ORIGINAL ARTICLE

Investigating Clinical and Biochemical Variances between Drug Resistant and Drug Susceptible Enteric Fever in Children

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Abstract

Background: Two main types of resistance are observed in Salmonella Typhi (S. Typhi): Multi-Drug Resistant (MDR) and Extensively Drug-Resistant (XDR). The treatment of MDR typhoid fever often involves oral medication and intravenous therapy. When treating XDR enteric fever, the choice of antibiotics depends on the patient's clinical condition.

Objective: To determine clinical and biochemical variances between drug-resistant and drug-susceptible enteric fever in children

Methods: The cross-sectional study was conducted in the Department of Pediatrics, Sambros Hospital, Karachi, from February to August 2018, a total of 143 patients were admitted from age 6 months to 13 years. Data collection and analysis were conducted using IBM SPSS, version 25.

Results: Out of the 143 patients, the majority were males (61.5%) and the mean age was 6.19±3.82 years. 15.4% had Drug-Susceptible Salmonella Typhi, while 84.6% had Drug-Resistant (including MDR and XDR) S. Typhi. Duration of fever (p=0.002) and hospital stay (p=0.025) were positively associated with drug-resistant enteric fever. Significant associations with hepatomegaly, splenomegaly, and mesenteric lymphadenopathy were noted in the drug-resistant group. None of the laboratory parameters was significant between the drug-sensitive and drug-resistant groups.

Conclusion: The incidence of drug-resistant enteric fever is very high with longer duration of fever and hospital stay more typhoid complications, which could have serious consequences in the future. Clinical findings including hepatomegaly, splenomegaly, and mesenteric lymphadenopathy were found to be significantly different among the two types of enteric fever whereas laboratory parameters were similar.

Keywords: *Clinical parameters, children, enteric fever, extensively drug-resistant (XDR), multi-drug resistant (MDR).*

INTRODUCTION

Enteric fever is a febrile systemic infection caused by gram-negative rods called Salmonella Typhi (typhoid fever) or by Salmonella parathyphi A, B, or C (paratyphoid fever). Although the global burden of this disease is decreasing, it remains a major cause of mortality and morbidity in Pakistan due to poverty, poor sanitation, and lack of access to proper treatment [1, 2].

Symptoms of enteric fever include abdominal pain, progressively rising fever, chills, headache, fatigue, *etc.* Without proper treatment, the patient may develop complications such as typhoid intestinal perforation (TIP), gastrointestinal hemorrhage, myocarditis, or shock, which can be fatal. Antibiotics are the mainstay of treatment for enteric fever [3]. However indiscriminate and non-judicious use of antibiotics has led to the emergence of multi-drug resistant and extended drug-resistant S. Typhi strains. Increasing cases of antibiotic resistance have been reported in Pakistan [4].

There are two main types of resistance observed in S. Typhi. Multi-drug resistant (MDR) S. Typhi strains that exhibit resistance to multiple antibiotics. These strains are typically resistant to ampicillin, trimethoprim-sulfamethoxazole, chloramphenicol, and/or fluoroquinolones. The treatment of MDR typhoid fever often involves intravenous ceftriaxone, which can be switched to oral cefixime once the patient's fever subsides and they can tolerate oral medications. Therapy with cephalosporin antibiotics is recommended for at least 14 days to effectively combat the infection [5]. Extensively Drug-resistant (XDR) Enteric Fever is a more severe form of the disease caused by S. Typhi strains that are resistant to all recommended antibiotics for enteric fever, except for carbapenems and azithromycin. When treating XDR enteric fever, the choice of antibiotics depends on the patient's clinical condition. If the patient is clinically stable, a course of azithromycin for 7-10 days is recommended. In hemodynamically unstable, stronger antibiotics like imipenem, meropenem, or ertapenem are recommended for a treatment duration of 10-14 days [5].

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A high incidence of enteric fever was reported in Bangladesh, Nepal, and Pakistan [6]. A report from Pakistan showed that children under 15 years had very high mortality and morbidity related to enteric fever [7]. This study aimed to determine the clinical and biochemical variances between drug-resistant (MDR, XDR) and drug-susceptible enteric fever in children in our study population, so better treatment plans can be developed.

SUBJECTS AND METHODS

This cross-sectional study was conducted at the pediatric department of The Sambros Hospital, Karachi, from October 7, 2022, to May 10, 2023, spanning 7 months after obtaining approval from the ethical review board. Prevalence of typhoid in children was taken as 11.3% 7 and the confidence level at 95%, with a margin of error d of approximately 0.0518 sample size was calculated to be 143 patients. Informed consent was obtained from the parents of the participating children for inclusion in the study and the use of their data for research purposes. The study included children aged 6 months to 13 years, who presented to the OPD/ER of Sambros Hospital, Karachi, with a history of fever persisting for more than one week despite antibiotic treatment provided by local healthcare practitioners, and whose blood cultures were positive for S. Typhi. Children with other diagnoses such as malaria, dengue, or other bacterial infections were excluded.

