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ANTIBIOTIC RESISTANCE PATTERNS OF SALMONELLA SPECIES AND SHIFTS IN EMPIRICAL TREATMENT: A STUDY FROM AYUB TEACHING HOSPITAL ABBOTTABAD, KPK, PAKISTAN

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Abstract

Background: Typhoid fever remains a critical public health issue in many developing countries, particularly due to the rise of antibiotic-resistant strains, which are aggravated by the frequent and often inappropriate use of antibiotics. This study evaluates the antibiogram patterns of *Salmonella* species isolated from blood cultures of patients admitted to a tertiary care hospital in Abbottabad, Khyber Pakhtunkhwa, Pakistan. The aim is to analyze current resistance trends and provide updated insights into antimicrobial susceptibility, thereby contributing to improved management strategies for typhoid fever in this region.

Materials and Methods: This retrospective cross-sectional study was conducted using data from a tertiary care government hospital in Abbottabad, Khyber Pakhtunkhwa, Pakistan. Patients diagnosed with enteric fever were identified based on positive blood cultures for *Salmonella* species. The study included a comprehensive analysis of 1,250 cases recorded between January 2022 and July 2023. Data collected included patient demographics, seasonal distribution, and detailed antibiotic susceptibility profiles of the isolated *Salmonella* strains.

Results: Out of the total 1,250 cases, males made up the majority, accounting for 62% (775 cases). A significant proportion of the cases were clustered among children and young adults aged between 8 and 28 years. The highest incidence was observed during the spring and summer months,

particularly from April to September. In terms of *Salmonella Typhi* isolates, notable resistancewas detected against first-line antibiotics, including amoxicillin/clavulanate (77.8%), co-trimoxazole/trimethoprim-sulfamethoxazole (63.4%), and chloramphenicol (83.5%). Resistance to ceftriaxone and ciprofloxacin was also significant, at 76.9% and 48.9%, respectively.
However, certain antibiotics demonstrated strong sensitivity profiles, with meropenem (98.1%), doripenem (99.0%), imipenem (96.9%), ertapenem (95.8%), polymyxin B (98.7%), colistin (97.5%), and tigecycline (96.8%) showing high effectiveness. The sensitivity rates for amikacin and gentamicin were 88.9% and 79.6%, respectively. Azithromycin, on the other hand, showed a concerning sensitivity rate of 64.3%. The antibiogram of *Salmonella* demonstrated marked shifts in resistance patterns, raising concerns about evolving therapeutic challenges.
Conclusion: This study highlights a higher incidence of typhoid fever among males, with a pronounced seasonal peak occurring during the spring and summer months. The most affected age group was between 8 and 28 years. The *Salmonella* isolates demonstrated substantial resistance to conventional first-line antibiotics, as well as to ciprofloxacin and third-generation cephalosporins. Additionally, azithromycin showed reduced sensitivity when compared to amikacin, gentamicin, and meropenem. Based on these findings, the study suggests that empirical treatment for typhoid fever in this region should prioritize the use of amikacin, gentamicin, and meropenem. The research emphasizes the need for regular monitoring of *Salmonella* resistance patterns, improved antibiotic stewardship, public health campaigns for awareness, and the implementation of vaccination programs to enhance prevention strategies.

Keywords: Antibiotic Resistance Patterns, Salmonella Species, Empirical Treatment

Introduction

Salmonella Typhi (S. Typhi), responsible for typhoid fever, and *Salmonella Paratyphi* (S. Paratyphi), which causes paratyphoid fever, are the pathogens behind enteric fever, an infection affecting the intestinal tract. Patients typically present with symptoms such as fever, malaise, constipation, and abdominal pain. Globally, there are approximately 21.6 million cases of typhoid fever and 5.4 million cases of paratyphoid fever annually, leading to around 250,000 deaths. Asia bears the burden of about 80% of these cases and fatalities. If left untreated, typhoid fever can result in significant morbidity and mortality, with an estimated fatality rate of 30% without proper treatment[1].

