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RESEARCH ARTICLE **OPEN ACCESS**

Pharmacotherapeutic Assessment of Three Major Infectious Disorders in District Abbottabad and Haripur

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Abstract:

Objective: The current study was focused on the assessment of pharmacotherapeutic practices and potential drug-drug interactions among patients suffering from three major infectious disorders, including Typhoid fever, Pneumonia, and urinary tract infection (UTI).

Methodology: The data collection process included 300 patients (with 100 cases belonging to each disease) visiting DHQ Hospital, Haripur, and Jinnah International Hospital, Abbottabad. Comprehensive patient profiles, including disease prognosis, diagnosis, and therapeutic management, were carefully assessed for each patient, along with their comparison with standard therapeutic guidelines for identification of potential drug-associated risks. Analysis was performed based on sex-disaggregated comparison to critically evaluate the variability regarding disease prevalence, therapeutic management, and therapeutic outcomes among male and female patients.

Results: Typhoid fever, caused by *Salmonella Typhi* (most frequently transmitted *via* contaminated food or water), was found to be more prevalent in females (70%) than male candidates (30%), though the majority of the sample (80%) was based on the adult population. Most of the cases belonged to the Abbottabad region, and the widal/typhidot test was considered the major diagnostic test. Therapeutic management was mainly comprised of antibiotics together with analgesics/antipyretics, anti-ulcer drugs, antiemetics, electrolytes, and vitamins. Parenteral and oral routes of administration were frequently used for drug administration, with injections (38.1%), infusions (23.8%), and tablets (23.8%) being commonly prescribed.

UTIs, predominantly caused by *Escherichia coli*, were found to be more prevalent in females (70%) than males, together with a sampled population mainly comprised of adults (90%). Diagnostic tests involved analysis of urine samples, while treatment consisted of antibiotics, antispasmodics, analgesics, probiotics, and supplements. Treatment was mainly comprised of Tablets and injection dosage forms (32.35%).

Pneumonia, caused by *Pseudomonas aeruginosa*, was found to be equally prevalent in both male and female

candidates, and the sampled population was based on adults only. Furthermore, the majority of pneumonia patients (80%) belonged to the district of Abbottabad. Chest X-rays and sputum cultures were analyzed as the main diagnostic parameters, while the treatment regimen contained antibiotics, bronchodilators, analgesics, and steroids, respectively. The oral and parenteral routes of drug administration were most frequently used, with tablets (42.2%) and injections (31.82%) being the most frequently prescribed dosage forms. Statistical analysis indicated significant gender-based variation in the prevalence of typhoid fever/UTI among ($p < 0.05$), while no such variation was observed among the pneumonia patients.

Eight cases with minor drug-drug interactions have been observed, with no potential drug interactions.

Discussion: The current study was focused on the prevalence rate and pharmacotherapeutic management of patients with typhoid, Pneumonia, and UTI patients of the districts of Abbottabad and Haripur. Generally, highly efficacious and rationalized therapeutic protocols were followed among all the assessed cases, with no potential drug-drug interactions being observed during analysis.

Conclusion: Current pharmacotherapy assessment aligned well with the standard clinical guidelines, presenting efficacious therapeutic management and ultimately improved patient outcomes. Moreover, focused disorders, particularly UTIs, share multiple risk factors, including poor hygiene and sanitation, along with excessive environmental exposures.

Keywords: Pneumonia, Typhoid fever, UTIs, Medicine, Pharmacotherapeutic managemnt, Standard clinical guidelines, Prevalence rate, Drug-drug interactions.

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1. INTRODUCTION

An infectious communicable disorder refers to any particular illness capable of transmission from one individual to another, and initially propagated by a living organism or its viable byproducts. Current disorders are propagated through the invasion of a particular harmful microbe, particularly bacteria, fungi, parasites, and viruses, into the host body [1, 2]. Transmission typically occurs through contaminated food or water, insect bites, or direct human contact. The severity of infectious diseases may vary greatly, ranging from mild to life-threatening, and may also be transmitted *via* animals or insects [3, 4]. Common symptoms include fever and fatigue, though the symptoms vary greatly depending on the causative agent/pathogen being involved. Though some non-severe infections may be effectively managed at home using natural remedies, including proper rest and basic care tactics, disease severity may necessitate hospitalization [5, 6]. A wide range of infectious diseases, including measles, mumps, and chickenpox, may be effectively prevented through vaccination. In addition, regular and thorough hand washing remained one of the most effective protection measures against the numerous infectious illnesses [7-9].

Bacterial infections are more predominant than viral disorders like tuberculosis, throat infections, and UTIs, responsible for infecting approximately two billion people around the globe. Viruses, though tinier than bacteria, are also responsible for numerous infectious disorders [10].

Infectious diseases commonly spread through direct contact with an infected individual or animal. Transmission may occur *via* touching, kissing, coughing, sneezing, or exchange of bodily fluids during sexual contact [11, 12]. Carriers, though presenting no symptoms, may transmit the disease. Handling animal waste may sometimes present health risks, such as diseases, including toxoplasmosis, transmitted from animals to humans. Infectious agents may also be transmitted from a pregnant mother to her fetus *via* the placenta or breast milk [13, 14]. Additionally, bacteria residing in the vaginal canal may also be transmitted from animals to infants during childbirth [15-17].

Transmission occurs through multiple mechanisms, including ingestion of meals contaminated by insects, contact with contaminated surfaces, and exposure to pathogen-laden environmental vehicles [18]. Vectors also present a noticeable impact on the rate of disease transmission based on their mobility and the potential of microorganisms transfer among the hosts, leading to the establishment of a critical health concern [19, 20].

The indirect way of disease transmission involves contact with a contaminated surface, like doorknobs or tabletops. Similarly, fomites and insect vectors, including fleas, lice, mosquitoes, and ticks, also play a pivotal role in the disease transmission by acting as vectors, thereby facilitating the transmission of pathogens from one host to another, such as the malarial parasite, West Nile virus, and Lyme disease bacteria [21, 22]. Furthermore, contaminated food and water also serve as a usual means of disseminating pathogenic microorganisms, leading to disease transmission to multiple individuals [23], such as the presence of *E. coli* in undercooked or raw food materials, like ham burgers and unpasteurized juices [24].

