Table 2 shows that 38.6% of the TB patients experienced a severe decrease in food intake, whereas 35.3% reported no change in food intake, and 26.1% reported a moderate decrease in food intake over the past three months. Moreover, 29.79% and 20.97% of the participants reported weight loss of more than 3 kg and between 1 and 3 kg, respectively. However, few TB patients reported a BMI <19 (5.47%). Furthermore, most of the TB patients (81.2%) took more than 3 prescription drugs per day.

Table 2. Nutritional and medical history of TB patients (n = 329).

Variables		Frequency (%)
Food intake declined due to loss of appetite or TB	Severe	127 (38.60)
	Moderate	86 (26.14)
	No change	116 (35.26)
Weight loss	Greater than 3 kg	69 (20.97)
	Between 1 and 3 kg	98 (29.79)
	Does not know	77 (23.40)
	No change	85 (25.84)
Patients' body mass index (BMI)	< 19	18 (5.47)
	19 and above but < 21	77 (23.40)
	21 and above but < 23	122 (37.08)
	23 and above	112 (34.04)
Take more than 3 prescription drugs per day	Yes	267 (81.2)
	No	62 (18.8)

Table 3 shows the nutritional, dietary, and anthropometric characteristics of the TB patients over the past 3 months. When patients were asked to describe their number of meals eaten per day, 65.3% of patients were eating two meals a day, followed by 18.8% and 15.8% patients who were eating one or three meals, respectively. The consumption markers for protein intake were relatively high, as 57.45% of patients had at least one serving of dairy products per day; 81.46% had two or more servings of legumes or eggs per week; and 53.8% had meat, fish or poultry every day. In addition, 83.9% of patients consumed two or more servings of fruit or vegetables per day. With respect to fluid, 51.37% of patients consumed 3 to 5 cups, followed by more than 5 cups (32.83%) and fewer than 3 cups (15.81%). Furthermore, almost two-thirds of the respondents reported having difficulty eating (69.3%), one-fifth reported having no difficulty eating, and 13.37% were unable to eat without assistance. In response to their self-reported nutritional status, 64.44% were unsure of their status, 18.84% considered themselves malnourished, and 16.72% considered that they were fit in terms of nutritional status. However, the malnutrition indicator score assessment revealed that 13.07% of the TB patients had a normal nutritional status, while half of the patients (50.46%) were at risk of malnourishment, and 36.47% were malnourished.

Table 3. Nutritional, dietary, and anthropometric characteristics of TB patients (n = 329).

Variables		Frequency (%)
Meal's frequency eaten per day	One meal	62 (18.84)
	Two meals	215 (65.35)
	Three meals	52 (15.81)
Consumption markers for protein intake	At least one serving of dairy products (such as yogurt, milk, and cheese) per day	189 (57.45)
	≥ 2 servings of eggs or legumes per week	268 (81.46)
	Poultry, fish or meat every day	177 (53.80)
Consuming ≥ 2 servings of vegetables or fruit daily	No	53 (16.11)
	Yes	276 (83.89)
Consuming fluid (such as tea, water, milk, juice, coffee) daily	< 3 cups	52 (15.81)
	3 – 5 cups	169 (51.37)
	> 5 cups	108 (32.83)
Mode of feeding	Unable to eat independently	44 (13.37)
	Requires minimal assistance to eat	228 (69.30)
	Eats without difficulty	57 (17.33)

Table 3. *Cont.*

Variables		Frequency (%)
Nutritional status	Perceives self as malnourished	62 (18.84)
	Unsure about personal nutritional status	212 (64.44)
	Perceives self as nutritionally adequate	55 (16.72)
Health status compared with other TB patients	Not as good	135 (41.03)
	Better	40 (12.16)
	As good	68 (20.67)
	Does not know	86 (26.14)
Mid-arm circumference (in cm)	< 21	96 (29.18)
	21 – 22	151 (45.90)
	> 22	82 (24.92)
Calf circumference (in cm)	< 31	88 (26.75)
	≥ 31	241 (73.25)
Malnutrition indicators score assessment	Normal nutritional status	43 (13.07)
	At risk of malnourishment	166 (50.46)
	Malnourished	120 (36.47)

Table 4 shows the associations of patients' sociodemographic factors (i.e., sex and marital status) and BMI with malnutrition status indicators. There was no statistically significant association between sex and malnourishment in TB patients ($p = 0.194$). Similarly, the marital status of the patients was statistically insignificant, indicating that being married or unmarried was associated with the same likelihood of being malnourished ($p = 0.339$). However, the association between patients' BMI and their nutritional status was significant ($p = 0.001$).

Table 4. Associations between sociodemographic factors, BMI and malnutrition status indicators.

Variables		Malnutrition Status Indicators		*p* value *
		Malnourished	Not Malnourished	
		N (%)	N (%)	
Gender	Male	80 (66.7)	128 (61.2)	0.194
	Female	40 (33.3)	81 (38.8)	
Marital status	Married	94 (78.3)	169 (80.9)	0.339
	Unmarried	26 (21.7)	40 (19.1)	
Body mass index	< 19	1 (0.5)	17 (14.2)	0.001 *
	19 – < 21	29 (13.9)	48 (40.0)	
	21 – < 23	85 (40.7)	37 (30.8)	
	≥ 23	94 (45.0)	18 (15.0)	

* Associations between variables were assessed using the chi-square test. ** Significant value ($p \leq 0.05$).

4. Discussion

This study focused on the sociodemographic characteristics, nutritional history, and nutritional status of TB patients. Most study participants were females who were married and urban residents. The majority of the patients were employed and belonged to different socioeconomic groups by income. A reduction in food intake and weight loss is reported by patients, but many patients are uncertain whether they are malnourished or not malnourished. However, the malnutrition indicator score assessment revealed that more than half of the respondents were at risk of malnutrition. Some of them were already malnourished. Furthermore, malnutrition status indicators were not affected by

sociodemographic indicators, but BMI was associated with the malnourished status of TB patients.

Our study results are consistent with those of the Burkinabé study, which revealed that 35.8% of TB patients were malnourished, with 7.7% being severely undernourished, 8.9% being moderately undernourished and 19.5% being minimally undernourished [24]. Similar results were reported in the Ethiopian study, with 40.4% of TB patients being underweight and 59.6% being normal or overweight according to their observed BMIs [25]. The findings from the Indian study were similar to ours, reporting high rates of malnourished TB patients. The study assessed the nutritional status of TB patients via anthropometric methods in rural settings and reported that 91.7% of the patients were malnourished [26]. Other studies conducted in different settings also reported high rates of malnutrition among TB patients, ranging from 44% to 48% [27,28].

In developing countries such as Pakistan, the high prevalence of malnutrition is attributed to poverty, food insecurity, and a shortage of food, which make it difficult for TB patients to access sufficient nutrition, ultimately worsening their health conditions [29,30]. In Pakistan's rural areas where healthcare and diagnostic facilities are limited and where locals must travel long distances for early diagnosis and treatment endeavors, such outcomes are anticipated [31]. The high rate of malnutrition may also be due to the lack of public nutritional support programs, which could improve patients' nutritional status [32]. This issue is further supplemented by a scarcity of resources and a shortage of trained staff in healthcare facilities, which hinders the implementation of effective nutritional support programs [33].

A study conducted in the Somali Region of East Ethiopia reported findings in contrast with our study results that female sex was a predictor of malnutrition [28]. However, a study from Myanmar reported no relationship between sex and malnutrition among TB patients, which is consistent with our study results [34]. Moreover, a study highlighted a strong association between BMI and malnutrition in TB patients, as well as the risk of developing TB [35]. Furthermore, an Indian-based study revealed that BMI, TB and TB prognosis are related [36]. Similarly, another Indian study reported that patients with lower BMIs are at risk of developing multidrug-resistant TB [37]. A study conducted among individuals in South Korea further confirmed the findings of the current study, showing that BMI is closely related to malnourishment among tuberculosis patients [38].

The differences and similarities between our study findings and those of other studies may be due to various geographical, economic, and social determinants. The varying associations between gender and malnutrition show that poverty and food scarcity can affect both genders, whereas some studies highlight cultural factors and limited access to healthcare, which may contribute to gender differences [31]. Moreover, the correlation between BMI and malnutrition may be attributed to the limitations of healthcare infrastructure and the lack of nutritional support programs [32].

Our study highlighted the nutritional status of TB patients from the underprivileged areas of Punjab Province and provided baseline data. Malnutrition was assessed via nutritional indicator scores, and the malnutrition status of patients was compared on the basis of sex, marital status, and BMI. However, the study did not explore the primary causes of malnutrition or the qualitative factors influencing nutritional behaviors among TB patients, which is a notable limitation. Despite this, the study's strength lies in providing crucial data on malnutrition in disadvantaged areas, offering a ground for future research and the development of nutritional support programs.

5. Conclusions

The study concluded that malnutrition is prevalent among TB patients, with 36.7% malnourished and 50.46% at risk of malnourishment. The findings revealed no significant associations between malnutrition and sex or marital status, but a significant relationship was observed between malnutrition and BMI, indicating the importance of addressing malnutrition as a critical component of TB management.

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Original Article

Understanding antibiotic use and resistance: knowledge, attitudes, practices, and training needs of paramedical students

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Abstract

The inappropriate and overuse of antibiotics is considered the main source of antimicrobial resistance (AMR). Therefore, this study aimed to assess the knowledge, attitudes, and practices of antibiotic use and resistance among paramedical students. In addition, the study also assessed the perceptions, knowledge gaps, and educational needs of paramedical students regarding antibiotic use, resistance and related training. This descriptive cross-sectional study was conducted at Khyber Medical University by recruiting 500 students from twelve different paramedic disciplines. The self-administered questionnaire was distributed online through email and WhatsApp, resulting in 364 completed responses and a response rate of 72.8%. The study revealed that 41.21% of paramedic students were using antibiotics without a prescription, 23.63% admitted that they discontinued their prescribed antibiotic course once they felt better, 95.88% recognized the term 'antibiotics', and 79.67% acknowledged that inappropriate use contributed to resistance. A sex comparison revealed that male students (81.32%) were significantly more likely to complete their prescribed antibiotic courses than their female counterparts were (67.29%) (p = 0.002). This study identifies gaps in paramedical students' knowledge, attitudes, and practices related to antibiotic use and resistance. Despite a general awareness of key concepts, misconceptions and improper practices were also common. Therefore, there is a dire need to upgrade the curriculum and implement integrated modules on antibiotic stewardship, infection control, and responsible antibiotic use, which could enhance students' knowledge, enable them to make informed decisions, and contribute significantly to combating antibiotic resistance.

Keywords

Paramedics; Health knowledge, attitudes, practices; Antibiotic resistance; Students

1. Introduction

Antibiotic resistance has emerged as a crucial issue over the last two decades, posing a significant challenge to healthcare systems worldwide [1]. In May 2015, a global action plan was endorsed by the World Health Organization (WHO) to provide safer antibiotics for the prevention and treatment of infectious diseases [2]. However, the spread of antimicrobial resistance (AMR) continues in several parts of the world, including developing countries such as Pakistan [3,4,5,6]. Some strains of bacteria become resistant to all the prescribed antibiotics and are known as panresistant organisms or superbugs. This can lead to increased hospitalization, increased hospital costs, poor clinical outcomes and increased mortality rates. Every year, an estimated seven million deaths occur due to drug resistance globally. If it continues at the current rate, by 2050, it is estimated to cost

a hundred trillion United States dollars (USD) in losses as well as more than ten million deaths per year globally [7].

The spread and involvement of multiresistant bacteria in infectious diseases worldwide are considered public health threats [8]. A direct relationship between AMR has been reported in many epidemiological studies, with the irrational use of antibiotics such as self-medication, multiple antibiotic prescriptions to a single patient, antibiotic use in nonbacterial infections, low doses, overdose, diversion from clinical guidelines, and preference for injection when oral formulations are more effective [9,10]. According to the WHO, antibiotics have prevented millions of deaths, but their effectiveness is diminishing because of their irrational use [11]. There is significantly more irrational use of antibiotics in developing countries than in developed nations. Studies from Europe reported a prevalence of 19% and 30%, whereas in developing countries, the prevalence ranged from 75% to 100% [9,10,12,13,14,15,16,17]. This ineffectiveness of antimicrobial agents may lead to an era where antibiotics are no longer available for the treatment of infections, and consequently, a minor bacterial infection will lead to death.