In Pakistan, enteric fever poses a serious public health challenge. Studies from Karachi have shown that children experience an annual incidence rate of 451 per 100,000 for *S. Typhi* and 76 per 100,000 for *S. Paratyphi*. One of the most serious complications of typhoid fever is intestinal perforation[2]. Other severe manifestations can include pneumonia, meningitis, endocarditis, osteomyelitis, and arthritis. The multi-organ involvement often leads to diagnostic challenges, making timely and accurate diagnosis essential. Blood culture remains the gold standard for confirming a typhoid fever diagnosis[3]. Historically, first-line antibiotics such as co-trimoxazole, ampicillin, and chloramphenicol were widely used to treat enteric fever. However, since the late 1980s, multidrug-resistant (MDR) *Salmonella* strains—resistant to all first-line antibiotics[4]—have been identified. For MDR typhoid strains susceptible to quinolones, fluoroquinolones were recommended by the World Health Organization (WHO) in 2003. However, overuse of fluoroquinolones has led to the emergence of nalidixic acid-resistant *Salmonella* strains, which exhibit reduced susceptibility to fluoroquinolones[5]. This trend has been observed in countries such as Nepal, with over 60% of typhoid fever isolates in cities like Kolkata and Karachi showing resistance to nalidixic acid[6]. In response, the use of third-generation cephalosporins has increased. However, cases of cephalosporin-resistant *Salmonella* strains have been reported in India and Nepal, and Pakistan saw a widespread outbreak of extensively drug-resistant (XDR) *S. Typhi* between 2016 and 2017[7]. The growing resistance to commonly used antibiotics, along with rising treatment costs and limited therapeutic options, is a major concern.
As drug-resistant strains continue to emerge, the use of first-line antibiotics has decreased, with these

drugs now seldom employed for treating enteric fever. Interestingly, recent reports from India and Nepal have indicated the re-emergence of *Salmonella* strains that are susceptible to first-line antibiotics. This highlights the importance of ongoing antibiogram surveillance in guiding empirical treatment decisions.[8]

The present study aims to assess the antibiogram profile of *Salmonella* species isolated from blood cultures of patients at Ayub Teaching Hospital (ATH), a 1,650-bed tertiary care hospital in Abbottabad, Khyber Pakhtunkhwa, Pakistan. By evaluating current resistance patterns, this study seeks to recommend appropriate empirical antibiotic treatments for enteric fever, in light of evolving resistance trends and shifting antibiograms.

Materials & Methods

This retrospective cross-sectional study was conducted from January 2022 to July 2023 at a tertiary care hospital in Abbottabad, Khyber Pakhtunkhwa, Pakistan. The primary objective was to evaluate the antibiogram profiles of *Salmonella* species isolated from the blood cultures of patients diagnosed with enteric fever. A non-probability consecutive sampling method was used, including a total of 1,250 positive blood cultures from patients ranging in age from 1 to 80 years.Demographic data, seasonal prevalence patterns, and antibiotic resistance profiles were collected and analyzed. The antibiotic susceptibility testing was conducted using WHONET and BACLINK (version 2023), in accordance with World Health Organization guidelines. The antibiotics assessed included ampicillin, amoxicillin/clavulanic acid, piperacillin/tazobactam, cefoperazone, ceftazidime, ceftriaxone, cefotaxime, cefepime, cefixime, aztreonam, doripenem, ertapenem, imipenem, meropenem, amikacin, gentamicin, ciprofloxacin, levofloxacin, moxifloxacin, co-trimoxazole (trimethoprim-sulfamethoxazole), colistin, polymyxin B, azithromycin, chloramphenicol, and tigecycline.Multidrug-resistant (MDR) strains were defined as those resistant to first-line antibiotics, including co-trimoxazole, chloramphenicol, and amoxicillin. Extensively drug-resistant (XDR) strains were identified as those resistant not only to these first-line antibiotics but also to fluoroquinolones, such as ciprofloxacin, and third- generation cephalosporins, such as ceftriaxone.One of the key limitations of this study was the inability to differentiate between specific *Salmonella* strains, as the hospital records only indicated the presence of *Salmonella* species without further strain identification. Ethical approval for this research was obtained from the hospital's Ethical Review Board (ERB).

This study's comprehensive methodology enabled a thorough investigation of *Salmonella* antibiogram profiles, providing critical insights into resistance patterns and helping to inform the treatment strategies for enteric fever in the region.

Results

In this study, we examined a total of 1,250 patients, consisting of 475 (38%) females and 775 (62%) males, as illustrated in Figure 1.