Though infectious diseases may affect anyone, however, the individuals with compromised immune systems are more likely to be affected [25, 26], including individuals taking immunosuppressive medications like steroids or organ-rejection medicines, individuals suffering from HIV/AIDS or other immune-related disorders, particularly cancer. Malnutrition, aging, and the use of implantable medical devices might also act as an intervening factor in a few subjects [27, 28].

1.1. Typhoid Fever

Typhoid Fever, also described as an enteric fever, is a serious systemic disorder caused by *Salmonella Typhi*, primarily caused by the utilization of contaminated food or water, and also poses a serious public health concern, particularly in populations living in regions of poor sanitation and hygienic conditions [29, 30].

Typhoid fever is more prevalent in Africa, Latin America, Asia, India, Southeast Asia, South-Central, and Pakistan, although the disease presents the highest mortality and/or morbidity rates around the globe [31, 32]. Disease progression is particularly associated with ladder-type fever (slowly increasing over a few days), together with gastrointestinal symptoms, leading to serious complications, including intestinal perforation and/or bleeding if kept untreated [33, 34]. Commonly used diagnostic tests include analysis of blood, urine, or stool samples and/or serological investigations, such as the Widal test and the Typhidot [35].

Effective treatment relies particularly on antibiotics tailored to regional resistance patterns, including fluoroquinolones, cephalosporins, and macrolides, together with targeted therapeutics and preventive interventions. Preventive strategies are critical and focused on improved sanitation, quality of drinking water, food safety practices, and vaccination/immunization, particularly in individuals of high-risk localities/travelers [36-38]. The emergence of antibiotic-resistant strains highlights the ongoing need for robust public health strategies and international disease surveillance.

1.2. UTI

UTI is a bacterial infection most commonly caused by Gram-negative bacteria, notably *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis,* and affects any part of the urinary system. The most common symptoms typically include dysuria, urgency to urinate, burning sensation during urination, frequent urination, hematuria, pelvic pain, foul-smelling urine, and sometimes fever and chills in severe cases [39, 40]. In upper UTIs, fever, flank pain, nausea, and vomiting are common. Older adults may exhibit atypical symptoms such as confusion [41, 42]. UTIs are among the most common infections, particularly in women. Approximately 50–70% of women will experience at least one UTI in their lifetime, and up to 30% may develop recurrent infections [14, 43, 44]. Young, sexually active, and postmenopausal women are especially at risk of developing the infection [45, 46].

Diagnostic tools include Urine culture (gold standard), Blood tests, imaging, and cystoscopy for recurrent/complicated cases [44, 47]. Treatment includes antibiotics (Nitrofurantoin, Trimethoprim-sulfamethoxazole, Fosfomycin, cephalosporins, fluoroquinolones, ciprofloxacin) and pain killers (paracetamol or ibuprofen) [48, 49].

1.3. Pneumonia

Pneumonia is a potentially life-threatening disorder affecting either one lung or both lungs, leading to fluid or pus accumulation in the air sacs (alveoli). Its severity varies depending on its causative pathogen, age factor, and underlying health status. Globally, pneumonia ranks as the third leading cause of death and is the foremost fatal communicable disorder, responsible for over 3 million annual deaths [50]. It is particularly deadly among children under five years of age, particularly in developing countries, including Pakistan, where the incidence rate of acute respiratory infections (ARIs) is comparatively high [49]. Numerous types of pneumonia, including aspiration pneumonia, CAP (community-acquired pneumonia), HAP (Hospital-acquired pneumonia), and VAP (ventilator-associated pneumonia), and aspiration pneumonia have been reported [51]. Numerous pathogenic microorganisms are accountable for pneumonia, including bacteria (specifically *Streptococcus pneumoniae*), fungi, viruses such as influenza, and atypical microbes, including *Mycoplasma pneumoniae* [52, 53].

Infants, the aged people, smokers, and individuals with compromised immune systems, particularly corresponding to chronic illness history in the past, are considered to be the high-risk subjects.

Disease transmission particularly occurs from the inhalation of airborne droplets, interaction with the contaminated surfaces, and/or aspiration of elements into the lungs [52, 54]. Pathological penetration mainly corresponds to the disruption of the local immune system, including macrophage stimulation, cytokine release, and alveolar inflammation. Cough, fever, chest pain, and

dysnea are the most commonly reported symptoms; however, they sometimes lead to more severe complications, like altered mental status, cyanosis, and respiratory distress [4, 55]. Chest x-ray, CBC, and pulse oximetry are the most commonly employed diagnostic tools, whereas vaccination (*e.g.*, pneumococcal and influenza vaccines), amoxicillin, azithromycin, cephalosporins, and fluoroquinolones are based on antibiotic treatment, and preventive measures like smoking cessation and immune health maintenance, together with oxygen therapy, are the most frequently used tactics for pneumonia management. Chronic phases may result in severe complications, including bacteremia, pleural effusion, and respiratory failure with ultimate requirement for immediate clinical intervention and hospitalization [56-58]. Robust immunization patterns and improved patient care systems are the key factors responsible for reduced morbidity and mortality rates around the globe. Keeping in view the reported biological and sociocultural variations impacting disease susceptibility, progression, and therapeutic outcomes among individuals, the current study also focused on sex-disaggregated analysis following SAGER guidelines (Sex and Gender Equity in Research). Biological variability and gender dependent factors like hygienic conditions, occupational environment, and health-seeking behaviors greatly impact the disease progression and ultimate therapeutic outcomes; therefore, sex dependent evaluation of pharmaceutical assessment is necessary to enhance the individualized treatment tactics and related public health interventions.

2. METHODOLOGY

2.1. Materials and Methods

The current retrospective observational study evaluated 300 confirmed cases of typhoid, pneumonia, and urinary tract infections (UTI) at JIH and DHQ, Abbottabad, for a duration of 1 year, *i.e.*, from October 2023 to October 2024. Data was collected using appropriately designed case profile records of individuals admitted to the medical ward of the aforementioned hospitals. The data collection form was established and authenticated for any corrections after being analyzed by 3 experts (one physician and two pharmacists holding PHD in specific fields) with consequent data collection. The study pattern was adopted in accordance with the previously reported one, with minute modifications [59]. Biological classification of patients (*i.e.*, male/female patients) was recorded in the hospital together with consideration of gender associated determinants, including lifestyle, occupational practices, and hygienic conditions, which were considered during interpretation of the findings. Furthermore, male and female patients were separately analyzed to assess the gender-based variabilities and therapeutic outcomes. the data analysis.