A holistic approach to overcoming AMR is promoting the reasonable utilization of antibiotics through antimicrobial stewardship (AMS) [18]. Prepresscription and postprescription are the two major approaches. The first approach requires prior authorization from the restrictive prescriptive authority for the use of antibiotics, whereas the postprescriptive approach is based on reviews and feedback of the recent antibiotic used, allowing the physician with the ability to change, adjust, continue, or halt antibiotics depending on the patient's clinical signs and symptoms and available results [19]. Excessive antibiotic use due to prescription is not restricted, whereas in the postprescription approach, rationalization of the prescription results in improved physician satisfaction and a decrease in antibiotic use [18,20].

Among low-resource countries, Pakistan ranks third in the consumption of antibiotics, and antibiotic resistance is a serious problem for healthcare. It is estimated that approximately 35,000 patients in Pakistan use antibiotics daily [21]. While self-medication is more prevalent in Pakistan, the majority of patients obtain antibiotics without a physician's prescription and do not complete antibiotic doses. Furthermore, antibiotics can easily be obtained from both medical stores and pharmacies without a prescription from a qualified physician, similar to over-the-counter medicines, contributing to a lack of awareness and misuse among consumers [22,23,24,25,26,27]. As future healthcare professionals, paramedical students play a crucial role in addressing this issue not only at healthcare facilities but also in the community [28,29]. Considering their direct involvement in patient care and medication administration, their knowledge and practices significantly influence antibiotic prescribing, use, and stewardship. Educating paramedical students about the risks of self-medication and the principles of antimicrobial use and antimicrobial stewardship is essential for reducing AMR [30]. However, the curriculum at the undergraduate level does not fully equip students with practical challenges related to antibiotic use in their professional lives [31,32,33].

To address this gap, it is crucial to evaluate the knowledge and perceptions of students, particularly those in paramedical sciences, as they represent the future of the healthcare system as specialized technologists. Therefore, this study aimed to assess the knowledge, attitudes, and practices of antibiotic use and resistance among paramedical students. In addition, the study also assessed the perceptions, knowledge gaps, and educational needs of paramedical students regarding antibiotic use, resistance and related training. Furthermore, a sexwise comparison was conducted to assess differences in practices related to antibiotic use.

2. Methods

2.1 Study design, duration, and setting

This descriptive cross-sectional study was conducted from August to September 2023 at the Institute of Paramedical Sciences, Khyber Medical University (KMU), Peshawar, Pakistan, which is the largest and only medical university in Khyber Pakhtunkhwa (KP) Province [34]. The institute offers a BS four-year program in twelve various technologies, i.e., medical lab technology, dialysis technology, dental technology, radiology, neurophysiology, cardiology, cardiac perfusion, respiratory therapy/intensive care, emergency, health, and anesthesia. It is a provincial-level institute and provides equal opportunity to all the residents of KP Province.

2.2 Selection criteria

The students who were enrolled in various paramedic programs irrespective of sex, who were 18 years or older and who voluntarily agreed to participate were included in the study. However, students with prior professional experience in pharmacology-related fields and those suffering from conditions such as chronic infections requiring frequent antibiotic use were excluded from the study.

2.3 Sampling technique and sample size

The participants were selected using purposive sampling to include paramedical students from KMU to ensure relevance, as it offers disciplines beyond paramedical programs while enabling targeted selection for efficient data collection.

The sample size for the study was calculated via an online epidemiological calculator, which assumes an expected overall knowledge score of 74% with a 95% confidence interval and a 5% margin of error [35,36]. The required sample size was determined to be 291 but was increased to 500 to account for an anticipated reduced response rate, maintain analytical strength and address potential nonresponse owing to electronic survey distribution challenges in Pakistan [37]. Given the overall digital divide in Pakistan, where internet access and digital literacy remain limited, particularly in certain regions and socioeconomic groups, missing or incomplete responses were expected, which could lead to data exclusion [38]. Therefore, a significant increase in sample size helped mitigate this issue to ensure valid responses for the study.

2.4 Questionnaire development

Following a thorough literature review, a self-administered questionnaire was adapted for this study [20,21,26]. The questionnaire consisted of five sections. The demographic and medication history section of the questionnaire collected information on age, sex, marital status, discipline of study, current program of study, plans for higher education, current academic year of enrollment, antibiotic use within the past month and the past six months, and the types of antibiotics most recently used. All other sections of the questionnaire assessed participants' knowledge (11 questions), attitudes (8 questions), and practices (4 questions) related to antibiotic usage and resistance. Additionally, these sections assessed perceptions (7 questions) and knowledge gaps (4 questions) concerning antibiotic education, training needs, and related suggestions. The pilot study included ten paramedic students to assess the questionnaire for clarity, unambiguity, and ease of response, which aligns with previous methodological recommendations, suggesting that small sample sizes (10–30) are adequate for pilot studies [39]. Moreover, the questionnaire was sent to two field experts for review to ensure content validity, relevance, and clarity before its final use. The pilot study data were excluded from the final results.

2.5 Data collection

Google Forms was used to develop the questionnaire, and an electronic link to the questionnaire was distributed among potential participants via email or WhatsApp.

2.6 Ethical approval

The study was conducted after the approval of the Ethical Review Committee of the KMU, Peshawar (No. 2091-26143-5). The participants were briefed about the procedures and objectives of the study. Informed consent was obtained from the students, with participation being entirely voluntary. The participants had the option to decline participation or exit the survey at any time without any obligation. Furthermore, data confidentiality was maintained according to the Helsinki Declaration and Data Protection Act (Organic Law 3/2018). After ensuring that all the aforementioned parameters were fulfilled, the email addresses or WhatsApp numbers of potential participants were added to the list for questionnaire distribution.

2.7 Statistical analysis

IBM SPSS Statistics (version 24) was used to analyze the data as frequencies and percentages. Moreover, the chi-square test was employed for a sexwise comparison to assess differences in practices related to antibiotic use. A p value < 0.05 was considered significant.

3. Results

3.1 Demographic information

Among the 500 questionnaires distributed, 364 paramedical students submitted their responses online, resulting in a response rate of 72.8%. Table 1 shows that most of the respondents were male (70.6%), and a significant portion of the students reported being single (89%). A total of 79.9% of the participants were aged between 18 and 23 years. Most of the participants were from radiology technology (15.11%), followed by medical lab technology (12.64%) and anesthesia technology (12.36%), along with students from other disciplines. Moreover, 98.4% of the students were currently studying undergraduate, whereas 1.65% had completed their undergraduate program but were awaiting a degree. Moreover, 37.6% and 29.12% of the students were in their third and fourth academic years of the program, respectively, and 90.1% were planning to pursue further higher education. Among the 364 respondents, 32.7% used antibiotics in the past month, whereas 69.3% used antibiotics in the last six months. Moreover, most of the participants identified commonly used antibiotics from the provided list. Among the reported antibiotics, ciprofloxacin (35.16%) was the most commonly used, followed by azithromycin (26.92%) and Augmentin (22.53%).

Table 1. Demographic profile and medication history of the study participants (n = 364).

Variables		Frequency (%)
Sociodemographic Indicators		
Age	18 – 23 years	290 (79.67)
	> 23 years	74 (20.33)
Sex	Male	257 (70.60)
	Female	107 (29.40)
Marital status	Married	40 (10.99)
	Unmarried	324 (89.01)

Table 1. *Cont.*

Variables		Frequency (%)
Discipline of study	Medical lab technology	46 (12.64)
	Radiology technology	55 (15.11)
	Anesthesia technology	45 (12.36)
	Emergency technology	33 (9.07)
	Respiratory therapy/ICU	32 (8.79)
	Dialysis technology	30 (8.24)
	Surgical technology	27 (7.42)
	Neurophysiology	27 (7.42)
	Cardiology technology	25 (6.87)
	Dental technology	22 (6.04)
	Health technology	16 (4.40)
	Cardiac perfusion	6 (1.65)
Current program of study	Undergraduate	358 (98.35)
	Under graduation completed	6 (1.65)
Students planning to pursue postgraduate studies	Yes	328 (90.11)
	No	36 (9.89)
Current academic year of the program in which the student is enrolled	First	56 (15.38)
	Second	59 (16.21)
	Third	137 (37.64)
	Fourth	106 (29.12)
	Completed but degree awaiting	6 (1.64)
Medication History		
Antibiotic use in the past month	Yes	119 (32.69)
	No	236 (64.84)
	Maybe	9 (2.47)
Antibiotic use in the past six months	Yes	252 (69.23)
	No	101 (27.75)
	Maybe	11 (3.02)
Types of antibiotics most recently used	Ciprofloxacin	128 (35.16)
	Azithromycin	98 (26.92)
	Augmentin	82 (22.53)
	Amoxicillin	78 (21.43)
	Vibramycin	66 (18.13)
	Metronidazole	56 (15.38)
	Erythromycin	49 (13.46)
	Streptomycin	11 (3.02)
	Sulfamethoxazole/Trimethoprim	8 (2.20)

3.2 Participants' knowledge, attitudes, and practices regarding antibiotic use

Table 2 shows the participants' knowledge, attitudes and practices related to antibiotic use and resistance; 95.88% of the participants recognized the term 'antibiotics', whereas 89.56% were aware of the term 'antibiotic resistance'. Approximately four-fifths of the participants (79.67%) acknowledged that the inappropriate use of antibiotics contributes to antibiotic resistance. Moreover, 79.12% of the students accurately recognized that antibiotics cannot kill viruses, 15.11% incorrectly stated that they could kill viruses, and 5.77% were unsure. In response to the knowledge regarding the proper course of antibiotics, 71.98% of the participants responded correctly, whereas 20.33% did not know, and 7.69% were uncertain. Most of the participants (85.71%) stated that bacteria

can develop resistance to antibiotics; however, 6.04% disagreed, while 8.24% were unsure. The identification rates of amoxicillin and ciprofloxacin as antibiotics were high, with 97.53% and 97.80% of the participants correctly identified them, respectively. However, only 15.66% knew that aspirin is not an antibiotic, with a majority (79.67%) incorrectly identified as one.

Table 2 further shows that half of the participants (51.65%) correctly believed that antibiotics should not be used for fever, and 63.19% correctly rejected their use for allergies. Most participants (64.29%) disagreed with the prevention of the use of antibiotics as soon as patients feel better. While 88.19% agreed that antibiotics should be used only when they are prescribed by a physician, 82.42% acknowledged that inappropriate use is a major cause of bacterial resistance, and 74.73% recognized antibiotic resistance as a significant problem in Pakistan, with 67.58% identifying it as a global issue.

In terms of practices, 76.37% of the participants reported that they completed their prescribed antibiotic course, whereas 23.63% admitted that they quit once they felt better. Most of the participants (60.16%) stated that they consulted a doctor when ill, but 41.21% mentioned that they used antibiotics without a prescription. For leftover antibiotics, 51.92% saved them for future use, and only 30.77% discarded them.

Table 2. Participants' knowledge, attitudes, and practices related to antibiotic use and resistance.