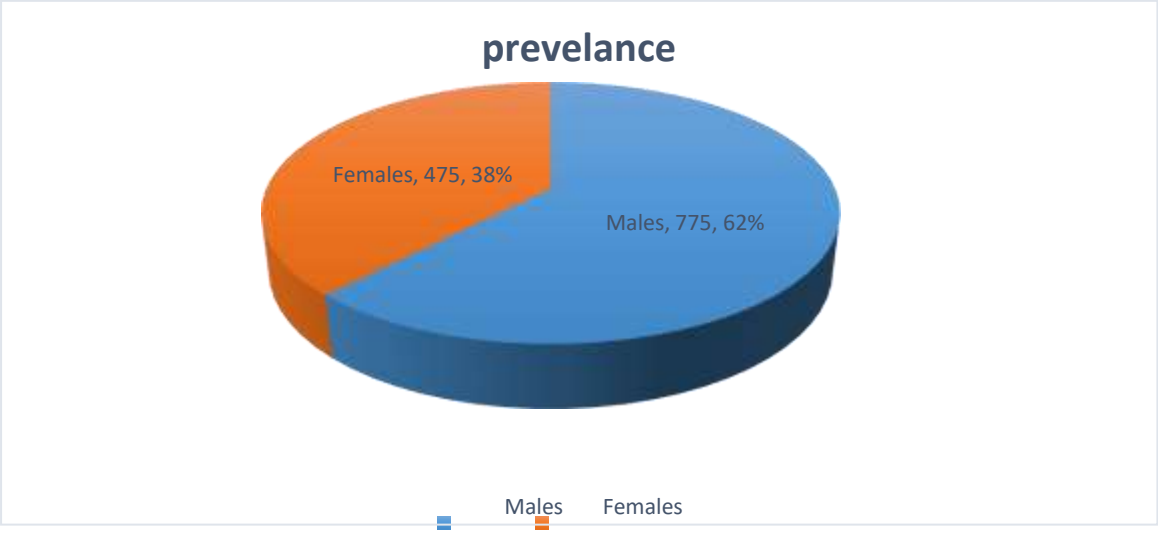

FIGURE 1: Gender-wise prevalence of typhoid fever

TABLE 2: Monthly base prevalence of typhoid fever

Month	Percentage (%)	Number of Cases (out of 1250)
January	5.30	66
February	7.80	98
March	8.60	108
April	13.20	165
May	17.10	214
June	13.60	170
July	10.70	134
August	5.40	68
September	4.80	60
October	4.40	55
November	4.80	60
December	4.40	55

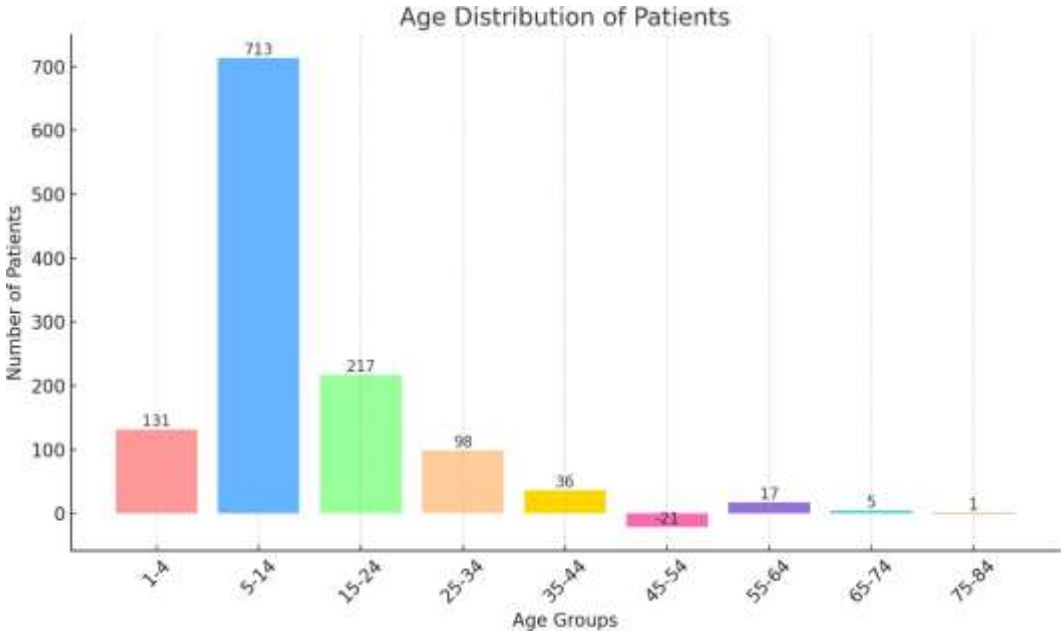

FIGURE 2: Age-wise prevalence. The highest prevalence seen was inage group 5-14 years age group (57.10%)