2.2. Inclusion Criteria

The following inclusion criteria were used.

I. Clinical profile of medical ward patients with appropriate diagnoses of typhoid, pneumonia, or UTI.

II. Patients of any age group, including both male and female genders includes all treatment regimens, including all the prescribed drugs (both regular and on-demand) from admission till discharge, and any other supplements if prescribed.

III. All the patients included in the study were incorporated after signing written informed consent from the patients, together with the provision of the study protocols [60, 61].

2.3. Exclusion Criteria

The current study excluded individuals with incomplete case histories and patients with whom confirmation of not suffering from typhoid, pneumonia, or UTI after diagnosis. Furthermore, candidates who refused to participate at any stage of the study or those who died during data collection, diagnosis, or therapy process, or during their hospital stay were also excluded from the study [62, 63].

2.4. Sample Size and Data Collection

Data was collected from 375 patients, with 125 case histories for each disease state, *i.e.*, typhoid, pneumonia, and UTI. Among them, 75 case histories (20 case histories of typhoid, 30 case histories of pneumonia, and 25 UTI case histories) were excluded based on inadequate demographic information, incomplete diagnostic test reports/results, insufficient drug prescribed/previously used information, leaving 300 complete cases for study [64].

2.5. Case Analysis

The data was generated and analyzed from the selected cases for frequency, percentage distribution, and statistical analysis. The major analysis parameters encountered are included.

2.6. Data and Material Availability

All the data related to the study was collected manually on printed copies of the SOAP form and might be provided on demand.

I. Demographic Investigation including

- Age-based Distribution
- Gender-based Distribution
- Region-based Distribution

II. Clinical Investigation including

- Mode of patient's admission
- Mode of drug administration
- Prescribed Dosage Forms
- Number of drugs prescribed and therapeutic class of prescribed drug
- Drug interactions [65]

Pharmacotherapeutic analysis involved a mixed subjective objective assessment plan (SOAP) format used for data compilation and case assessment with respect to the aforementioned data variables. Subjective data was comprised of patient symptoms, observations, or other related information, whereas physical examinations

encompassed the primary source of objective information [66]. Objective information included diagnostic test results such as serum drug concentration, ultrasonography, echocardiogram, biochemical testing, *etc*. [63, 67]. The standard template was designed by a researcher after following the guidelines provided by the research supervisor to encompass both subjective (S) and objective (O) information for each (**Supplementary Material**).

2.7. SAGER Statement

The study adhered well to the SAGER guidelines. Sex-disaggregated data were analyzed and reported accordingly. Similarly, sex related biological variations were also considered during the study design, analysis, and interpretation. Gender-associated determinants were discussed where applicable.

3. RESULTS

3.1. Demographic Investigation

3.1.1. Age-based Distribution

The age-based distribution of patients with Typhoid fever indicated that patients were present in the age group of 1-50 years (Table **1**). Data analysis indicated 10 patients in the age group of 1-10 (10%) and 11-20 years (10%) respectively, along with 20 patients between 21-30 years (20%), 10 patients between 31- 40 years of age, and 50 patients in the age range of 41-50 years (50%) respectively.

Table 1. Distribution of typhoid fever, UTIs, and pneumonia patients in numerous age groups with observed frequency/percentage.

Age (years)	Frequency	Percentage	Disease
1-10	10	10%	Typhoid
11-20	10	10%	Typhoid
	10	10%	UTI
21-30	20	20%	Typhoid
	10	10%	Pneumonia
	10	10%	UTI
31-40	10	10%	Typhoid
	10	10%	Pneumonia
	20	20%	UTI
41-50	50	50%	Typhoid
	20	20%	Pneumonia
	20	20%	UTI
51-60	20	20%	Pneumonia
	10	10%	UTI
61-70	10	10%	Pneumonia
	10	10%	UTI
71-80	30	30%	Pneumonia
	20	20%	UTI

Similarly, the age-based classification of pneumonia patients presented patients existing between the age groups of 21-80 years. Data analysis presented 10 patients in the age group of 21-30 years (10%), 31-40years (10%), and 61-70 years (10%) respectively, together with 20 patients in the age range of 41-50 years and 51-60 years while 30 patients in age group of 71-80 years (30%) respectively (Table **1**).

Furthermore, UTI patients covered an age range of 10-80 years (Table **1**). Data analysis presented 10% patients in the age group of 11-20 years (10), 21-30 years (10), 51-60 years (10), 61-70 years (10), with 20% patients existing in the age range of 31-40 years, 41- 50 years (20), and 71-80 years respectively.

3.1.2. Gender-based Distribution

The gender-based distribution of typhoid fever and UTI patients presented a higher prevalence in females as compared to males (70% of females were affected in comparison to that of male patients, *i.e.*, 30%) (p<0.05). Recurrent UTIs were more commonly observed in female cases, consistent with anatomical predisposition. In contrast, pneumonia presents equal (or 50%) prevalence in both male and female subjects (Table **2**), though pneumonia was more prevalent in older patients with comorbidities; however, sex variation itself does not interfere with poor therapeutic outcomes.

Table 2. Gender wise distribution of patients of typhoid fever, UTIs, and pneumonia into male and female candidates' groups with perceived frequency/percentage.

Gender	Frequency	Percentage	Disease
Male	30	30%	Typhoid/UTI
	50	50%	Pneumonia
Female	7	70%	Typhoid/UTI
	50	50%	Pneumonia

3.1.3. Region-based Distribution

Regional distribution indicated that the majority of patients visiting Jinnah International Hospital and DHA belonged to Abbottabad and Haripur, with frequency rate significantly (p < 0.05) higher from Abbottabad in comparison with other regions, particularly Haripur (Table **3**).

Table 3. Region-based distribution of typhoid fever, UTIs, and pneumonia patients, together with frequency/percentage.

Area	Frequency	Percentage	Disease
Haripur	20	20%	Typhoid/UTI
	30		Pneumonia
Abbottabad	80	80%	Typhoid/UTI
	70		Pneumonia

4. CLINICAL INVESTIGATION

4.1. Mode of Patient Admission

Based on the mode of admission of patients within the hospitals, the patients were divided into two groups: Group 1, representing patients who visited the outpatient department (OPD), and Group 2, including patients admitted to the Emergency unit (Table **4**). Based on the mode of patient's admission in the aforementioned hospital units, the visit of UTI and pneumonia patients was superior in OPD as compared to emergency units, while the typhoid patient indicated an equal ratio of visits to both sections.