Comprehensive diagnostic evaluation: A total of 143 patients were admitted and underwent a thorough diagnostic evaluation, including assessments such as a complete blood count (CBC) and blood culture.

Treatment plan: All patients were initiated on intravenous ceftriaxone. If fever persisted beyond the fourth day of treatment, azithromycin was administered at 20 mg/kg/day once daily. Those responding to azithromycin continued the treatment until four days after defervescence. In cases where fever persisted despite a four-day azithromycin course, intravenous Imipenem was introduced at a dose of 30 mg/kg every eight hours. Blood cultures were taken, and where XDR (Extensively Drug-Resistant) Salmonella was isolated, sensitivity to both Imipenem and azithromycin was assessed, with these antibiotics being continued four days after defervescence as appropriate.

Blood culture: Blood cultures and sensitivity profiles were examined using standard bacteriological techniques to identify pathogens. Antimicrobial susceptibility testing was performed *via* the Kirby-Bauer disc diffusion method, as recommended by the Clinical and Laboratory Standards Institute (CLSI). Multidrug resistance (MDR) was defined as resistance to ampicillin, chloramphenicol, and trimethoprim-sulfamethoxazole.

Data collection and analysis were conducted using IBM SPSS, version 25. Post-stratification chi-square tests were applied, with a p-value of < 0.05 considered significant.

RESULTS

Out of the 143 patients, 88 (61.5%) were male and 55 (38.5%) were female. The mean age in our study was 6.23±3.20 years, and the mean weight was 20.76±8.66 kgs. According to blood culture and sensitivity 22 (15.4%) cases had Drug susceptible S. Typhi 121 (84.6%) had Drug Resistant (MDR and XDR) S. Typhi with 27 (18.9%) MDR S. Typhi, and 94 (65.7%) XDR S. Typhi. In the patient population, 3 (2.1%) had received typhoid vaccination, while 140 (97.9%) had not been vaccinated against typhoid.

The majority of patients, 79 (55.2%), received IV ceftriaxone before blood culture and sensitivity (C/S) testing, followed by IV cefixime in 47 (32.9%) and IV ciprofloxacin in 15 (10.5%) patients. Most patients, 96 (67.1%), had been on antibiotic therapy for 5-7 days before blood C/S. After C/S, 76 (53.1%) patients were switched to a combination of IV Imipenem or Meropenem with IV Azithromycin. Other regimens included IV Azithromycin alone in 24 (16.8%) and IV Augmentin in 18 (12.6%) patients. A significant number, 107 (74.8%), required antibiotic therapy for more than 7 days following blood C/S results. This highlights the extensive use of broad-spectrum antibiotics and prolonged treatment durations presented in Table **1**.

Among the 143 patients, drug-resistant enteric fever was more prevalent, observed in 121 (84.6%) patients

Table 1: Antibiotic usage and duration before and after blood culture results.

Variables	Frequency (%)
Use of Antibiotic Before Blood C/S	
IV Ceftriaxone	79 (55.2)
IV Cefixime	47 (32.9)
IV Ciprofloxacin	15 (10.5)
IV Augmentin	2 (1.4)
Duration of Therapy Before Blood C/S	
3-5 days	36 (25.2)
5-7 days	96 (67.1)
> 7 days	11 (7.7)
Antibiotic Use After C/S	
Continuation of IV Augmentin/IV Ceftriaxone	2 (1.4)
IV Ceftriaxone + IV Azithromycin	12 (8.4)
IV Augmentin + IV Azithromycin	1 (0.7)
IV Imipinem/Meropenum + IV Azithromycin	76 (53.1)
IV Azithromycin	24 (16.8)
IV Augmentin	18 (12.6)
IV Ceftriaxone	7 (4.9)
IV Ciprofloxacin	3 (2.1)
Duration of Therapy After Blood C/S	
3-5 days	1 (0.7)
5-7 days	35 (24.5)
> 7 days	107 (74.8)

Blood C/S- Blood Culture and Sensitivity, IV-Intravenous, Other symptoms-nausea, vomiting

Table 2: Demographics characters, various symptoms, duration of fever and hospital stay and percentage of weight loss at discharge in study population.