TABLE 3: Antibiogram of Salmonella species

Antibiotic	Number of Cases Tested	% Sensitive	Number of Cases Sensitive	% Resistant	Number of Cases Resistant
Amoxicillin/Clavulanate	1250	22.2%	278	77.8%	972
Co-trimoxazole	1250	36.6%	458	63.4%	792
Chloramphenicol	1250	16.5%	206	83.5%	1044
Ceftriaxone	1250	23.1%	289	76.9%	961
Ciprofloxacin	1250	51.1%	639	48.9%	611
Meropenem	1250	99.1%	1239	0.9%	11
Doripenem	1250	99.6%	1245	0.4%	5
Imipenem	1250	96.9%	1211	3.1%	39
Ertapenem	1250	95.8%	1197	4.2%	53
Polymyxin B	1250	98.7%	1234	1.3%	16
Colistin	1250	97.5%	1219	2.5%	31
Tigecycline	1250	96.8%	1210	3.2%	40
Amikacin	1250	88.9%	1111	11.1%	139
Gentamicin	1250	79.6%	995	20.4%	255
Azithromycin	1250	64.3%	804	35.7%	446

FIGURE 4: Salmonella antibiogram susceptibility pattern

AMP: Ampicillin, AMC: Amoxicillin/Clavulanic acid, TZP: Piperacillin/tazobactum, CFP: Cefoperazone, CAZ: Ceftazidime, CRO: Ceftriaxone, CTX: Cefotaxime, FEP: Cefepime, CFM: Cefixime, ATM: Aztreonam, DOR: Doripenem, ETP: Ertapenem, IPM: Imipenem, MEM: Meropenem, AMK: Amikacin, GEN: Gentamicin, CIP: Ciprofloxacin, LVX: Levofloxacin, MFX:

Moxifloxacin, SXT: Trimeth0prim/sulfamethoxazole, , COL: Colistin, POL: Polymyxin B, AZM: Azithromycin, CHL: Chloramphenicol, TGC: Tigecycline.