Table 4. Mode of admission-based division of typhoid fever, UTIs, and pneumonia patients in Group 1 and Group 2, respectively.

Mode of Patient Admission	Frequency	Percentage	Disease
Group 1 (OPD)	50	50%	Typhoid
	70	70%	UTI/Pneumonia
Group 2 (Emergency)	50	50%	Typhoid
	30	30%	UTI/Pneumonia

4.2. Mode of Drug Administration

According to the results of patients suffering from typhoid fever, about 61.9% patients were treated with the parenteral (injectable and infusion) route of drug administration, while 38.1% patients were treated with the oral route of drug administration, including 23.8% patients treated with tablets, 11.1% being treated with syrups, and 3.2% being treated using the capsule dosage form (Table **5**).

Accordingly, in the case of patients suffering from UTIs, about 50.3% were treated with the parenteral route of drug administration, including 32.35% patients being treated with injection and 17.95% being treated with infusion. Similarly, 48.52% of individuals were treated with the oral route of drug administration, including 32.35% patients being effectively managed using tablets, followed by 8.82% cases being treated using syrup, while 4.41% were treated with capsule dosage form, and 2.94% with sachets, respectively. In case of UTIs, about 1.47% cases were also prescribed topical dosage form, *i.e.*, creams (Table **5**).

Furthermore, in case of findings obtained from the results of pneumonia patients, approximately 54.54% patients were treated with oral dosage forms, including tablets (42.42%), syrups (9.09%), and capsules (3.03%), followed by 38.42% patients being treated with the parenteral route, including 31.82% injection and 6.06% infusion dosage form. Moreover, 7.58% pneumonia patients were also managed using the nasal route of drug administration, *i.e.*, Nebulizer (Table **5**).

4.3. Therapeutic Class of Drugs Prescribed

According to the findings, medication from numerous classes was prescribed for patients suffering from typhoid fever, including Antibiotics, Anti-malarial, Antiemetic, Analgesic/anti-pyretic drugs, proton pump inhibitors, and supplemental nutritional medicaments being administered *via* parenteral route (Table **6**).

Similarly, management of UTI also included medication from numerous classes depending upon the patient's signs/symptoms and included Antibiotics, Anti-malarial, Antispasmodics, Analgesic/anti-pyretic drugs, Antihypertensive, Laxatives, Protein pump inhibitors, and supplemental medications being administered *via* oral and parenteral route (Table **7**).

Table 5. Classification of typhoid fever, UTIs, and pneumonia patients based on route of drug administration.

Typhoid Fever			
Route	**Dosage Form**	**Frequency**	**Percentage**
Oral	Syrup	70	11.1%
	Tablet	150	23.8%
	Capsules	20	3.2%
Parenteral	Injection	240	38.1%
	Infusion	150	23.8%
UTIs			
Oral	Syrup	60	8.82%
	Tablet	220	32.35%
	Capsules	30	4.41%
	Sachet	20	2.94%
Parenteral	Injection	220	32.35%
	Infusion	120	17.95%
Topical	Creams	10	1.47%

(Table 5) contd.....

Typhoid Fever			
Route	**Dosage Form**	**Frequency**	**Percentage**
Pneumonia			
Oral	Syrup	60	9.09%
	Tablet	280	42.42%
	Capsules	20	3.03%
	Sachet	20	2.94%
Parenteral	Injection	210	31.82%
	Infusion	40	6.06%
Nasal	Nebulizer	50	7.58%

Table 6. Medications used for the treatment of patients suffering from typhoid fever.

Therapeutic Class	Brand (Generic) Name	Number of Cases
Antibiotics		
Cephalosporin Nitroimidizole Cephalosporin + β-lactam Macrolides Fluoroquinolone	Rocephin, Oxidil, Tefon (Ceftriaxone) Flagyl (metronidazole) Cebac (cefoperazone + sulbactam) Azomax (azithromycin) Novidate (ciprofloxacin)	80 50 10 20 10
Analgesics/Antipyretics		
Para-amino phenol derivatives	Panadol/Provas (Paracetamol)	70
Protein Pump Inhibitors		
Anti-secretory agents	Nexum (Esomeprazole) Risek (Omeprazole)	50 50
Anti-Malarial		
Artemisinin derivatives	Gen-M (Artemether + Lumefantrine)	20
Anti-Emetic		
5-HT3 Serotonin antagonist H1-Receptor antagonist D1 Receptor antagonist D2 Receptor antagonist	Onset (Ondensetron) Gravinate (Dimenhydrinate) Pelton (Domeperidone) Metomide (Metochlopramide)	60 40 20 10
Anti-Asthmatic		
Bronchodilator	Acefylline piperazine	20
Other		
Supplements	Normal saline (0.9% sodium chloride) Ringer lactate	50 40

Table 7. Medications that are utilized for the treatment of patients suffering from UTIs.

Therapeutic Class	Brand (Generic) Name	Number of Cases
Antibiotics		
Cephalosporin Nitroimidazole Cephalosporin + β-lactam Phosphonic acid antibiotic Fluoroquinolones	Oxidil (ceftriaxone) Flagyl (metronidazole) Cebac/2Sum/ Sulzone (Cefoperazone + Sulbactam) Fosin Ultra (Fosfomycin Trometamol) Ciprofloxacin	20 30 80 10 30
Analgesics/Antipyretics		
Para-amino phenol derivatives Opioid analgesic Analgesics and muscle relaxants	Provas (Paracetamol) Tramadol (Ketorolac+Tromethamine) Nuberol Forte (Paracetamol + Orphenadrine)	30 10 10
Proton Pump Inhibitors		
Anti-secretory agent	Ezium (Esomeprazole) Risek (Omeprazole)	70

(Table 7) contd.....