Variables		Frequency (%)
Knowledge		
Do you know what antibiotics are?	Yes	349 (95.88)
	No	2 (0.55)
	Maybe	13 (3.57)
Are you familiar with the term 'antibiotic resistance'?	Yes	326 (89.56)
	No	23 (6.32)
	Maybe	15 (4.12)
Do you know that inappropriate use of antibiotics can lead to antibiotic resistance?	Yes	290 (79.67)
	No	35 (9.62)
	Maybe	39 (10.71)
Do you know that antibiotics can kill bacteria?	Yes	345 (94.78)
	No	3 (0.82)
	Maybe	7 (1.92)
Do you know that antibiotics can kill viruses?	Yes	55 (15.11)
	No	288 (79.12)
	Maybe	21 (5.77)
Are you aware of the proper course of antibiotics?	Yes	262 (71.98)
	No	74 (20.33)
	Maybe	28 (7.69)
Do you know that bacteria can develop resistance to antibiotics?	Yes	312 (85.71)
	No	22 (6.04)
	Maybe	30 (8.24)
Do you know that Amoxicillin is an antibiotic?	Yes	355 (97.53)
	No	2 (0.55)
	Maybe	7 (1.92)
Do you know that Ciprofloxacin is an antibiotic?	Yes	356 (97.80)
	No	3 (0.82)
	Maybe	5 (1.37)

Table 2. *Cont.*

Variables		Frequency (%)
Do you know that Aspirin is not an antibiotic?	Yes	57 (15.66)
	No	290 (79.67)
	Maybe	17 (4.67)
Do you know that inappropriate use of antibiotics exists?	Yes	283 (77.75)
	No	45 (12.36)
	Maybe	32 (8.79)
Attitudes		
Do you believe antibiotics can be used for the treatment of fever?	Yes	136 (37.36)
	No	188 (51.65)
	Maybe	40 (10.99)
Do you believe antibiotics can be used for the treatment of allergies?	Yes	96 (26.37)
	No	230 (63.19)
	Maybe	38 (10.44)
Do you believe patients may stop antibiotics as soon as they start feeling better?	Yes	91 (25.00)
	No	234 (64.29)
	Maybe	39 (10.71)
Do you think colds/coughs should always be treated with antibiotics for quick recovery?	Yes	152 (41.76)
	No	157 (43.13)
	Maybe	55 (15.11)
Do you believe that antibiotic resistance is the biggest problem the world faces?	Yes	246 (67.58)
	No	35 (9.62)
	Maybe	83 (22.80)
Do you agree that antibiotics should only be used when prescribed by a physician?	Yes	321 (88.19)
	No	18 (4.95)
	Maybe	25 (6.87)
Do you think antibiotic resistance is a significant problem in Pakistan?	Yes	272 (74.73)
	No	31 (8.52)
	Maybe	61 (16.76)
Do you agree that inappropriate use of antibiotics is the main cause of bacterial resistance?	Yes	300 (82.42)
	No	18 (4.95)
	Maybe	46 (12.64)
Practices		
Do you complete the prescribed course of antibiotics?	Yes	278 (76.37)
	No, I quit the course when I feel better	86 (23.63)
Do you use antibiotics without a prescription?	Yes	150 (41.21)
	No	196 (53.85)
	Maybe	8 (2.20)
How do you respond to illness or disease?	Allow it to recover naturally	55 (15.11)
	Consult a doctor	219 (60.16)
	Use self-medication	69 (18.96)
	Take medicines based on random suggestions	21 (5.77)
What do you do with leftover antibiotics?	Save for future use	189 (51.92)
	Return to the pharmacy	25 (6.87)
	Discard	112 (30.77)
	Give to others	38 (10.44)

3.3 Perception of training on antibiotics in different paramedical specialties

Table 3 shows that 53.02% of the participants felt that they had enough education to select the best antibiotic for infections, whereas 45.05% believed that they could decide on the right antibiotic regimen. However, a notable proportion remained uncertain or unaware in both cases. Most of the participants (87.64%) were interested in more education on antibiotic use and resistance, and 90.66% considered microbiology and infection control knowledge important for their careers. Most participants (47.53%) suggested teaching antibiotics during their second year of study, and 92.58% believed that awareness sessions on antibiotics would be helpful.

Table 3 further shows the self-reported knowledge gaps among paramedical students; 96.70% stated that they needed more knowledge about antibiotics, and 65.38% admitted that they lacked sufficient information to answer specific questions. A vast majority (90.66%) of the participants emphasized the need for thorough microbiology and infectious disease knowledge, and 93.41% highlighted the importance of drug knowledge before starting practicums.

Table 3. Perceptions and knowledge gaps in antibiotic education and training needs.

Variables		Frequency (%)
Perceptions		
Do you have enough education to select the best antibiotic for infections?	Agree	193 (53.02)
	Disagree	24 (6.59)
	Not sure	117 (32.14)
	Don't know	30 (8.24)
Do you have enough education to decide on the right antibiotic regimen?	Agree	164 (45.05)
	Disagree	38 (10.44)
	Not sure	115 (31.59)
	Don't know	47 (12.91)
Would you like more education on antibiotic use and resistance?	Agree	319 (87.64)
	Disagree	7 (1.92)
	Not sure	29 (7.97)
	Don't know	9 (2.47)
Is microbiology and infection control knowledge important for your career?	Agree	330 (90.66)
	Disagree	7 (1.92)
	Not sure	24 (6.59)
	Don't know	3 (0.82)
When should institutes spend more time teaching antibiotics?	First year	97 (26.65)
	Second year	173 (47.53)
	Third year	59 (16.21)
	Fourth year	24 (6.59)
	No required	11 (3.02)
Should the use of antibiotics be reduced?	Yes	235 (64.56)
	No	62 (17.03)
	Maybe	67 (18.41)
Would awareness sessions on antibiotics be helpful?	Yes	337 (92.58)
	No	7 (1.92)
	Maybe	20 (5.49)
Knowledge Gaps		
Do you need more knowledge about antibiotics?	Yes	352 (96.70)
	No	2 (0.55)
	Maybe	10 (2.75)

Table 3. *Cont.*

Variables		Frequency (%)
Do you lack information to answer certain questions?	Yes	238 (65.38)
	No	63 (17.31)
	Maybe	63 (17.31)
Is detailed microbiology and infectious diseases knowledge necessary?	Yes	330 (90.66)
	No	11 (3.02)
	Maybe	23 (6.32)
Is drug knowledge essential before starting practicum?	Yes	340 (93.41)
	No	7 (1.92)
	Maybe	17 (4.67)

3.4 Sexwise comparison of practices related to antibiotic use among paramedical students

Table 4 shows a sexwise comparison of practices related to completing prescribed antibiotic courses. A greater proportion of males (81.32%) reported completing their antibiotic courses than females did (67.29%) ($X^2 = 9.220$, df = 1, $p = 0.002$). However, there were no significant differences observed between males and females in the use of antibiotics without a prescription, with similar proportions reported ($X^2 = 0.130$, df = 2, $p = 0.937$).

Table 4. Sexwise comparison of practices related to antibiotic use among paramedical students.

Practices		Gender		*p* value *
		Male N = 257	Female N = 107	
		Frequency (%)	Frequency (%)	
Do you complete the prescribed course of antibiotics?	Yes	209 (81.32)	72 (67.29)	0.002 *
	No	48 (18.68)	35 (32.71)	
Do you use antibiotics without a prescription?	Yes	105 (40.86)	44 (41.12)	0.937
	No	140 (54.47)	58 (54.21)	
	Maybe	12 (4.67)	5 (4.67)	

* Variables were compared using the chi-square test. ** Significant value ($p \leq 0.05$).

4. Discussion

Our study revealed that most of the study participants were male, single, aged between 18 and 23 years, and studying in the third and fourth professional years of undergraduate programs. Most of the participants were aware of antibiotics and antibiotic resistance and had used antibiotics in the past six months. Four-fifths of the participants agreed that inappropriate use of antibiotics can cause resistance. More than half of the participants agreed that antibiotics should not be used in fever and prophylaxis and should be used as per prescription from a physician. Fewer than half of the participants believed that they were able to choose the right antibiotic regimen. The vast majority agreed that they require more knowledge and training for microbiology, infectious diseases and antibiotic use. Furthermore, male participants were more likely to complete the antibiotic course than their female counterparts were, whereas there was no significant difference among the sexes in the use of antibiotics without a prescription.

Our study results regarding knowledge of antibiotic resistance among study participants were supported by a Nigerian study that included healthcare students and reported that 88.3% of the students had a better understanding of AMR [40]. Similarly, an African study revealed that 96% of healthcare students were familiar with the term AMR; how-

ever, a significant proportion were not aware of the concept of antibiotic stewardship [41]. A study conducted at the University of Zambia reported that 87.3% of medical students had good knowledge about antibiotic use and resistance, and 75% had good practices toward antibiotic use [42]. Another Saudi Arabian study revealed that 78.2% of medical students believed that unnecessary use of antibiotics reduces their effectiveness, reflecting awareness of the potential consequences of antibiotic misuse [43].

A study conducted in Cairo reported that 79.7% of university students had poor knowledge of antibiotics, 92.2% lacked awareness of antibiotic resistance, and only 30.6% were familiar with the term AMR [44]. Moreover, a study conducted among pharmacy students in Punjab, Pakistan, reported that 59.8% of the students had an average understanding of antibiotic use, 42.6% were aware of antibiotic resistance, and 48% were aware of the mechanics of antibiotic resistance. Furthermore, only 21.6% of the students were familiar with the antibiotic stewardship program [4]. Another Pakistani study reported that only 43% of university students were aware of AMR, and 30% were aware that the irregular use of antibiotics would lead to resistance [45]. A Saudi Arabian study that targeted pharmacy and nursing students reported above-average knowledge of the students toward antibiotics and AMR [46]. A study targeting pharmacy and medical students in East Africa reported that only 36.6% of all the students had overall knowledge about antibiotics [47]. The same finding was reported in an Indian study, which reported a poor level of knowledge about antibiotics and AMR [48].

The lack of guidance among educators impedes the inclusion of important topics in courses for paramedic students at the national level. Moreover, the unavailability of elective courses on crucial topics such as AMS and antibiotic prescription taught by experts to undergraduate students also affects their practical behavior [49]. These courses can play a crucial role in enhancing students' knowledge and raising awareness about the importance of the responsible and effective use of antibiotics, thereby helping to reduce the risk of resistance [50,51].

A Bangladeshi study reported a better attitude of students toward antibiotic use, and 90% of the students consumed antibiotics as per the prescription of a registered medical practitioner; however, their adherence to the therapy was not satisfactory [52]. A study conducted among pharmacy students in three Asian countries reported that students had moderate knowledge about antibiotic use, resistance, and stewardship; however, they had poor knowledge about antibiotic therapy [53]. Moreover, a Malaysian study reported that a large proportion of medical students believed that antibiotics could treat viral infection, and half of the respondents completed an antibiotic course. Furthermore, gender, race, family income, and nationality were significantly associated with antibiotic knowledge and use among students [54]. The undergraduate curriculum for healthcare students may not be sufficiently updated and often fails to address practical problems effectively. A possible reason for this could be inadequate training provided to students at universities on the appropriate use of antibiotics in infections, which may influence their confidence in selecting and using antibiotics correctly [55,56]. Additionally, the marketing strategies of pharmaceutical companies potentially glamorize antibiotic use as a cure for all types of infections. Poorly monitored drug stores by regulatory authorities, allowing easy access to antibiotics without prescriptions, and limited consumer awareness could also contribute to the misuse of antibiotics [57].

Our study focused exclusively on paramedical students from various disciplines at one of the largest institutions in the province, providing an in-depth understanding of their knowledge and practices regarding antibiotic use and resistance. The study employed a tool developed after a comprehensive literature review, incorporating key aspects of the topic, and included a substantial number of participants. However, this study

does not explore qualitative dimensions or include open-ended questions to identify potential reasons, which may be considered a limitation. Additionally, cultural beliefs, healthcare accessibility, and systemic issues such as over-the-counter antibiotic availability may influence knowledge, attitudes, and practices (KAP) in Pakistan, highlighting the need for further qualitative investigation. Moreover, the generalizability of the findings is limited because of the use of purposive sampling, which may introduce potential selection bias. Additionally, there is a likelihood of response bias stemming from the self-reported nature of the data used to assess participants' attitudes and practices. Finally, this study did not use a scoring method to assess knowledge, attitudes, and practices; future studies can address this gap for a more detailed evaluation. The study was carried out in constrained healthcare environments with limited resources, a small sample size, and a restricted set of variables. These limitations hinder the ability to perform advanced analytical techniques that can clarify the complex relationships among the variables involved.

5. Conclusions

This study highlights gaps in the knowledge, attitudes, and practices of paramedical students regarding antibiotic use and resistance. Although there was a general awareness of key concepts, misconceptions and improper practices were also common. To increase students' knowledge and decision-making in combating antibiotic resistance, the curriculum should be upgraded with integrated modules on antibiotic stewardship, infection control, and responsible antibiotic use. Additionally, the study recommends incorporating detailed antibiotic and chemotherapeutic content into undergraduate curricula and introducing mandatory short courses and hands-on workshops as part of educational policy reforms.

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Original Article

Surgical outcomes of patients with corrosive ingestion: a retrospective analysis

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Abstract

Corrosive ingestion can cause severe complications, including perforation, stricture, and fistula, which often require surgical intervention to prevent further damage. This retrospective observational study analyzed surgical outcomes and gender differences in ingestion types (accidental vs. suicidal) and causative substances (acid, alkali, ammonia, detergent, or mixed) among 99 patients at a tertiary care hospital in Rawalpindi from January 2002 to January 2024. The average age of the patients was 30.36 ± 10.18 years, with 61.62% female patients and 38.38% male patients. Accidental ingestion was more common in males (94.74%), whereas suicidal ingestion was more common in females (21.31%, $p = 0.026$). Mixed substances were the most common substances ingested, particularly among females (60.66%, $p = 0.048$). All patients underwent upper gastrointestinal endoscopy, and diagnostic laparoscopy or feeding jejunostomy was the most common surgical procedure (57.58%). The esophagus (68.69%) was the most affected site. Surgical site infections (16.16%) and strictures (11.11%) were the most frequent complications, with a mortality rate of 4.04%. Our study concluded that timely surgical management could reduce the risk of complications and enhance patient outcomes. Corrosive ingestion often affects multiple areas of the gastrointestinal tract that require several surgical interventions. In certain cases, complex procedures, such as colon interposition and total laryngopharyngoesophagectomy (TLPO), which require skilled surgeons as well as advanced management centers, are performed to manage corrosive injuries. Therefore, improving these patients' outcomes via interventions focused on training in complex surgical procedures is crucial. However, more research is needed to identify the most effective approaches for the surgical management of corrosive ingestion.