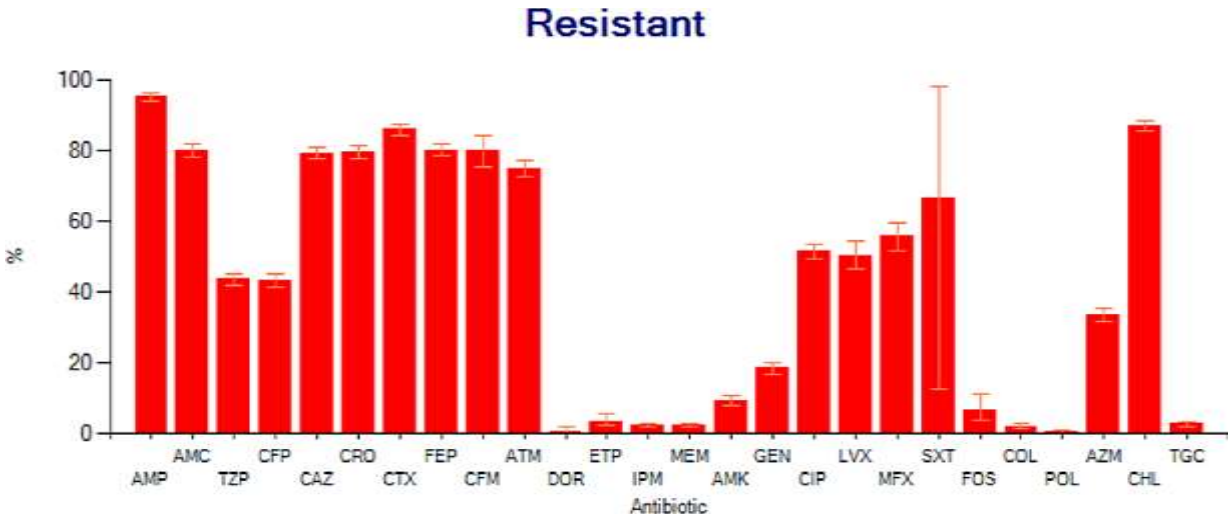

FIGURE 5: Salmonella antibiogram resistant pattern

AMP: Ampicillin, AMC: Amoxicillin/Clavulanic acid, TZP: Piperacillin/tazobactum, CFP: Cefoperazone, CAZ: Ceftazidime, CRO: Ceftriaxone, CTX: Cefotaxime, FEP: Cefepime, CFM: Cefixime, ATM: Aztreonam, DOR: Doripenem, ETP: Ertapenem, IPM: Imipenem, MEM: Meropenem, AMK: Amikacin, GEN: Gentamicin, CIP: Ciprofloxacin, LVX: Levofloxacin, MFX: Moxifloxacin, SXT: Trimeth0prim/sulfamethoxazole, , COL: Colistin, POL: Polymyxin B, AZM: Azithromycin, CHL: Chloramphenicol, TGC: Tigecycline.

The antibiotic susceptibility profiles observed over the years demonstrate a steady sensitivity to meropenem, imipenem, ertapenem, doripenem, colistin, tigecycline, and polymyxin B. In contrast, resistance remains an issue with co-trimoxazole/trimethoprim-sulfamethoxazole, chloramphenicol, amoxicillin, ceftriaxone, and fluoroquinolones. This persistent resistance highlights the need for ongoing monitoring and evaluation of antibiotic efficacy to ensure effective treatment strategies.

Discussion

Typhoid fever, caused by *Salmonella Typhi* (S. Typhi), and paratyphoid fever, caused by *Salmonella Paratyphi* (S. Paratyphi), are significant contributors to enteric fever, an infectious disease transmitted through contaminated food and water[9]. If left untreated, these infections can lead to serious morbidity and even mortality. The majority of cases are concentrated in Asia[1], with the Indian subcontinent identified as an endemic region for enteric fever [10]. In Pakistan, enteric fever poses a substantial public health challenge, exacerbated by the issue of antibiotic resistance. A notable outbreak of ceftriaxone-resistant S. Typhi occurred in Pakistan between 2017 and 2018[11]. To effectively treat enteric fever, it is crucial to understand the local antibiogram of *Salmonella* species and implement appropriate antibiotic stewardship practices. This study aimed to assess the antibiogram profiles, prevalence based on age and gender, and the emerging antibiotic trends in cases of typhoid fever treated at KTH and HMC, Peshawar, Pakistan, from January 2017 to July 2023.In our findings, a significant male predominance was observed, consistent with previous studies[12,15]. This trend can be attributed to cultural factors, where men are more likely to engage in outdoor activities and consume street food, increasing their risk of exposure to the bacteria[13,15]. The consumption of street food is a recognized risk factor for enteric fever, as demonstrated in a study conducted in Karachi, which revealed a high prevalence of *Salmonella* carriage among food handlers working in food stalls[16].Age distribution analysis indicated that the most affected demographic was between 8 and 28 years old. Similar findings were reported by Sharvani et al[1], highlighting that the same factors influencing male predominance also elevate the risk of disease exposure among children and adolescents. Furthermore,