Therapeutic Class	Brand (Generic) Name	Number of Cases
Anti-Hypertensive		
Calcium channel blocker Angiotensin II receptor blocker β-blocker	Norvasc (Amlodipine) Eziday (Losartan) Zafnol (Atenolol)	10 10 10
Anti-Malarial		
Artemisinin derivatives	Gen-M (Artemether + Lumefantrine)	10
Anti-Spasmodic		
Tri-nitro benzene derivatives	Spadix (Phloroglucinol hydrate + Trimethylphloroglucinol)	10
Anti-Fibrinolytic Agents		
Plasmin inhibitor (synthetic lysine analogue)	Transamin (Tranexamic acid)	10
Anti-Convulsant		
Neuropathic pain	Gabica (Pregabalin)	10
Alkalizing Agents		
Urinary alkalizer	Citralka (disodium hydrogen citrate)	10
Laxatives		
Disaccharide lactose derivative	Lilac (lactulose)	10
Anti-Lipidemic Agents		
HMG-COA reductase inhibitors	Rosuvastatin (Rosuvastatin)	10
Other		
Supplements	Normal saline (0.9% sodium chloride) Ringer lactate Neurobion (cyanocobalamin)	70 10 10

Table 8. Medications that are prescribed for the management of pneumonia patients.

Therapeutic Class	Brand (Generic) Name	Number of Cases
Antibiotics		
Cephalosporin Penicillin + β-lactam Cephalosporin + β-lactam Macrolides Fluoroquinolone Fluoroquinolone	Oxidil, Clafron (Ceftriaxon) Augmentin (Amoxicillin and Clavulanic Acid) 2Sum (Cefoperazone + Sulbactam) Azitine, Azomax (Azithromycin) Moxiget (Moxifloxacin) Levofloxacin	40 10 10 30 20 10
Analgesics/Antipyretics		
Para-amino phenol derivatives Analgesic/anti-inflammatory	Panadol, Provas (Paracetamol) Digesic (Dextropropoxyphene)	60 10
Anti-Asthmatic		
Bronchodilator anticholinergic	Tiovair (Tiotropium) Atem (Ipratropium bromide)	50 50
Anti-Allergic		
Anti-histamine	Softin (Loratidine)	10
Proton Pump Inhibitors		
Anti-secretory agent	Risek, Lovenzo (Omeprazole)	40
Laxatives		
Disaccharide lactose derivative	Duphalac (Lactulose)	20
Anti-Thrombotic/Antiplatelet Agents		
ADP receptor blocker NSAIDs	Low-platelet (Clopidogrel) Loprin (Aspirin)	10 40
Leukotriene Modifiers		
Leukotriene receptor antagonist	Myteka (Montelukast)	30
Corticosteroids		
Anti-inflammatory	Dexa (Dexamethasone)	10
Oral Anti-Diabetics		
DPP4 inhibitors/biguanides	Inosita plus (Sitagliptin + Metformin)	10

(Table 8) contd.....

Therapeutic Class	Brand (Generic) Name	Number of Cases
Prostate/Urinary Bladder Muscle Relaxants		
Alpha-1 adrenergic antagonist	Tamsol-D (Tamsulosin)	10
Anti-Lipidemic Agents		
HMG-COA reductase inhibitors	Lipiget (Atorvastatin)	10
Others		
Supplement	Normal saline (0.9% sodium chloride) Ringer lactate	30 10

Table 9. Drug-drug interactions observed in medications prescribed for the treatment of typhoid fever, UTI, or pneumonia, together with their possible consequences and management.

Typhoid Fever		
Interactions	**Consequences**	**Management**
Ondansetron + Artemether/ Lumefantrine	Concomitant drug administration may prolong the QT interval, increasing the risk of life-threatening arrhythmias.	ECG monitoring is advised in patients at risk of QT prolongation. Use with caution, especially in patients with preexisting cardiac conditions or electrolyte imbalances
Omeprazole + Ciprofloxacin	Omeprazole may reduce the absorption of ciprofloxacin due to an increase in gastric fluid pH, with ultimate reduced absorption/ bioavailability of ciprofloxacin.	Space administration of omeprazole and ciprofloxacin by at least 2 hours. Consider monitoring for reduced effectiveness of ciprofloxacin
Metronidazole + Artemether/Lumefantrine	Metronidazole can increase the risk of QT prolongation when used with Artemether/Lumefantrine. Both drugs can also interact with the liver enzyme system, leading to potential toxicity.	Monitor ECG and avoid combining with other QT-prolonging drugs. If necessary, adjust dosages and ensure close monitoring of cardiac/hepatic functioning.
Azithromycin + Artemether /Lumefantrine	Concomitant drug administration may significantly prolong the QT interval, greatly increasing the risk of serious arrhythmias.	This combination should generally be avoided unless necessary. If co-administration is required, ensure ECG monitoring and consider electrolyte monitoring.
UTIs		
Interaction	**Consequences**	**Management**
Metronidazole + Artemether/Lumefantrine	Metronidazole can increase the risk of QT prolongation when used with artemether/Lumefantrine. Both drugs can also interact with the liver enzyme system, leading to potential toxicity.	Monitor ECG and avoid combining with other QT-prolonging drugs. If necessary, adjust dosages and ensure close monitoring of liver function
Pneumonia		
Interaction	**Consequences**	**Management**
Amoxicillin + Aspirin	Co-administration may increase the risk of gastrointestinal issues (*e.g.*, stomach irritation or bleeding).	If necessary, consider using a gastroprotective agent (*e.g.*, a proton pump inhibitor like omeprazole) to protect the stomach lining.
Diphenhydramine + Ipratropium bromide	Both are anticholinergic, so using them together may increase the risk of side effects like dry mouth, constipation, urinary retention, or confusion.	Use with caution, especially in elderly patients, and monitor for anticholinergic side effects.
Diphenhydramine + Tamsulosin	Diphenhydramine may worsen the orthostatic hypotension caused by tamsulosin, increasing the risk of dizziness or fainting.	Monitor blood pressure closely, especially when changing positions (sitting to standing). Consider alternatives to diphenhydramine for allergy relief if needed.
Dexamethasone + Levofloxacin	Both drugs can increase the risk of tendon rupture, especially in older adults or those using corticosteroids.	Use with caution. Patients were advised to report any tendon pain, swelling, or inflammation immediately and avoid excessive physical activity.

Likewise, the medications prescribed for the management of pneumonia included medications from different classes depending upon the patient's sign/symptoms, and included Antibiotics, Anti-asthmatic, Anti-allergic, Anti-spasmodics, Analgesic/anti-pyretic drugs, Corticosteroids, Leukotriene modifiers, Laxatives, Oral anti-diabetic drugs, Anti-platelet agent, Proton Pump Inhibitors, and supplemental medications being administered *via* oral and parenteral route (Table **8**).