Keywords

Corrosive ingestion; Surgical management; Complications; Retrospective analysis

1. Introduction

Corrosive ingestion refers to the intentional or accidental ingestion of corrosive substances, such as acids or alkalis, which can cause severe damage to the digestive tract. This can lead to serious complications, including perforation of the esophagus and stomach. Corrosive ingestion is a major public health issue globally [1,2]. It is more prevalent in developing countries, but it is also common in developed countries. Even in the United States, approximately 5,000–15,000 corrosive ingestions are reported annually [3]. Annually, more than 40,000 cases of corrosive ingestion are reported in England and Wales.

In developing countries such as Pakistan, it is very prevalent, although most cases are not reported due to cultural barriers [4]. The lack of safe "childproof" containers, un-

regulated access to corrosive agents, a culturally specific inclination to ingest corrosives for suicidal purposes, and the absence of standard medical care in rural areas [4,5,6]. The medical literature concerning the epidemiology and clinical presentation of corrosive ingesting patients is inadequate. The World Health Organization (WHO) reported that in the past 17 years, only 37 papers concerning corrosive ingestion in low- and lower-middle-income countries have been published [7].

Surgical intervention plays a crucial role in the management of corrosive ingestion patients, particularly in cases where severe damage to the gastrointestinal tract has occurred [8,9]. The type of surgical intervention depends on the damaged area, and multiple surgical approaches can be used in multiple affected areas [9]. Surgical evaluation is essential for assessing the extent of damage caused by corrosive substances [10]. This may involve various diagnostic procedures, such as endoscopy, imaging studies (e.g., CT scans), and clinical assessments, to determine the severity and location of the injury. Corrosive ingestion can lead to a range of complications, including perforation, stricture, and fistula in the gastrointestinal tract [11]. Surgical intervention may be necessary to address these complications, such as repairing perforations, dilating strictures, or performing bowel resections in severe cases. Surgical intervention aims to prevent further damage to the gastrointestinal tract and surrounding structures. Therefore, the present study was conducted to retrospectively analyze the surgical outcomes of patients managed surgically for corrosive ingestion. Moreover, sex differences in ingestion types (accidental and suicidal) and ingested causative substances (acid, alkali, ammonia, detergents, and mixed) were assessed in corrosive ingestion cases.

2. Methods

2.1. Study design

This was a retrospective observational study that assessed the surgical outcomes of patients who ingested corrosive substances.

2.2. Study duration

Data from January 2002 to January 2024 were retrieved from the database and patients' medical records at a tertiary care hospital in Rawalpindi.

2.3. Ethical considerations

The study adhered to ethical guidelines and received all necessary approvals. The study obtained ethical approval from the Ethical Committee/Institutional Review Board, Combined Military Hospital, Rawalpindi (No. 267).

2.4. Sample size

The sample size was calculated using the proportion of patients with corrosive ingestion injuries who underwent surgical procedures (6.2%) at a 95% confidence level and a 5% margin of error [12,13]. The final sample size was calculated as 90, which was further increased to 99 to strengthen the study findings.

2.5. Selection criteria

The study included admitted patients who underwent surgical intervention for corrosive ingestion and who were 5 years of age or older, with documented corrosive ingestion durations of 3 months or longer, and who were receiving surgical management. Patients who presented with malignant or other benign strictures were excluded. In addition, all patients whose medical records were incomplete were excluded from the study.

2.6. Statistical analysis

The data were analyzed via SPSS (version 27.0) by calculating frequencies, percentages, means, and standard deviations (SDs). The chi-square test was applied to assess the gender-wise comparison of ingestion types and causative substances in corrosive ingestion cases. The results were considered significant at $p < 0.05$.

3. Results

Table 1 shows that the average age of the patients was 30.36 ± 10.18 years, with 61.62% female patients and 38.38% male patients. Most of the cases (84.85%) were accidental, whereas 15.15% were suicidal ingestion cases. Among the 99 patients, 72.73% had no comorbidities. Among the ingested substances, a mixed combination (55.56%) was most common, followed by acid ingestion (25.25%).

Table 1. Sociodemographic indicators and medical history of corrosive ingestion cases (n = 99).

Variables		Frequency (%)	Mean ± Std. Deviation
Age (in years)		-	30.36 ± 10.18
Gender	Male	38 (38.38)	-
	Female	61 (61.62)	-
Comorbidity	Hypertension	15 (15.15)	-
	Diabetes	2 (2.02)	-
	Diabetes, hypertension	7 (7.07)	-
	Any other	3 (3.03)	-
	No comorbidity	72 (72.73)	-
Ingestion	Accidental	84 (84.85)	-
	Suicidal	15 (15.15)	-
Ingested causative substance	Acid	25 (25.25)	-
	Detergents	9 (9.09)	-
	Alkali	5 (5.05)	-
	Ammonia	5 (5.05)	-
	Mixed	55 (55.56)	-

Table 2 shows that accidental ingestion was more common among males (94.74%) than females (78.69%), whereas suicidal ingestion was significantly greater among females (21.31%) than males (5.26%) ($p = 0.026$). Moreover, compared with males, most of the females (60.66%) ingested mixed substances, while 29.51% ingested acid (47.37% and 18.42%, respectively), and these differences were statistically significant ($p = 0.048$).

Table 2. Sexwise comparison of ingestion types and causative substances in corrosive ingestion cases (n = 99).

Variables		Gender		Degree of Freedom (df)	Chi-Square Value (X^2)	*p* value *
		Male Frequency (%)	Female Frequency (%)			
Ingestion	Accidental	36 (94.74)	48 (78.69)	1	4.691	0.026 *
	Suicidal	2 (5.26)	13 (21.31)			
Ingested causative substance	Acid	7 (18.42)	18 (29.51)	4	9.577	0.048 *
	Alkali	3 (7.89)	2 (3.28)			
	Ammonia	4 (10.53)	1 (1.64)			
	Detergents	6 (15.79)	3 (4.92)			
	Mixed	18 (47.37)	37 (60.66)			

* Variables were compared using the chi-square test. ** Significant value ($p \leq 0.05$).

Table 3 shows that all patients underwent upper gastrointestinal endoscopy, whereas contrast studies were performed in 97.98% of patients. Moreover, diagnostic laparoscopy or feeding jejunostomy was the most common surgical procedure (57.58%), followed by complete esophagectomy with gastric pull-up (34.34%). Furthermore, complex surgeries, such as esophagogastrectomy with colonic interposition and Roux-en-Y, were performed in 21.21% of patients. The most affected site of injury was the esophagus (68.69%), followed by the pylorus (36.36%) and gastroesophageal junction (23.23%). Among the complications, surgical site infections or abscesses were the most common (16.16%), followed by stricture formation (11.11%) and respiratory complications such as empyema, pneumonia, or atelectasis (10.10%). Mortality was recorded in 4.04% of the 99 patients.

Table 3. Procedures, injuries, management, and complications in corrosive ingestion cases.

Variables		Frequency (%)
Evaluation procedures	Upper gastrointestinal endoscopy	99 (100.00)
	Contrast study	97 (97.98)
	Bronchoscopy	18 (18.18)
Injury location/extent	Esophagus	68 (68.69)
	Pylorus	36 (36.36)
	Gastroesophageal junction	23 (23.23)
	Proximal stomach	19 (19.19)
	Distal stomach	17 (17.17)
	Pharynx/hypopharynx	2 (2.02)
Surgical procedures	Diagnostic laparoscopy/feeding jejunostomy	57 (57.58)
	Complete esophagectomy with gastric pull-up	34 (34.34)
	Pyloroplasty	25 (25.25)
	Esophago-gastrectomy, colonic interposition, Roux-en-Y	21 (21.21)
	Gastrojejunostomy	7 (7.07)
	Partial esophagectomy with gastric pull-up	6 (6.06)
	Tracheoesophageal fistula repair	3 (3.03)
	Total laryngopharyngoesophagectomy	2 (2.02)
	Esophagectomy, colonic interposition, Roux-en-Y	1 (1.01)
Complications	Abscess/surgical site infections	16 (16.16)
	Stricture formation	11 (11.11)
	Empyema/pneumonia/atelectasis	10 (10.10)
	Cardiac arrythmias	8 (8.08)
	Recurrent laryngeal nerve injury	7 (7.07)
	Hemorrhage	5 (5.05)
	Anastomotic leak	4 (4.04)
	Mortality	4 (4.04)
	Conduit necrosis	3 (3.03)

4. Discussion

The current study reported the surgical management of patients who ingested corrosive substances. Most of the cases were accidental, and mixed substances were reported as the most commonly ingested materials. The majority of the patients did not have comorbidities. Moreover, sex differences were significant in terms of ingestion patterns as well as the types of substances ingested. All patients underwent upper gastrointestinal endoscopy, and diagnostic laparoscopy or feeding jejunostomy was the most frequently performed surgical procedure. The esophagus was the most affected site of in-

jury, followed by the pylorus and gastroesophageal junction. Furthermore, postoperative complications were common, with surgical site infections and strictures being the most commonly reported, whereas mortality and anastomotic leaks were rare.

Corrosive ingestion triggers full-thickness esophagogastric necrosis, which represents the most severe form of injury to the alimentary tract. The degree of severe damage is typically associated with the ingestion of large quantities of concentrated corrosive agents, often in cases of suicidal intent, as observed in most cases in our study. The injuries are generally confined to the esophagus and stomach, with the duodenum being relatively spared. This sparing is likely owing to pyloric spasm triggered by the corrosive substance or the alkaline environment of the duodenum. Severe metabolic complications, including acidosis and dehydration, often accompany such injuries. Furthermore, disruption of the gut mucosal barrier, in addition to contamination of the peritoneal and mediastinal spaces, often leads to life-threatening sepsis.

The management of corrosive ingestion requires immediate resuscitation to correct fluid, electrolyte, and acid–base imbalances, along with the administration of broad-spectrum antibiotics and timely surgical intervention. Significant differences in mortality rates were observed between the surgical group (67%) and the supportive treatment group (100%) in a comparative study involving 27 patients [14]. In contrast, our study reported a mortality rate of 4%, which may be attributed to effective management strategies, the extent of injury, and the retrospective design of our study, which did not include long-term patient follow-up. In such cases, surgical treatment generally focuses on excising nonviable tissue and ensuring effective peritoneal and mediastinal drainage. There is a dearth of literature on the management and outcomes of severe esophagogastric injuries owing to corrosive ingestion. Cattan et al., in their review, reported immediate postoperative mortality in 2 out of 9 patients, with further deaths occurring in the months after surgical resection [15]. Moreover, a review on the outcome of gastric perforation resulting from corrosive ingestion revealed that patients with gastric necrosis and perforation had poor survival outcomes, whereas those with isolated perforation that was repaired primarily experienced improved survival [16].

Higher mortality rates have been reported when a thoracoabdominal approach is employed for esophageal resection following severe corrosive injuries. In a study by Lai et al., 18 patients who underwent emergency surgery were recruited, and the overall mortality rate was reported to be 66.7%, with four deaths occurring among patients who underwent esophagectomy and stomach resection via the thoracoabdominal method [14]. In contrast, mortality was lower (37.5%) in patients who underwent esophageal stripping with stomach resection through the abdominal route. These findings suggest that esophageal stripping is a safer alternative to the thoracoabdominal approach in such cases.

Despite the severity of injuries and the extensive surgical resection often needed, the perioperative mortality rate reported in the literature is relatively low [17]. Factors associated with improved outcomes include aggressive resuscitation, timely surgical intervention to limit further injury, complete excision of necrotic tissue, transhiatal esophageal resection, and postoperative nutritional support provided through jejunostomy feeding [18]. Additionally, corrosive-induced periesophageal edema has been suggested to aid in transhiatal resection by reducing procedural complexity and minimizing morbidity [19].