our study identified a clustering of cases during the summer and spring months. Khan et al. linked this seasonal pattern to increased consumption of commercially made ice, chilled beverages, and flooding[10]. This seasonal trend aligns with observations made in India by Sur et al. and Mohanty et al[14,17].Resistance patterns among *Salmonella* isolates indicated significant resistance to first-line antibiotics, including amoxicillin, co-trimoxazole, chloramphenicol, as well as fluoroquinolones and cephalosporins. These results corroborate findings from studies conducted by Qamar et al. and Khan et al., which reported high levels of multidrug-resistant (MDR) *Salmonella* strains in Karachi and Hyderabad[2,13]. Additionally, Leghari et al. noted reduced sensitivity to ceftriaxone and cefixime. In contrast, research from India and Nepal suggested lower resistance rates to first- line antibiotics and a decreased prevalence of MDR strains in *S. Typhi*[1,9].Our study observed robust sensitivity to carbapenems, polymyxin B, tigecycline, and colistin. Amikacin demonstrated a sensitivity rate of 89.7%, while gentamicin maintained a high sensitivity of 80.5%. These antibiotics represent promising treatment options for managing typhoid fever, given their favorable sensitivity profiles and cost-effectiveness. A study in India also reported enhanced in vitro activity for amikacin and gentamicin. However, prolonged aminoglycoside treatment can increase the risk of nephrotoxicity, with the likelihood rising to 50% for courses extending beyond 14 days.Azithromycin showed an overall sensitivity of 66.5%, with a concerning downward trend. In Northern Pakistan, a study on extensively drug-resistant (XDR) *S. Typhi* indicated that sensitivity was limited primarily to azithromycin and meropenem[11]. Yousafzai et al. highlighted a similar antibiotic sensitivity profile during an outbreak of ceftriaxone-resistant *S. Typhi* in Hyderabad from 2016 to 2017, with an emphasis on meropenem, imipenem, and azithromycin[12].Annual analysis of antibiotic resistance and susceptibility profiles for *S. Typhi* from 2017 to 2023 revealed a marked increase in resistance to amoxicillin, co- trimoxazole, chloramphenicol, third-generation cephalosporins, and fluoroquinolones. This contrasts with prior studies from Pakistan, Nepal, and India, which reported increased sensitivity to first-line drugs and cephalosporins[8,12,13]. This discrepancy raises concerns regarding the evolving resistance landscape.At Ayub Teaching Hospital, azithromycin was administered at a dose of 500 mg once daily for seven days, while meropenem was given at 1 gm thrice daily for 10 days. However, our findings suggest that for empirical treatment of typhoid fever, alternatives such as amikacin, gentamicin, and meropenem should be considered. Although current guidelines do not recommend aminoglycosides, further clinical trials are needed to assess their efficacy in treating enteric fever. In Pakistan, amikacin is more cost-effective than meropenem, and demonstrating its effectiveness could address this issue. Conversely, fluoroquinolones, cephalosporins, co-trimoxazole, and azithromycin are not recommended due to their declining sensitivity trends.To combat the growing challenge of antibiotic resistance, continuous antibiogram surveillance is essential for monitoring resistance patterns and guiding empirical treatment strategies. Implementing antimicrobial stewardship programs will be crucial in addressing the rising incidence of antibiotic resistance. Public awareness campaigns should focus on educating the population about the risk factors and transmission routes of enteric fever, thereby promoting preventive measures. Additionally, health authorities may consider initiating Salmonella vaccination campaigns as a strategic intervention to reduce the disease burden.

Conclusions

This investigation reveals a troubling increase in the prevalence of Salmonella infections, with a notable predominance among males, particularly during the spring and summer seasons. The demographic most impacted includes individuals within the age range of one to 24 years.

Alarmingly, a substantial proportion of Salmonella isolates demonstrate resistance not only to commonly used first-line antibiotics but also to ciprofloxacin and third-generation cephalosporin. Furthermore, sensitivity to azithromycin is notably lower in comparison to amikacin, and gentamicin. Given these alarming trends, it is crucial to take immediate and decisive action. Our findings advocate for the empirical administration of amikacin, gentamicin, and meropenem in treating typhoid fever in Pakistan. However, the efficacy of amikacin, and gentamicin necessitates further investigation

through clinical trials. To effectively tackle the rising challenge of antibiotic resistance, it is essential to establish continuous surveillance of Salmonella antibiograms and implement robust antibiotic stewardship initiatives. Moreover, enhancing public health education efforts, alongside introducing vaccination programs for Salmonella, is vital for the primary prevention of this disease. By embracing these strategies, we can confront the critical issue of antibiotic resistance and protect public health within our communities.

Additional Information

Disclosures

Approval is here by granted to Dr.Ahmad zeb and his team, Resident Physician at Ayub Teaching Hospital Abbottabad,to collect data from ATH,for research titled "Antibiotic Resistance Patterns of Salmonella Species and Shifts in Empirical Treatment:A Study from Ayub teaching hospital Abbottabad,Kpk, Pakistan'. During this study, all personal information of subjects were kept confidential.

Conflicts of Interest: None

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Authors Contribution

Concept & Design of Study; Waleed Asif Khurshid, Muhammad Firdous Khan,Ahmad Zeb

Drafting; Muhammad Saad Rasheed, Dawood Khan, Sauleh Hassan.

Data Analysis; Imad Akbar, Shakir Ali Khan, Raees Khan,Shahkar Khan, Ahmad Zeb, Sauleh Hassan

Critical Review: Waleed Asif Khurshid, Muhammad Firdous Khan,Ahmad Zeb

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