4.4. Drug Interactions

Concomitant administration of numerous medications indicated minor to moderate level interactions encountered among medications of numerous therapeutic classes, including co-administration of a) Ondansetron, Azithromycin, and Metronidazole with Artemether/ Lumefantrine, b) Omeprazole with Ciprofloxacin, Amoxicillin with Aspirin, Diphenhydramine with Ipratropium bromide, Diphenhydramine with Tamsulosin, and Dexamethasone with Levofloxacin, respectively (Table **9**). Upon

therapeutic analysis of the included cases' profiles suffering from Typhoid fever, UTI, or pneumonia, the interactions noticed along with their possible consequences and management have been shown in Table **9**. It has been observed that all the interactions were easily manageable except the concomitant administration of Antimalarial drug (Artemether/Lumefantrine) with other medications (antiemetic and antimicrobial/antibiotics), creating serious complications, particularly for patients suffering from cardiac complications. In such cases, critical monitoring of patients *via* daily ECG record maintenance was strictly recommended, as shown in Table **9**.

4.5. Treatment Outcomes by Disease Group

Almost all the patients suffering from the aforementioned infectious disorders (Typhoid fever, Pneumonia, and UTIs) indicated a positive response towards the provided therapeutic regimen, except for few cases such as 4% individuals suffering from typhoid fever (Case: 25, 37, 61 and 93) indicated no remarkable improvement in their symptomatic conditions upon the given treatment protocols based on which they were suggested subsequent diagnostic tests including diagnostic evaluation for malaria and dengue fever. No mortality cases associated with the current disorder were reported upon analysis. Similarly, for pneumonia patients, approximately 7% individuals presented a weak response to the therapeutic regimen, particularly cases 11, 13, 41, 62, 67, 83, and 95, respectively. Most of these candidates belonged to the age group of 61 to 90 years. Most of the patients who indicated a weak therapeutic case response to the given medications were considered to be associated with age-related immunocompromised conditions, altered pharmacokinetics and renal/hepatic functioning, together with patients suffering from multiple comorbidities such as diabetes mellitus, COPD/Asthma, chronic renal dysfunction, and patients indicating complicated pneumonia associated with pleural effusion, lungs abscess and empyema, respectively. Some of these patients were referred to Ayub Teaching Hospital, Abbottabad, while others were suggested further diagnostic procedures. Furthermore, all the patients suffering from UTIs presented a positive response to the therapeutic regimen, except for 5% individuals (Case 31, 55, 79, 88, 98), representing recurrent/complicated UTIs for which the prescribed therapeutic regimen was changed and also suggested follow up visit following 1 week of therapy, based on consideration that a weak therapeutic response might be associated with antibiotic resistance.

4.6. Complications and Mortality Rates

All those patients who died during the treatment procedure or at any stage in the hospital were excluded from the study. Furthermore, no cases were observed to develop life-threatening complications as the majority of patients responded well to the recommended therapy protocols. Though non-improvement cases were not observed, prolonged recovery times were particularly associated with smokers upon comparison with non-smokers (particularly in pneumonia patients), and a slower therapeutic response was observed in patients associated with patients suffering from comorbidities among patients of all three infectious diseases.

4.7. Risk Factors and Comorbidities

Certain cases among all the disease groups included in the current study were associated with certain comorbidities, particularly diabetes mellitus, hypertension, COPD, Asthma, weakened immune system, anemia, obesity, *etc*.

The patients of Typhoid fever (29%) indicated the following comorbidities: diabetes mellitus (11%), malnutrition (particularly observed cases with age groups of 1-10 and 40-50 years), immunocompromised conditions (7%), gastrointestinal complications (4%), together with some cases presenting poor hygienic conditions (2%), together with utilization of unsafe food/water (2%) and smoking abuse (3%) (Table **10**). Similarly, the pneumonia patients (24%) also presented certain comorbidities, like age-related immunocompromised conditions (3%), altered pharmacokinetics, renal or hepatic malfunctioning (3%), diabetes mellitus (4%), COPD/Asthma (4%), Anemia (1%), gastrointestinal reflux disease (GERD) (1%), obesity (3%), and symptoms of complicated pneumonia such as pleural effusion, lung abscess, and empyema (5%), particularly associated with previous or current smoking history. Furthermore, in the case of UTI patients (18%), the following comorbidities have been observed: Diabetes mellitus (3%), hypertension (6%), dehydration (2%), urine burning (1%), incomplete bladder emptying, urinary retention, and recurrent UTIs (6%).

5. PHARMACOTHERAPEUTIC MANAGEMENT AND ROLE OF CLINICAL PHARMACISTS

Clinical pharmacists, as core members of the healthcare team, played a pivotal role in the management of Typhoid fever, pneumonia, and UTIs to ensure the safe, efficacious, and evidence-based utilization of medications. Health care professionals, *i.e.*, a pharmacist, played a pivotal role leading to the occurrence of minimal complications, particularly related to current infections *via* proper medication review, management of antimicrobial resistance occurrence, effective patient education & counselling; factors directly impacting therapeutic outcomes. In the current study, pharmacists contributed to the evaluation of the prescribed antibiotic regimen to ensure their alignment with standard therapeutic protocols defined by the WHO and hospital policies. The selection of an appropriate antibiotic corresponding to the patient's age, disease etiology, severity of illness, resistance pattern, and presence of comorbidities was carefully observed for the patients. Clinical pharmacist also inspected dose accuracy, therapeutic duplication, practice of polypharmacy, and dose adjustment in case of renal or hepatic impairment to prevent adverse drug reactions and therapeutic failure.

Table 10. Common co-comorbidities observed in patients of typhoid fever, pneumonia and UTI along with associated risk factors and common contributing factors.