Our study findings revealed significant gender-based differences in patterns of substance ingestion. Accidental ingestion was more prevalent among males, which may be linked to occupational or environmental exposures associated with male-dominated activities [20,21,22]. Conversely, suicidal ingestion occurs more frequently among females,

which may be due to psychological and sociocultural factors, as females may experience higher levels of emotional distress and societal pressures that contribute to self-harm [23,24]. Additionally, females were more likely to ingest mixed substances, whereas males were more likely to ingest acid. These findings highlight the need for tailored prevention strategies, such as promoting workplace safety for males and providing targeted mental health support for females, to address the specific needs and underlying factors associated with these behaviors [25,26]. To explore related qualitative factors and determine the contributing sociodemographic parameters unaddressed by the current study, further research is needed, which is a potential weakness of this study.

5. Conclusions

Our study concluded that timely surgical management could reduce the risk of complications and enhance patient outcomes. Corrosive ingestion often affects multiple areas that require several surgical interventions. In certain cases, complex procedures, such as colon interposition and total laryngopharyngoesophagectomy (TLPO), which require skilled surgeons as well as advanced management centers, are performed to manage corrosive injuries. Therefore, improving these patients' outcomes via interventions focused on training in complex surgical procedures is crucial. Further research is needed to identify the most effective approaches for the surgical management of corrosive ingestion.

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Original Article

Assessment of acute kidney injury associated with the concomitant use of piperacillin/tazobactam and vancomycin in pediatric cancer patients

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Abstract

This study aimed to evaluate the renal safety of concomitant piperacillin/tazobactam (Pip-Taz) and vancomycin in pediatric cancer patients by assessing changes in the serum creatinine (SCr) and blood urea nitrogen (BUN) levels. The hospital information system at Shaukat Khanum Memorial Cancer Hospital and Research Centre was used to extract the required information, and laboratory test results were collected for 100 randomly selected patients in whom both Pip-Taz and vancomycin were used. Patients were randomly selected using a computer-generated list to minimize selection bias. The data obtained were statistically analyzed using the Friedman test. Most patients who received Pip-Taz and vancomycin suffered from pre-B lymphocytic leukemia. The Friedman test revealed significant within-group differences in SCr and BUN over time ($\chi^2 = 299.945$, $p < 0.001$ for males; $\chi^2 = 170.162$, $p < 0.001$ for females), but all posttherapy values remained within normal physiological ranges. Posttherapy, vancomycin-treated patients had slightly lower SCr and BUN levels than did those receiving Pip-Taz, although all values remained within normal ranges. A similar trend was observed in females. These findings suggest that concomitant Pip-Taz and vancomycin did not result in significant nephrotoxicity, as all renal biomarker changes remained within normal ranges. No patients met the acute kidney injury (AKI) criteria during therapy. However, vancomycin-treated patients presented slightly greater reductions in creatinine and BUN levels than did Pip-Taz-treated patients, although this does not indicate improved renal function. Despite these findings, vancomycin's potential for nephrotoxicity remains an important consideration in pediatric treatment decisions.

Keywords

Acute kidney injury; Piperacillin-tazobactam; Vancomycin; Blood urea nitrogen; Nephrotoxicity; Creatinine; Pediatrics

1. Introduction

Piperacillin/tazobactam (Pip-Taz) is a combination antibiotic in which piperacillin inhibits bacterial cell wall synthesis, whereas tazobactam enhances its efficacy by inhibiting beta-lactamase enzymes [1,2]. It has been proven safe and effective in treating serious infections such as pelvic inflammatory disease, pneumonia, intra-abdominal infection, cellulitis, and sepsis [3,4]. This combination exhibits broad-spectrum activity against gram-positive bacteria (*Enterococcus faecalis, Staphylococcus epidermidis, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes, and viridans group streptococci*), aerobic/facultative gram-negative microorganisms (*Acinetobacter bau-*

mannii, Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Pseudomonas aeruginosa), and gram-negative anaerobes (Bacteroides species) [5].

Vancomycin is a glycopeptide antibiotic primarily used to treat serious gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci [6]. Vancomycin also has activity against streptococci, enterococci, and certain anaerobic bacteria [7]. However, it is ineffective against gram-negative bacteria [8]. Owing to its limited spectrum, vancomycin is typically reserved for infections caused by gram-positive bacteria that are resistant to other antibiotics [9].

In clinical practice, vancomycin and Pip-Taz dosages in pediatric patients are weight-based [10]. Vancomycin is typically administered at 40–60 mg/kg/day every 6–8 hours, with dosing adjusted on the basis of therapeutic drug monitoring (TDM) to maintain target serum trough levels [11,12]. Pip-Taz is given at 90 mg/kg QID on the basis of the piperacillin component [13]. Renal function tests, especially creatinine clearance, are important for assessing vancomycin and Pip-Taz dosing since both drugs are renally excreted. Pip-Taz, vancomycin, and their combination are frequently used in the management of febrile neutropenia [14,15]. Their coadministration provides broad-spectrum coverage against bacterial infections in immunocompromised patients [16,17,18,19].

Several studies have reported an increased risk of acute renal toxicity associated with Pip-Taz, often evidenced by elevations in baseline serum creatinine (SCr) levels determined at hospital admission [20,21]. Studies in adult patients have reported an increased risk of acute kidney injury (AKI) with concomitant Pip-Taz and vancomycin use, with the incidence of AKI reaching 34.8% in some cohorts. However, limited data exist regarding this risk in pediatric oncology patients, necessitating further investigation [22]. Given the limited pediatric data on this topic, this study aimed to evaluate the renal safety of concomitant Pip-Taz and vancomycin in pediatric cancer patients by assessing changes in SCr and blood urea nitrogen (BUN) levels.

2. Materials and methods

The study included pediatric oncology patients diagnosed with febrile neutropenia at Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan. A total of 100 pediatric oncology patients meeting the inclusion criteria were randomly selected using a computer-generated list to minimize selection bias. The laboratory test results were retrieved for analysis. Patients who had a fever (> 38.5 °C on one event or > 38 °C on at least two events within 12 hours) were eligible for inclusion in the retrospective analysis. For each included patient, the SCr and BUN values were obtained from the hospital's laboratory information system. These laboratory tests are routinely conducted as part of standard patient care for febrile neutropenia and were not performed specifically for this study.

AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in SCr of ≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times the baseline level within 7 days. None of the patients in this study met these criteria. Nephrotoxicity was assessed on the basis of these creatinine changes, whereas changes in BUN were analyzed but not used as a primary criterion for nephrotoxicity.

The study was conducted between June 2021 and December 2022. The study population comprised male and female pediatric oncology patients with various infections. Among the 100 patients included in the study, 64 were male and 36 were female, with ages ranging from 3 months to 15 years. All these patients received several courses of piperacillin–tazobactam and vancomycin during the study period, but only the primary course with a minimum of seven days of therapy was used in the analysis. Patients with

missing or inadequate laboratory samples, those treated exclusively in the outpatient department (OPD), and those who received preoperative antibiotics were excluded. Patients with chronic kidney disease or other preexisting renal conditions and those who received less than 48 hours of empiric Pip-Taz and vancomycin therapy were also excluded. This was a retrospective cohort study, as the data were collected from the Hospital Information System, and this study was exempt from ethical review by the Shaukat Khanum Memorial Hospital Institutional Review Board (IRB) (No. EX-04-05-23-01), as it involved a retrospective analysis of existing data without direct patient intervention.

Statistical analysis was conducted using SPSS (v26.0). Categorical variables (sex, diagnosis) are reported as percentages and frequencies. The Friedman test, a nonparametric test for repeated measures, was used to assess within-group changes in renal biomarkers over time. Statistical significance was set at $p < 0.05$.

3. Results

Table 1 summarizes the primary diagnoses of the study population. The most common diagnosis in males was pre-B-cell acute lymphoblastic leukemia (n = 23), followed by Burkitt's lymphoma (n = 9) and osteosarcoma (n = 8). In females, pre-B-cell acute lymphoblastic leukemia (n = 14) was the most prevalent, with Hodgkin lymphoma (n = 5) and Burkitt's lymphoma (n = 4) also occurring frequently. Other diagnoses included anaplastic large-cell lymphoma (n = 4), diffuse large B-cell lymphoma (n = 8), and Wilms tumor (n = 8). Males were more commonly affected (64%) than females (36%) across most diagnoses, except for rhabdomyosarcoma (RMS), where the male-to-female ratio was equal (2:2).

Table 1. Primary diagnosis across the selected population for studies (N = 100).

Diagnosis	Male (n = 64)	Female (n = 36)
	Frequency (%)	Frequency (%)
Anaplastic large-cell lymphoma	2 (2.00)	2 (2.00)
Burkitt's	9 (9.00)	4 (4.00)
Diffuse large B-cell lymphoma	6 (6.00)	2 (2.00)
Ewing Sarcoma	5 (5.00)	2 (2.00)
Hodgkin lymphoma	1 (1.00)	5 (5.00)
Non-Hodgkin lymphoma	2 (2.00)	1 (1.00)
Osteosarcoma	8 (8.00)	2 (2.00)
Pre-B-Cell Acute lymphoblastic leukemia	23 (23.00)	14 (14.00)
Rhabdomyosarcoma	2 (2.00)	2 (2.00)
Wilms Tumor	6 (6.00)	2 (2.00)

Figure 1 shows the distribution of gram-positive infections, with the most frequent being Streptococcus aureus in wounds (24%), followed by MRSA in blood (18%) and Streptococcus viridians in blood (13%). Other infections include Streptococcus aureus in the blood (12%), MSSA in the blood (11%), and MSSA in the wound (7%), along with Enterococcus in the blood (4%), MRSA in the wound (3%), cellulitis (2%), and abnormal X-ray (6%). These infections were observed in all 100 patients.

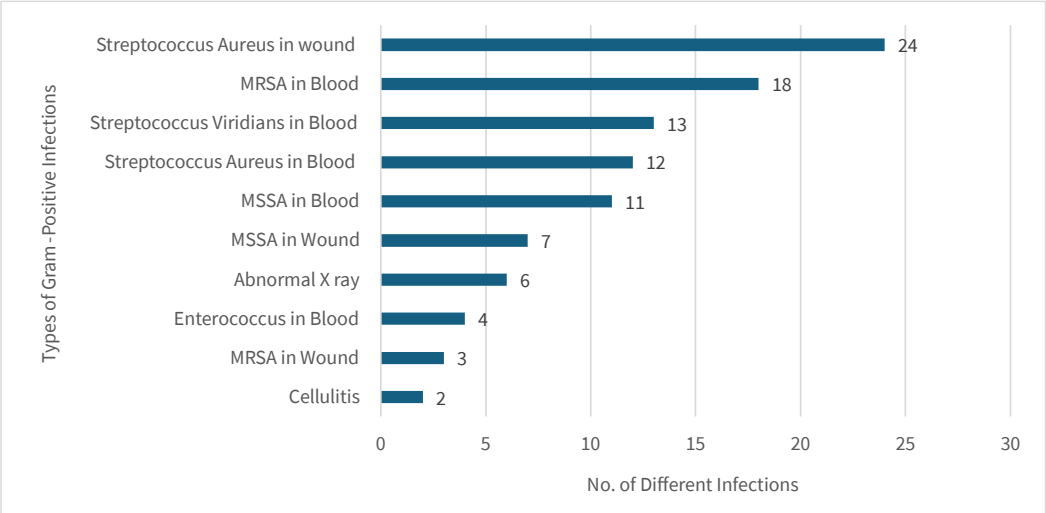

Figure 1. Types of gram-positive infections.

Figure 2 illustrates the distribution of gram-negative infections, with Pseudomonas in the blood being the most common at 41% (41 cases). This is followed by febrile neutropenia, which accounts for 25% (25 patients), and *E. coli* in the urine, which is found in 13% (13 patients). Respiratory distress was observed in 8% (8 patients), *E. coli* in the blood in 6% (6 patients), Pseudomonas in the urine in 4% (4 patients), and intraabdominal infection in 3% (3 patients). These results represent a total of 100 cases, accounting for 100% of the gram-negative infections.