Targeted Disease	Patients presenting Comorbidities (%)	Associated Comorbidity/ Risk Factor	Percentage (%)	Remarks
Typhoid Fever	29%	DM	11%	Most frequently observed among typhoid patients in age group of 35-55 years
		Malnutrition	Unspecified	Most frequently observed among typhoid patients in age group of 1–10 and 40–50 years
		Immunocompromised Conditions	7%	Augmented susceptibility to infectious disorders
		Gastrointestinal Complications	4%	Associated GI disturbances
		Poor Hygienic Conditions	2%	Contributing environmental factor
		Unhygienic Food and Water Utilization	2%	Major Risk factor for disease transmission
		Smoking Abuse	3%	Associated lifestyle modulations
Pneumonia	24%	Age-associated Immunocompromised Conditions	3%	Mostly frequently observed in elderly patients
	24%	Altered Pharmacokinetic, Renal or Hepatic Functioning	3%	Complicated therapeutic outcomes
	24%	Diabetes Mellitus	4%	Common metabolic disorders
	24%	COPD/Asthma	4%	Respiratory comorbidity
	24%	Anemia	1%	Reduced oxygen-carrying capacity
	24%	GERD	1%	Gastrointestinal association
	24%	Obesity	3%	Increased complication risk
	24%	Complicated Pneumonia (Pleural Effusion, Lung Abscess, Empyema)	5%	Most frequently observed in cases with smoking history
UTIs	18%	DM	3%	Predisposing factor
	18%	Hypertension	6%	Most frequently observed in patients with age group of 35-45 years
	18%	Dehydration	2%	One of the contributing factors particularly in patients with age group of 1-20 years
	18%	Urine Burning	1%	Observed in patients of all age groups
	18%	Incomplete Bladder Emptying, Urinary Retention and Recurrent UTIs	6%	Recurrent urinary complications

The most pivotal role of a pharmacist in the current situation was the careful monitoring of adverse drug reactions, such as focus on combinatorial utilization of antibiotics, PPIs, analgesic/antipyretics, bronchodilators, or antispasmodics, though no potential drug interactions were observed during the management of current disorders. The pharmacist also played a vital role in the antibiotic stewardship program corresponding to monitoring of antibiotic utilization duration, discontinuation duration, and shift over from parenteral to oral route of administration when it seemed suitable. All these efforts help to reduce antimicrobial resistance, rationalize therapeutic efficacy, and improve resource utilization available in hospitals. Patient-oriented services being provided by the clinical pharmacist include medication adherence, supportive treatments, hydration/ hygiene practices, and counseling upon recognition of any alarming signs/symptoms requiring medical attention, as it ultimately leads to therapeutic non-compliance or risk of infection recurrence, particularly in pneumonia and UTIs.

Overall, the effectual contribution of clinical pharmacists enhanced the pharmacotherapeutic quality and safety, leading to the appropriate selection of individually safe and effective therapeutic regimens consistent with standardized clinical protocols.

6. DISCUSSION

According to the results of the typhoid fever, women are more commonly affected than men; that might result from numerous intervening factors, including increased exposure of working women to contaminated water or food sources, together with unhygienic food-keeping conditions in home settings, where women are typically in charge of cooking and cleaning [68]. During cooking and cleaning, women are more likely to come in contact with contaminated objects or environments frequently, which also raises their risk of contracting the illness [69].

Accordingly, Adults account for a higher prevalence as compared to children, accounting for 20% prevalence, which might be due to engagement of adults in different activities, including working outside the home, traveling, buying food from street vendors, and most probably being exposed to contaminated environmental sources [70].

The majority of the patient population that visited JIH and DHQ belonged to Abbottabad, with about 20% population from Haripur. Easy access of local people to nearby hospitals, together with variations in population density, access to clean water, and sanitation infra-structure, might be the cause of these differences [71]. Haripur is a comparatively smaller locality with less population and fewer cases of waterborne disorders

(including Typhoid Fever), based on lower transmission rates in contrast to Abbottabad, which is a larger city with denser inhabitants, with probably a higher potential for these diseases to spread [68].

The lack of significant drug-drug interactions indicated that caution was exercised while prescribing the medication for patients with typhoid fever [69, 72]. Any interactions observed were of a mild or moderate type, suggesting strict attachment to conserved prescription guidelines.

According to the results of UTI, a higher prevalence was noticed in females in comparison to males (30%) [73]. Higher incidence of UTI in females might be attributed to anatomical differences, including shorter urethras, facilitating easier bacterial migration to the bladder with consequent infections. Similarly, hormonal fluctuations influencing urogenital flora might also increase the risk of UTIs in women, especially during pregnancy and menopause [73, 74]. Furthermore, their socio-cultural role, including domestic responsibilities and hygiene-related factors, greatly contributes to their exposure to the infectious organisms, particularly typhoid fever.

While only 10% UTI patients belonged to the younger age, with the bulk of patients (90%) belonging to adulthood might correspond to their involvement in sexual activity and the use of certain contraceptives like diaphragms, making adults more susceptible to UTIs. Furthermore, menopause, weakened immune systems, and other chronic conditions might also contribute to compromising UTIs, making the older population, particularly females, more susceptible [74]. From a regional point of view, the higher patient population belonged to Abbottabad, which might be due to the availability of extensive healthcare facilities in Abbottabad, together with variations in hygienic infrastructure and availability of clean water, may indirectly affect the prevalence of illnesses like UTIs [75]. Further, Abbottabad's urban environment may possibly provoke a higher transmission rate.

Additionally, no significant gender based variation in the incidence and/or transmission of pneumonia has been noticed in both sexes, which might be attributed to lifestyle and environmental factors, including exposure to atmospheric pollutants, bacterial or viral contact, and smoking [76].

Pneumonia was mainly diagnosed in adults rather than children, which might correlate with weaker immune systems caused by smoking and chronic conditions, including diabetes mellitus, cardiovascular disease, and prolonged pulmonary disorders [77, 78]. Adults might also be more susceptible to pneumonia based on augmented exposure to hazardous components or environmental toxins commonly associated with respiratory illnesses [78, 79].

Higher prevalence rate of pneumonia in Abbottabad might correspond to numerous interconnected demographic and environmental factors, including its location acting as a central healthcare hub for adjoining rural and semi-urban regions, providing a little bit better access to different healthcare facilities, drawing patients from surrounding districts to seek healthcare facilities from Abbottabad with respect to less resourceful areas.