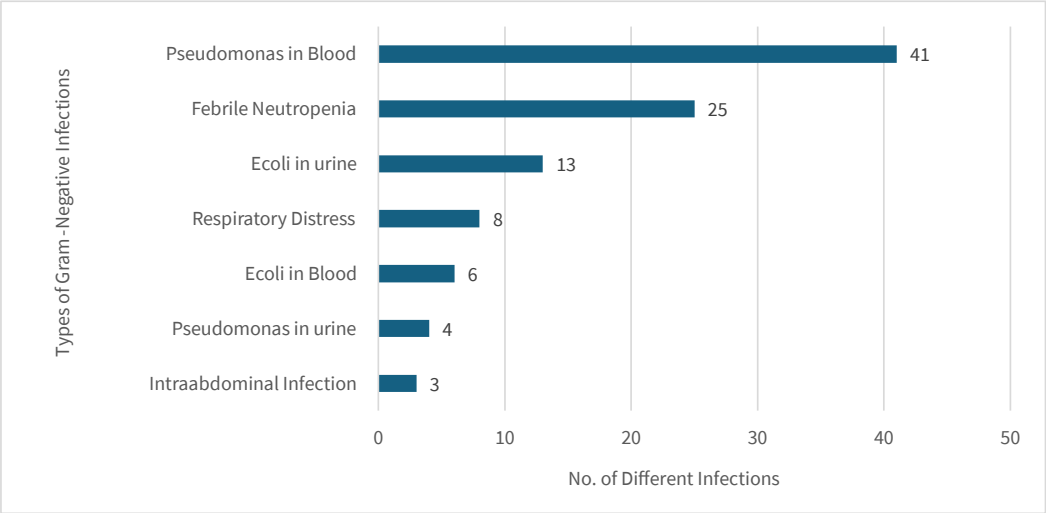

Figure 2. Types of gram-negative infections.

Table 2 compares pre- and posttherapy creatinine and BUN levels to assess changes in renal function. The study included 36 female patients (mean age: 5.1 ± 1.03 years) and 64 male patients (mean age: 5.2 ± 2.05 years). Among females, creatinine levels ranged from 0.29 to 0.76 mg/dL before therapy and from 0.29 to 0.77 mg/dL after therapy. For males, creatinine levels ranged from 0.31 to 0.70 mg/dL before therapy and from 0.31 to 0.72 mg/dL after therapy. Similarly, BUN levels in females ranged from 7 to 15 mg/dL before therapy and from 9 to 16 mg/dL after therapy, whereas in males, BUN levels ranged from 5 to 14 mg/dL before therapy and from 6 to 15 mg/dL after therapy. These findings indicate minor fluctuations in renal biomarkers posttherapy, but all values remained within normal physiological limits, suggesting no significant renal impairment.

Table 2. Descriptive statistics of renal function parameters by sex before and after treatment with vancomycin and Pip-Taz.

Gender	Age (in years)	Creatinine (mg/dl)	Creatinine After Pip-Taz (mg/dl)	Creatinine After Vancomycin (mg/dl)	Baseline BUN (mg/dl)	BUN After Pip-Taz (mg/dl)	BUN After Vancomycin (mg/dl)
	Mean ± SD	**Min – Max**	**Min – Max**	**Min – Max**	**Min – Max**	**Min – Max**	**Min – Max**
Female	5.1 ± 1.03	0.29 – 0.76	0.29 – 0.86	0.29 – 0.77	7.00 – 15.00	8.00 – 15.00	9.00 – 16.00
Male	5.2 ± 2.05	0.31 – 0.70	0.29 – 0.71	0.31 – 0.72	5.00 – 14.00	5.00 – 14.00	6.00 – 15.00

Range: [Min – Max].

Table 3 presents the Friedman test results, which revealed statistically significant within-group differences in renal function parameters (creatinine and BUN) over time. The changes in renal function parameters were significant in both males ($\chi^2 = 299.945$, $p < 0.001$) and females ($\chi^2 = 170.162$, $p < 0.001$) after treatment with Pip-Taz and vancomycin.

In males, the baseline creatinine level was 0.491 ± 0.119, with a mean rank of 2.85, which decreased after treatment with both drugs. Posttreatment, the creatinine level decreased to 0.475 ± 0.119 (mean rank 1.87) with Pip-Taz and to 0.465 ± 0.121 (mean rank 1.28) with vancomycin, although these changes remained within normal ranges and did not indicate a direct renal benefit. Similarly, the baseline BUN level was 11.31 ± 2.130 (mean rank 5.77), which decreased to 10.19 ± 1.934 (mean rank 4.99) with Pip-Taz and to 8.98 ± 2.250 (mean rank 4.24) with vancomycin. The chi-square value of 299.945 and p value < 0.001 confirmed significant within-group changes; however, all values remained within normal physiological limits, indicating no renal dysfunction or improvement.

Among females, the creatinine level decreased from 0.501 ± 0.148 (mean rank 2.90) to 0.484 ± 0.158 (mean rank 1.97) with Pip-Taz and further decreased to 0.454 ± 0.146 (mean rank 1.13) with vancomycin. However, these reductions do not suggest improved renal function but rather normal physiological variations. Similarly, the baseline BUN level was 12.83 ± 1.96 (mean rank 5.71), decreasing to 11.89 ± 1.72 (mean rank 5.10) with Pip-Taz and further to 10.19 ± 1.47 (mean rank 4.19) with vancomycin. The chi-square value of 170.162 and p value < 0.001 indicated statistically significant within-group differences across time points.

Both Pip-Taz and vancomycin were associated with reductions in creatinine and BUN levels. Vancomycin resulted in greater decreases in both parameters; however, these changes remained within normal ranges and did not imply improved renal function.

Table 3. Changes in renal function parameters over time with Pip-Taz and vancomycin treatment.

Gender		Measure	N	Mean ± SD	Mean Rank	Chi-Square (χ^2)	df	*p* value
Male	Creatinine	Baseline	64	0.491 ± 0.119	2.85	299.94	5	< 0.001 *
		Post Treatment Piptaz		0.475 ± 0.119	1.87			
		Post Treatment Vancomycin		0.465 ± 0.121	1.28			
Female	BUN	Baseline	36	11.310 ± 2.130	5.77			
		Post Treatment Piptaz		10.190 ± 1.934	4.99			
		Post Treatment Vancomycin		8.980 ± 2.250	4.24			
Male	Creatinine	Baseline	64	0.501 ± 0.148	2.90	170.16	5	< 0.001 *
		Post Treatment Piptaz		0.484 ± 0.158	1.97			
		Post Treatment Vancomycin		0.454 ± 0.146	1.13			
Female	BUN	Baseline	36	12.830 ± 1.960	5.71			

Gender	Measure	N	Mean ± SD	Mean Rank	Chi-Square (χ^2)	df	*p* value
	Post Treatment Piptaz		11.890 ± 1.720	5.10			
	Post Treatment Vancomycin		10.190 ± 1.470	4.19			

[*] Changes were assessed using the Friedman test. [**] Significant value ($p \leq 0.05$). [***] BUN = Blood urea nitrogen

4. Discussion

This study assessed renal function changes associated with concomitant Pip-Taz and vancomycin in pediatric cancer patients by evaluating creatinine and BUN levels. The primary finding was that although mild fluctuations in creatinine and BUN levels were observed, all posttherapy values remained within normal physiological limits. Importantly, no cases of AKI were identified, and all biomarker variations were within the expected ranges. These findings suggest that the combination of Pip-Taz and vancomycin did not result in clinically significant nephrotoxicity in this study population.

Previous studies have reported a higher incidence of nephrotoxicity with vancomycin monotherapy and combination therapy with Pip-Taz, particularly in adult and critically ill patients. A reported nephrotoxicity rate of 3.8% for vancomycin monotherapy and 23.6% for combination therapy has been reported in hospitalized children [23]. However, our study did not observe nephrotoxic effects meeting the AKI criteria. This discrepancy may be due to differences in patient demographics, treatment duration, baseline renal function, or antibiotic dosing and monitoring strategies used in pediatric oncology patients.

Our findings align with prior research indicating that vancomycin-associated nephrotoxicity is dose dependent and primarily occurs at sustained trough concentrations > 20 mg/L [24]. Since our study population maintained vancomycin trough levels between 8–15 mg/L, the absence of AKI may reflect appropriate dosing strategies in pediatric oncology patients.

Therapeutic monitoring of vancomycin through the area under the curve/minimum inhibitory concentration (AUC/MIC) is used to ensure adequate bacterial killing while preventing excessive drug accumulation, which can lead to nephrotoxicity [25,26]. However, this study did not assess AUC/MIC values. Future studies should investigate how individualized vancomycin dosing strategies, including AUC-guided dosing and TDM, influence renal outcomes in pediatric patients.

Some studies have reported an association between Pip-Taz use and nephrotoxicity in pediatric patients with neutropenic fever [27]. However, our study did not observe significant renal function impairment with Pip-Taz use. It remains possible that renal function could be impacted in higher-risk subgroups or with prolonged exposure. Further investigations are needed to determine long-term renal safety in pediatric patients receiving combination therapy.

Although previous research has suggested that vancomycin exposure beyond 72 hours increases nephrotoxicity risk [28], our study did not specifically evaluate the effect of treatment duration on renal outcomes. Future studies should assess whether limiting vancomycin duration reduces nephrotoxicity in pediatric oncology patients.

Overall, this study provides valuable insight into the renal safety of Pip-Taz and vancomycin in pediatric cancer patients. No significant nephrotoxicity was observed, and all renal biomarker fluctuations remained within normal physiological ranges. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and evaluate the impact of treatment duration and cumulative drug exposure.

5. Conclusions

While previous studies have reported nephrotoxicity with Pip-Taz and vancomycin, our study revealed that these antibiotics were well tolerated in pediatric cancer patients, with no significant renal impairment observed. Importantly, all posttherapy creatinine and BUN levels remained within normal physiological limits, and no cases of AKI were identified.

Patients in this study received varying durations of therapy, with some receiving extended courses of Pip-Taz and vancomycin. No significant changes in SCr or BUN were observed, although the impact of therapy duration on renal function requires further investigation. Similarly, even patients who received vancomycin within the upper limit of therapeutic trough levels (8–15 mg/L) did not show significant changes in kidney function. However, further research is needed to determine the renal safety of higher trough levels in pediatric oncology patients.

Overall, this study provides evidence that concomitant Pip-Taz and vancomycin did not result in clinically significant nephrotoxicity in this population. Further research with larger cohorts and longer follow-up periods is needed to confirm these findings and assess the impact of treatment duration on renal function.

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Consent to participate: Not Applicable.

Data availability: The data supporting this study's findings are available from Ali Akhtar upon reasonable request.

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Conflicts of interest: The authors declare no conflicts of interest.

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Original Article

A comparison of clinical and patient-reported treatment outcomes in chronic hepatitis C patients treated with direct-acting antivirals with and without cirrhosis: a prospective cohort study

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Abstract

Managing patients with chronic hepatitis C and progressive liver conditions poses significant challenges for healthcare professionals. This research sought to evaluate and compare the clinical outcomes and patient-reported treatment experiences of individuals with chronic hepatitis C, differentiating between those with and without cirrhosis, all of whom were receiving standard direct-acting antiviral (DAA) therapy. This prospective cohort study enrolled outpatients who were diagnosed with hepatitis C virus (HCV) infection and who were recruited from a major public tertiary care hospital. The participants received a standard 12-week antiviral regimen consisting of 400 mg of sofosbuvir (SOF) and 60 mg of daclatasvir (DCV) once daily, with or without ribavirin (RBV) at a dose of 400 mg taken two to three times daily. The primary outcome was the cure rate, which was defined as an undetectable viral load at the end of the 12-week treatment period. The secondary outcomes included patient-reported outcomes (PROs), such as health-related quality of life (HRQoL), which were measured via the EuroQol 5-Dimensions 3-Levels (EQ-5D-3 L) questionnaire, and work productivity loss, which was assessed via the Work Productivity and Activity Impairment (WPAI) questionnaire. A total of 300 participants were assessed, comprising 150 cirrhotic and 150 noncirrhotic patients. Group B (cirrhosis) had a greater proportion of treatment-experienced patients and elevated aspartate aminotransferase (AST) levels (48 ± 22 vs. 131 ± 165, $p < 0.001$), along with significantly lower platelet counts ($p = 0.024$). An end-of-treatment response (ETR) was observed in 92.7% of patients without cirrhosis, whereas a significantly lower rate of 52.7% was observed in those with cirrhosis ($p < 0.001$). A significant increase in HRQoL was noted in both groups across all the EQ-5D-3 L domains ($p < 0.001$); however, patients with cirrhosis experienced relatively smaller improvements in the areas of pain/discomfort and anxiety/depression. A small subset of noncirrhotic patients showed no improvement in mobility (−0.59 ± 0.62). Regarding work productivity, both groups experienced substantial reductions in overall impairment (43.0% in noncirrhotic patients, 32.3% in cirrhotic patients), absenteeism, and activity limitations ($p < 0.001$). However, presenteeism increased slightly in both groups, suggesting a return to work with residual functional limitations. The study concluded that SOF-based regimens were highly effective in noncirrhotic patients, who showed greater improvements in virological response, quality of life, and work productivity. In contrast, cirrhotic patients demonstrated lower treatment response rates and smaller gains in patient-reported outcomes despite receiving similar therapies.

Keywords

Hepatitis C, Liver cirrhosis, Sofosbuvir, Daclatasvir, Patient-reported outcome measures, Clinical pharmacy, Quality of life

1. Introduction

Hepatitis C virus (HCV) remains a major contributor to chronic liver disease and related complications globally and continues to significantly impact morbidity, mortality, and healthcare expenditures [1,2]. If left untreated or inadequately managed, over time, HCV infection can progress to severe hepatic complications such as hepatocellular carcinoma, fibrosis, and cirrhosis [3,4]. HCV infection poses a major public health challenge, particularly in low- and middle-income countries (LMICs), where timely diagnosis and access to standardized care remain constrained [5,6]. Recent global estimates show that HCV has affected more than 185 million people worldwide—an increase of nearly 2.8% in the past decade and a half [7]. In Pakistan, where the national prevalence of chronic HCV exceeds 5%, the burden is particularly high. Punjab, the country's most populous province, has reported prevalence rates as high as 6.5% [8]. Transmission primarily occurs through unsafe injection practices, transfusions, needlestick injuries, and intravenous drug use [9].

The primary objective in managing HCV is to achieve a virological cure, either through a sustained virological response (SVR)—defined as undetectable viral levels at 12 weeks (SVR12) or 24 weeks (SVR24) posttherapy—or by achieving an end-of-treatment response (ETR) [10]. With the advent of treatment modalities such as direct-acting antivirals (DAAs), the clinical landscape of HCV management has undergone a paradigm shift. Compared with earlier interferon-based therapies, DAAs, such as sofosbuvir (SOF)-based regimens, offer high rates of SVR, shorter treatment durations, improved tolerability, and minimal adverse effects [11,12]. Current clinical guidelines aim for SVR12, which is widely accepted as a surrogate marker for virologic cure [13]. These therapies have been proven effective across a wide range of patient profiles, including naïve to treatment, experienced treatment, and those with compensated liver cirrhosis [14,15].

Nevertheless, while clinical outcomes such as SVR and liver function normalization are well documented, there remains a critical gap in understanding how these treatments influence patients' lived experiences, particularly in LMICs such as Pakistan [16,17]. Patient-reported outcomes (PROs), which highlight the perspectives of patients without clinician interpretation, are increasingly recognized as essential components of treatment evaluation [18,19]. While viral eradication remains the cornerstone of therapeutic success, it does not fully capture how patients perceive their recovery, nor does it reflect the treatment's influence on daily functioning, mental well-being, social participation, and work productivity [20,21].

Notably, advanced liver disease presents complex clinical challenges, and patients with cirrhosis may experience different therapeutic responses, symptom burdens, and quality-of-life outcomes than those without cirrhosis. There is a lack of empirical data from Pakistan exploring distinctions, especially concerning PROs. The lack of such data limits the development of evidence-based, patient-centered treatment strategies across healthcare systems globally. Therefore, this study compared both patient-reported treatment experiences and clinical outcomes among chronic hepatitis C patients with and without cirrhosis receiving standard DAA therapy. By integrating clinical indicators such as SVR12 with PROs assessed through the EuroQol 5-Dimensions 3-Levels (EQ-5D-3 L) and Work Productivity and Activity Impairment (WPAI) instruments, this study aims to gen-

erate holistic, locally relevant evidence to inform treatment guidelines, clinical counseling, and public health strategies in Pakistan.

2. Methodology

2.1. Study design and duration

This prospective cohort study was carried out over a six-month period spanning from May to November 2020.

2.2. Ethics approval

This study obtained ethics clearance from the Services Institute of Medical Sciences (SIMS), Lahore (No. IRB/2020/734/SIMS), and was approved by the Institutional Review Board (IRB) of Lahore College for Women University (LCWU), Lahore.

2.3. Study settings

This study was conducted at the Services Hospital, Lahore, a 1325-bed tertiary care referral and teaching hospital located in Lahore, Pakistan [22]. The hospital has a specialized clinic for liver and hepatitis, offering outpatient services for diagnosing, treating, and managing hepatitis C and other chronic liver diseases.

2.4. Sample size and sampling technique

The study sample was obtained via the OpenEpi online sample size calculator (version 3.01) [23], with a minimum of 101 participants per group calculated on the basis of a 95% confidence level, a 5% margin of error, and an anticipated proportion of 93% [24]. To increase the study's statistical power, the sample size was expanded to 150 participants per group, totaling 300 chronic HCV patients—150 with cirrhosis and 150 without cirrhosis—selected through a nonprobability purposive sampling technique.

2.5. Selection criteria

The study recruited adults (≥ 18 years) diagnosed with chronic hepatitis C, verified through detectable levels of HCV ribonucleic acid (RNA). Both naïve to treatment and experienced patients for treatment were included, provided that they had not previously received DAA therapy. Patients with or without cirrhosis, as confirmed through clinical or radiological evaluation, were enrolled. All participants needed to be eligible for the standard antiviral regimen of daclatasvir (DCV) and SOF, with or without ribavirin (RBV), and had to provide informed consent for enrollment and follow-up assessments at baseline and 12 weeks posttreatment. Patients with hepatitis B virus (HBV) or human immunodeficiency virus (HIV) coinfection, hepatocellular carcinoma, decompensated liver disease, pregnancy, lactation, treatment with investigational or nonstandard HCV therapies, or psychiatric or cognitive impairments that could obstruct the completion of PRO questionnaires were excluded.

2.6. Data collection procedure

All patients with chronic hepatitis C were screened for cirrhosis via the aspartate aminotransferase-to-platelet ratio index (APRI). Laboratory values for platelet count and aspartate aminotransferase (AST) levels were obtained from patient records. An APRI score of ≥ 1.5 was used to classify patients as cirrhotic, whereas a score < 1.5 indicated noncirrhosis [25,26].

The patients were categorized into two groups: Group A included individuals with chronic hepatitis C without cirrhosis, whereas Group B included those with cirrhosis. All patients received a standardized treatment regimen consisting of SOF 400 mg once daily and DCV 60 mg once daily. RBV 400 mg was additionally administered either twice or three times daily on the basis of clinical judgment and the specific characteristics of each patient. The treatment protocol was the same for both naïve patients and experienced patients; the latter had previously received interferon-based regimens but not DAAs [27]. Participants were prospectively followed over the 12-week treatment course to monitor their clinical response and assess changes in PROs at baseline and posttreatment.

2.7. Data collection tools

The EQ-5D-3 L is a commonly used instrument for evaluating health-related quality of life (HRQoL) [28]. It consists of two primary sections: a descriptive system of health states and a self-rated health assessment. The descriptive system includes five areas: self-care, mobility, pain/discomfort, usual activities, and anxiety/depression. Participants assessed their overall health status via a visual analog scale (VAS) at the time of evaluation.

The WPAI questionnaire is a well-established tool for assessing disruptions in both work performance and daily activities [29]. In this study, participants provided insights into how the hepatitis C virus (HCV) affects their productivity at work and in routine daily tasks. The work impairment score reflects the combined impact of missed work (absenteeism) and reduced efficiency while on the job (presenteeism) and was evaluated only for those who identified as employed. Conversely, the activity impairment score captures limitations in nonwork-related daily functions and was assessed across all participants, irrespective of their job status. Notably, high scores on this instrument correspond to worse health-related outcomes.

Each domain was calculated as a percentage (%) via the standard WPAI scoring formula:

$$\text{Absenteeism} = (\text{Total hours scheduled to work} \div \text{Hours missed due to health}) \times 100 \quad (1)$$

$$\text{Presenteeism} = (\text{Self-rated impairment at work} \div 10) \times 100 \quad (2)$$

$$\text{Work productivity loss} = \text{Absenteeism} + [(1 - \text{Absenteeism}) \times \text{Presenteeism}] \quad (3)$$

$$\text{Activity impairment} = (\text{Self-rated activity impairment} \div 10) \times 100 \quad (4)$$

Individual scores were calculated for each patient via these formulas [30]. The mean percentage scores for each domain were then computed by averaging the individual values:

$$\text{Mean score (\%)} = (\text{Sum of all individual percentage scores}) \div (\text{Number of individuals}) \quad (5)$$

In addition to the five dimensions of the EQ-5D-3 L descriptive system, the study also assessed absenteeism, presenteeism, work productivity, and activity limitations before and after treatment. The instrument used for data collection was divided into five sections: informed consent from participants, demographic details, laboratory test results, self-reported patient outcomes, and the clinical management of hepatitis C.

2.8. Statistical analysis

Descriptive statistics were used to summarize the collected data via SPSS, version 25.0 (SPSS Inc., Chicago, IL, USA). An independent samples t test was applied to compare

the mean values between the cirrhotic and noncirrhotic groups. Paired samples t tests were conducted to assess within-group changes in PROs, including HRQoL, as measured by the EQ-5D-3 L, and work-related impairments, as measured by the WPAI questionnaire, before and after treatment.

3. Results

3.1. Participant characteristics

Among the 300 patients evaluated in this study, half (n = 150) did not have cirrhosis and were placed in Group A, whereas the other half (n = 150) had cirrhosis and were assigned to Group B. In Group A, 39 (26.0%) were aged 20–40 years, 98 (65.3%) were aged 41–60 years, and 13 (8.7%) were older than 60 years. In Group B, 44 (29.3%) were between 20–40 years, 93 (62.0%) were 41–60 years, and 13 (8.7%) were older than 60 years. The sex distribution in Group A was 50% male (n = 75), and that in Group B was 54.7% male (n = 82). Most participants in both groups were married: 95.3% and 97.4% in both groups, respectively. With respect to economic status, 72.7% and 80.0% of the respondents in both groups reported monthly incomes of less than 15,000 rupees. A smaller percentage earned between 15,000 and 50,000 rupees, 26.7% and 20% in both groups, respectively. Only one individual (0.7%) in Group A earned above this range. Employment was reported by 64 participants (42.7%) and 54 (36.0%) in the two groups, respectively.

In terms of clinical indicators, 107 (71.3%) noncirrhotic patients had HCV viral loads exceeding 10/IU/mL, whereas 115 (76.7%) patients in the cirrhotic group did. AST levels were elevated in 98.0% (n=147) of Group B patients compared with 51.3% (n = 77) of Group A patients ($p < 0.001$). Platelet counts were lower in cirrhotics, averaging 121 ± 56 versus 253 ± 73 in noncirrhotics ($p = 0.024$). Ultrasound findings revealed a coarse liver texture in 63.3% of the cirrhotic patients, whereas only 9.3% (n = 14) of the noncirrhotic patients had similar findings. The source of infection was unknown in 30.7% and 28.7% of patients in both groups, whereas nonoccupational or iatrogenic transmission accounted for 68.0% and 70.0%, respectively, in both groups. Drug abuse was reported in 1.3% of both groups. Additionally, 88.7% (n =133) of the noncirrhotic patients were treatment naïve, whereas 70.0% (n = 105) of the cirrhotic patients were treatment naïve.

Table 1. Baseline sociodemographic and clinical features of the patients (N = 300).

Variables		Noncirrhotic Group A n = 150	Cirrhotic Group B n = 150
		Frequency (%)	**Frequency (%)**
Age	20 – 40 years	39 (26.0)	44 (29.3)
	41 – 60 years	98 (65.3)	93 (62.0)
	> 60 years	13 (8.7)	13 (8.7)
Male		75 (50.0)	82 (54.7)
Marital status (married %)		142 (95.3)	145 (97.4)
Income per month (in Pakistani rupees)	< 15,000	109 (72.7)	120 (80.0)
	15,000 – 50,000	40 (26.7)	30 (20.0)
	> 50,000	1 (0.7)	0 (0.0)
Employed		64 (42.7)	54 (36.0)
HCV viral load n > 10^6 (%)		107 (71.3)	115 (76.7)
AST > Upper limit normal (ULN) (Mean ± SD) *		48 ± 22	131 ± 165 **
n > ULN		77 (51.3)	147 (98.0)
Platelets 10^9/l (Mean ± SD) *		253 ± 73	121 ± 56 ***
Liver coarseness on ultrasonography		14 (9.3)	95 (63.3)

Variables		Noncirrhotic Group A n = 150	Cirrhotic Group B n = 150
		Frequency (%)	**Frequency (%)**
Source of Infection	Unspecified	46 (30.7)	43 (28.7)
	Nonoccupational/iatrogenic	102 (68.0)	105 (70.0)
	Drug abuse	2 (1.3)	2 (1.3)
	Treatment naïve	133 (88.7)	105 (70.0)

[*] Independent samples t test used to compare group means. [**] *p* value < 0.001. [***] *p* value = 0.024.