Additionally, a denser population, particularly residing in congested residential settings, further increases the likelihood of respiratory infection. Similarly, exposure to air pollutants like vehicle emissions, smoke generated from domestic heating resources, and industrial pollution may also exacerbate respiratory health conditions, with higher susceptibility to pneumonia, particularly among vulnerable groups, including children, the elderly, and individuals presenting pre-existing lung disorders. Further, weather conditions of Abbottabad, particularly in the winter season, also contribute well to the progression of common cold and flu that, if left untreated, may result in respiratory malfunction [78, 79]. Prescribing patterns most frequently focused on parenteral preparations, including injection/infusion, and oral dosage forms like tablets, capsules, and syrups, respectively [80]. Emergency treatment was dependent upon parenteral preparations for providing immediate symptomatic relief, while oral dosage forms cover subsequent therapy for preventing severe drug administration-related adverse effects, particularly arising from IV preparations [79-81].

Current disorders are analyzed critically, illuminating their occurrences and the pharmacotherapeutic approach employed for their management, particularly in the districts of Abbottabad and Haripur. Therapeutic management of typhoid fever, pneumonia, and UTIs was mainly dependent upon the utilization of the appropriate medications, with minimal chances of potential drug-drug interactions. The treatment method frequently preferred the oral route of drug administration, though injections and infusion were also employed for efficacious management of severe signs/symptoms being perceived by patients, particularly during an initial hospital visit (stay). Although a therapeutic regimen presented quite consistent results during observation among patients of different sexes, gender-based pharmacotherapeutic variabilities, like variation in body fat composition, renal clearance rate, and hormonal variations, greatly affect the drug metabolism, particularly of antibiotics and ADRs. Hence, further investigation regarding sex associated pharmacokinetic and pharmacodynamic assessment is needed.

Geographic and demographic analysis indicated the need for public health interventions, particularly for the adult population encompassing both males and females. The observations of prolonged treatment time and slower therapeutic response, particularly associated with smoking and comorbidities, suggested the importance of an integrated management system including both physicians, doctors, and pharmacists capable of earlier risk determination, particularly in hospitals exhibiting limited diagnostic and monitoring systems.

7. LIMITATIONS

Despite the valuable insights provided by the current pharmacotherapeutic assessment of three major infectious

disorders, certain limitations of the study included a retrospective analysis, including the data extracted from hospital records of case profiles that might be associated with poor documentation quality, potential recall errors, and incomplete diagnostic or therapeutic profiles. Though 300 profiles have been observed, some intervening factors, such as socioeconomic and nutritional factors, and previous utilization or adherence to antimicrobials, have not been accurately covered. Secondly, the data was collected from two hospitals only, including JIH (Abbottabad) and DHQ hospital (Haripur), which may not represent the entire regional population, leading to potential bias due to differences in demographic and clinical outcomes of the patients belonging to regional or rural health care centers. The selection of broader and more diverse health care settings might enhance generalizability.

Similarly, the micro-organism's susceptibility and resistance pattern towards the selected antimicrobial medicaments were not evaluated in the current study, which might be correlated to check the pathogen-specific therapeutic efficacy of antimicrobial drugs. The study could be more from inclusion of microbial cultures and antibiograms to effectively check the therapeutic efficacy of prescribed antibiotics, particularly against the resistant bacterial strains *(*such as *S. Typhi, E. coli, and S. Pneumoniae).*

Though sex disaggregated prevalence was included, particularly sex specific therapeutic variabilities were not assessed in detail. Similarly, gender associated socio-cultural determinants were not measured quantitatively, limiting their impact on risk of disease occurrence, progression, and therapeutic outcome.

Furthermore, the study only covered Drug-Drug interactions, while not quantifying the pharmacokinetic variations among cases of variable age groups or patients with comorbidities leading to variable therapeutic responses, particularly among the geriatric and mal-nourished population. Extending the studies using multivariable regression analysis in future studies would be beneficial to draw inferences among patients and possible therapeutic outcomes. At the end, long-term follow-up analysis has not been tracked to check relapse rates and a clear picture of therapeutics effectiveness and possible resistance occurrence. Thus, an integrated pharmacovigilance system and electronic medical record-based monitoring will ultimately result in real-world treatment effectiveness.

CONCLUSION

Typhoid, pneumonia, and urinary tract infections (UTIs) share multiple risk factors, including poor sanitation, inadequate hygiene, and environmental exposures. Typhoid is more prevalent in densely populated areas and disproportionately affects females due to domestic exposure to unhygienic conditions. Pneumonia impacts both sexes, with risk amplified by pollution, cold exposure, and compromised immunity, especially in adults. UTIs are more common in women due to anatomical predispositions, worsened by poor hydration and hygiene.

Understanding disease epidemiology and therapeutic management based on the inclusion of sex-disaggregated investigation was performed, which might be extended to sex-related pharmacokinetic/pharmacodynamic evaluation in the future, with the corresponding development of individualized therapeutics, particularly for gender sensitive public health interventions.

Prevention through addressing these risk factors is essential to reduce disease incidence and severity. These infections can lead to severe complications, particularly in immunocompromised and elderly individuals, emphasizing the need for proper care and adherence to treatment protocols. The study indicates effective antibiotic use without significant drug-drug interactions. Continuous monitoring, appropriate antibiotic selection (oral or injectable), and individualized treatment plans are vital for optimal outcomes. Pharmacists and other healthcare professionals play a critical role in ensuring therapeutic safety, efficacy, and compliance, thereby improving patient recovery and minimizing adverse effects.

AUTHORS' CONTRIBUTIONS

The authors confirm contribution to the paper as follows: N.A. and S.B.: Study conception and design; S.Q. and M.: Analysis and interpretation of results; N.M. and M.I.S.: Data collection; U.S. and A.S.: Draft manuscript; M.A. and R.A.: Methodology. All authors reviewed the results and approved the final version of the manuscript.

LIST OF ABBREVIATIONS

AIDS	=	Acquired Immunodeficiency Syndrome
ARIs	=	Acute Respiratory Infections
CAP	=	Community Acquired Pneumonia
ECG	=	Electrocardiograph
GERD	=	Gastroesophageal Reflux Disease
OPD	=	Out-Patient Department
PPI	=	Proton Pump Inhibitors
SOAP	=	Subjective Objective Assessment Plan
WHO	=	World Health Organization

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the ethical committee of the Department of Pharmacy, The University of Lahore, Sargodha Campus, Pakistan (REF: Pharm/ETH/2024-038).

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

All the patients included in the study were incorporated after signing written informed consent from the patients, together with the provision of the study protocols.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available from the corresponding author [A.S] upon reasonable request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the Publisher's website.

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