3.2. Prescribed treatment and cure rate

In the noncirrhotic patient group, 65.3% (n = 98) were treated with SOF/DCV, whereas the remaining 34.7% (n = 52) received a combination of SOF/DVC and RBV. In contrast, among the cirrhotic patients, 60.7% (n = 91) were administered SOF/DCV/RBV, and 39.4% (n = 59) were given SOF/DCV. ETR, marked by an undetectable viral load after 12 weeks, was achieved by 92.7% (n = 139) of individuals in the noncirrhotic patient group. Only 52.7% (n = 79) of the cirrhotic patients achieved this outcome, indicating a statistically significant difference ($p < 0.001$).

3.3. Effect of treatment on PROs (EQ-5D-3 L)

In the noncirrhosis group, the mean improvements in the EQ-5D-3 L domains from baseline to posttreatment were as follows: 0.58 (mobility), 0.11 (self-care), 0.43 (usual activities), 0.43 (pain/discomfort), and 0.69 (anxiety/depression). In the cirrhosis group, the corresponding mean improvements were 0.59, 0.24, 0.46, 0.16, and 0.46, respectively (all $p < 0.001$; Table 2).

In the cirrhosis group, the PRO scores significantly improved across all the domains ($p < 0.001$ for each). By the end of the 12-week treatment period, the noncirrhotic group demonstrated significant improvements in pain/discomfort, usual activities, and anxiety/depression. However, a subset of these patients showed no improvement in mobility (mean score: 0.59) (Table 2).

Table 2. Effect of treatment on PROs in noncirrhotic and cirrhotic patients who achieved ETR.

EQ-5D-3 L Domains	Noncirrhotic Group A			Cirrhotic Group B		
	MD ± SD	**95% CI (difference) Lower – Upper**	***p* value** [*]	**MD ± SD**	**95% CI (difference) Lower – Upper**	***p* value** [*]
Mobility	-0.58 ± 0.49	-0.67 to -0.49	< 0.001 [*]	-0.59 ± 0.62	-0.70 to -0.47	< 0.001 [**]
Self-care	-0.11 ± 0.32	-0.17 to -0.06	< 0.001 [*]	-0.24 ± 0.54	-0.35 to -0.14	< 0.001 [**]
Usual activities	-0.43 ± 0.64	-0.55 to -0.32	< 0.001 [*]	-0.46 ± 0.67	-0.85 to -0.33	< 0.001 [**]
Pain/discomfort	-0.43 ± 0.54	-0.52 to -0.33	< 0.001 [*]	-0.16 ± 0.45	-0.24 to -0.07	< 0.001 [**]
Anxiety/depression	-0.69 ± 0.50	-0.78 to -0.60	< 0.001 [*]	-0.46 ± 0.64	-0.58 to -0.34	< 0.001 [**]

[*] Paired samples t test. [**] $p < 0.05$, statistically significant. [***] Patients who achieved SVR12 were included in the analysis and completed both pre- and posttreatment EQ-5D-3 L assessments. [****] Of the 150 patients initially enrolled per group, only 122 from Group A (noncirrhotic) and 62 from Group B (cirrhotic) were included due to incomplete data or missed assessment timelines. [*****] The instrument's descriptive system covers five core dimensions, including self-care, mobility, pain/discomfort, usual activities, and anxiety/depression, denoted as SC, MB, PD, UA, and AD, respectively.

3.4. Effect of treatment on WPAI

Among noncirrhosis patients, significant improvements were observed across all WPAI domains following treatment. The mean work productivity impairment score de-

creased from 65% (95% CI: 57.3–72.7) at baseline to 22% (95% CI: 17–27) after 12 weeks of treatment, reflecting a 43.0% absolute improvement ($p < 0.001$). Similarly, absenteeism was significantly reduced from 15.4% (95% CI: 8.5–22.3) to 1.3% (95% CI: −0.7–3.3) ($p < 0.001$), representing a 14.1% absolute decrease. However, presenteeism increased slightly from 40.8% (95% CI: 31.9–49.7) to 52.0% (95% CI: 45.5–58.8) ($p < 0.001$), suggesting that patients remained at work but perceived reduced effectiveness. Notably, activity impairment significantly decreased from 55.0% (95% CI: 46.5–63.5) to 25.0% (95% CI: 22–28) ($p < 0.001$), indicating a 30.0% improvement in daily functioning. (Table 3).

In the cirrhosis group, similar patterns of improvement were observed. Work productivity impairment declined from 74.3% (95% CI: 67.4–81.2) to 42.0% (95% CI: 34.5–49.3), representing a 32.3% reduction ($p = 0.003$). Absenteeism decreased significantly from 22.9% (95% CI: 14.2–31.6) to 9.4% (95% CI: 4.6–14.1) ($p < 0.001$). However, presenteeism increased from 40.1% (95% CI: 30.2–49.9) to 51.9% (95% CI: 41.5–62.3) ($p < 0.001$), echoing findings in the noncirrhotic group. A marked improvement in activity impairment was observed, decreasing from 82.9% (95% CI: 79.8–85.9) to 54.0% (95% CI: 50.4–58.2) ($p < 0.001$), corresponding to a 28.9% absolute reduction (Table 3).

Table 3. Comparison of WPAI domains before and after 12 weeks of antiviral therapy in cirrhotic and noncirrhotic patients.

Domain	Group	Before Treatment	After 12 Weeks	Absolute Change (%)	*p* value
		Mean Score (%) 95% CI	Mean Score (%) 95% CI		
Work productivity impairment	Non-Cirrhosis	65.0 (57.3–72.7)	22.0 (17–27)	↓ 43.0	< 0.001 ***
	Cirrhosis	74.3 (67.4–81.2)	42.0 (34.5–49.3)	↓ 32.3	0.003 ***
Absenteeism	Non-Cirrhosis	15.4 (8.5–22.3)	1.3 (-0.7–3.3)	↓ 14.1	< 0.001 ***
	Cirrhosis	22.9 (14.2–31.6)	9.4 (4.6–14.1)	↓ 13.5	< 0.001 ***
Presenteeism	Non-Cirrhosis	40.8 (31.9–49.7)	52.0 (45.5–58.8)	↑ 11.2	< 0.001 ***
	Cirrhosis	40.1 (30.2–49.9)	51.9 (41.5–62.3)	↑ 11.8	< 0.001 ***
Activity impairment	Non-Cirrhosis	55.0 (46.5–63.5)	25.0 (22–28)	↓ 30.0	< 0.001 ***
	Cirrhosis	82.9 (79.8–85.9)	54.0 (50.4–58.2)	↓ 28.9	< 0.001 ***

* Paired samples t tests were used to assess within-group changes in WPAI scores before treatment and at SVR12. ** Mean percentage scores were calculated by averaging individual WPAI domain scores across each group. *** $p < 0.05$, statistically significant. **** A higher WPAI score indicates greater impairment in work or activity, whereas a lower score reflects improved functioning and less impairment. ***** Absolute change was calculated as the difference between the mean score before treatment and after 12 weeks: (before treatment mean − after treatment mean).

4. Discussion

This study examined three key aspects of hepatitis C in patients with or without cirrhosis. First, we assessed the cure rates after a 12-week antiviral therapy course. The results revealed that noncirrhotic patients had higher cure rates than did patients with cirrhosis. Second, the study evaluated PROs before and after treatment. Initial findings indicated that both groups experienced significant impairments in PROs, including lower HRQoL and decreased work productivity. However, treatment with DAAs resulted in substantial improvements in these areas, regardless of cirrhosis status. The standard regimen, which included SOF/DCV/RBV, played a major role in these improvements. Finally, the study compared the two groups. Cirrhotic patients had more severe impairments in HRQoL and work productivity at baseline. While both groups improved after treatment, noncirrhotic patients gained relatively greater benefits.

Our finding that outcomes are better in noncirrhotic patients is supported by research on hepatitis C virus-related hepatocellular carcinoma and indicates that the fibrosis patterns in noncirrhotic HCC patients differ on the basis of the underlying cause of

their liver disease. Furthermore, even patients with advanced hepatocellular carcinoma who do not have cirrhosis experience significantly longer survival than those with cirrhosis [31]. In a British study, the median survival of patients with cirrhotic hepatocellular carcinoma was 19.6 months, which was lower than the 24.5-month median survival for those with noncirrhotic HCC ($p = 0.05$) [32]. An American study indicated that HCV treatment significantly reduces the incidence of nonhepatic cancers among HCV-infected patients. These findings suggest that treating HCV can decrease the risk of extrahepatic cancers associated with chronic HCV infection, despite differences among specific cancer types or HCV therapy subgroups [33]. However, a study conducted at the University Hospital in Bern reported no significant differences in complication rates between patients with cirrhosis and those without cirrhosis [34].

The literature has shown differences in treatment outcomes between patients with genotype 2 and genotype 3 disease, indicating that those with genotype 3 disease typically require a longer course of therapy to achieve a sustained virologic response [35]. A randomized controlled trial revealed high sustained virologic response rates with SOF in patients with genotypes 2 and 3, who had no further treatment options after interferon-based therapy failed [36]. A previous investigation involving HCV-infected individuals examined the impact of cirrhosis and related complications on PROs during therapy with newly introduced anti-HCV treatments. The findings indicated that both cirrhotic and noncirrhotic patients were generally able to tolerate treatment regimens containing SOF and RBV, with or without pegylated interferon-alpha, as reflected by their PRO scores. Following an SVR12 via an interferon-free regimen, individuals with cirrhosis demonstrated improvements in certain dimensions of their PROs [25]. Another study utilized four different instruments to assess HRQoL and functional outcomes: HRQoL, including the Short SF-36, FACIT-F, CLDQ-HCV, and WPAI questionnaires. Compared with the placebo, the use of SOF and velpatasvir, either alone or in combination with voxilaprevir, has been shown to increase PRO scores. These results highlight the broad therapeutic advantages of these regimens, both during the course of treatment and following the achievement of SVR [29].

A randomized phase III study evaluated a 12- to 16-week treatment course featuring a combination of SOF, DCV, and RBV for patients with genotype 3 HCV and advanced liver disease. These results suggest that combination therapy is effective and generally well tolerated in genotype 3 patients, irrespective of their treatment history, whether treatment-naïve or previously treated [27]. A prospective observational study demonstrated the effectiveness of DAAs on the HRQoL of patients with chronic hepatitis C. HRQoL was assessed via the EQ-5D-3 L questionnaire at the beginning and again after 12 weeks of treatment. The findings revealed notable enhancements in mobility, pain management, anxiety levels, daily activities, and self-care [37]. A prospective cohort study reported that patients receiving interferon-free antiviral therapies show notable improvements in PROs. However, comorbid conditions such as diabetes mellitus, cirrhosis, and HIV coinfection tend to negatively influence HRQoL before, throughout, and following hepatitis C treatment [38]. Furthermore, incorporating RBV into treatment regimens may adversely impact HRQoL scores during therapy [39].

This study provides valuable insights by integrating both clinical outcomes and PROs to assess the effectiveness of DAAs among individuals with chronic hepatitis C, regardless of cirrhosis status, particularly in low-resource settings. The prospective design, use of validated tools (EQ-5D-3 L and WPAI), and real-world data from a high-volume tertiary care liver clinic increase the study's applicability and relevance. However, the study is limited by its single-center design, which may affect generalizability, and the relatively short follow-up period was restricted to 12 weeks posttreatment, which may

not capture longer-term PROs. Additionally, potential recall bias in self-reported data and the lack of genotype-specific analysis could influence the results.

5. Conclusions

This study revealed that chronic hepatitis C patients without cirrhosis who received SOF/DCV/RBV standardized treatment experienced significantly greater improvements in HRQoL and other PROs than did patients with cirrhosis, who showed smaller gains and less improvement in clinical outcomes. In both groups, improved PROs were accompanied by better work productivity and reduced activity impairment.

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