Variables	Groups	Type of Enteric Fever		Total n(%)	p-value
		Drug Susceptible n(%)	Drug Resistant n(%)		
Gender	Male	12(8.4)	76(53.1)	88(61.5)	0.460
	Female	10(7.0)	45(31.5)	55(38.5)	
Age	upto 5 years	10(7.0)	46(32.2)	56(39.2)	0.496
	5.1-10 years	8(5.6)	38(26.6)	46(32.2)	
	>10years	4(2.8)	37(25.9)	41(28.7)	
Duration of fever	Upto 7 days	3(2.1)	5(3.5)	8(5.6)	0.002
	8-10 days	18(12.6)	66(46.2)	84(58.7)	
	11-14 days	1(0.7)	50(35.0)	51(35.70)	
Duration of hospital stay	Upto 7 days	20(14)	74(51.7)	94(65.7)	0.025
	8-10 days	2(1.4)	43(30.1)	45(31.5)	
	11-14 days	0(0)	4(2.8)	4(2.8)	
Percentage of weight loss at discharge	No weight loss	5(3.5)	12(8.4)	17(11.9)	0.217
	Less than 5%	17(11.9)	108(75.5)	125(87.4)	
	more than 5%	0(0)	1(0.7)	1(0.7)	
Symptoms	Anorexia	0(0.0)	3(2.1)	3(2.1)	0.624
	Diarrhea	0(0.)	2(1.4)	2(1.4)	
	Other symptoms*	22(15.4)	116(81.1)	138(96.5)	

Other symptoms*: abdominal pain, constipation, headache, nausea, vomiting, and malaise.

compared to drug-susceptible cases, which were found in 22 (15.4%). No significant differences were noted between males and females regarding susceptibility (p=0.460).

The majority of patients with drug-resistant enteric fever were aged under 10 years, accounting for 84 (58.7%) cases. A significant association was observed with the duration of fever, as patients with fever lasting 8-14 days were more likely to have drug-resistant enteric fever (p=0.002). Similarly, a longer hospital stay (8-10 days) was significantly associated with drug resistance (p=0.025). Weight loss at discharge was less than 5% for most patients, regardless of drug susceptibility (87.4%, p=0.217). The most common symptoms, besides anorexia and diarrhea, were classified as "other symptoms," affecting 138 (96.5%) patients, with no significant difference between groups (p=0.624), as presented in Table **2**.

There was a strong correlation between the choice of antibiotics used after blood culture/sensitivity (C/S) testing and the emergence of drug resistance (p<0.001). The combination of IV Imipenem/Meropenem with IV Azithromycin was particularly dominant among drug-resistant cases, accounting for 75 (52.4%) patients. The duration of therapy after C/S also displayed significant results, with the majority of drug-resistant cases (88 out of 107) receiving treatment for more than 7 days (p=0.014). Complications were observed, with gastrointestinal (GI) bleeding being reported in 13 (9.1%) drug-resistant patients; however, this was not statistically significant (p=0.193).

The presence of hepatomegaly was significantly associated with drug resistance, with 111 (77.6%) patients presenting this complication (p=0.042). Additionally, splenomegaly showed a significant relationship with drug resistance, with 51 (35.7%) cases in the drug-resistant group (p=0.003), as presented in Table **3**.

Table 3: Association of antibiotic use, duration of therapy, complications and clinical examination findings with drug sensitive enteric fever and drug resistant enteric fever.

Variables	Groups	Type of Enteric Fever		Total n(%)	p-value
		Drug Suseptible n(%)	Drug Resistant n(%)		
Antibiotic use after C/S results	IV Augmentin/ IV Ceftriaxone	1(0.7)	1(0.7)	2(1.4)	<0.001
	IV Ceftriaxone + IV Azithromycin	3(2.1)	9(6.3)	12(8.4)	
	IV Augmentin + IV Azithromycin	0(0)	1(0.7)	1(0.7)	
	IV Imipinem/ Meropenum + IV Azithromycin	1(0.7)	75(52.4)	76(53.1)	
	IV Azithromycinmycin	0(0)	24(16.8)	24(16.8)	
	IV Augmenten	17(11.9)	1(0.7)	18(12.6)	
	IV Ceftriaxone	7(4.9)	0(0)	7(4.9)	
	IV Ciprofloxacin	3(2.1)	0(0)	3(2.1)	
Duration of therapy after C/S	3-5 days	1(0.7)	0(0)	1(0.7)	0.014
	5-7 days	2(1.4)	33(23.1)	35(24.5)	
	More than 7 days	19(13.3)	88(61.5)	107(74.8)	

Variables	Groups	Type of Enteric Fever		Total n(%)	p-value
		Drug Suseptible n(%)	Drug Resistant n(%)		
Complications	GI bleeding	0(0)	13(9.1)	13(9.1)	0.193
	Neurological	0(0)	3(2.1)	3(2.1)	
	Intestinal perforation	0(0)	6(4.2)	6(4.2)	
	None	22(15.4)	99(69.2)	121(84.6)	
Fever	100-102 °F	15(10.5)	65(45.5)	80(55.9)	0.209
	102.1-104 °F	7(4.9)	56(39.2)	63(44.1)	
Pulse rate	Less than 100bpm	1(0.7)	13(9.1)	14(9.8)	0.542
	101-120 bpm	21(14.7)	106(74.1)	127(88.8)	
	More than 120 bpm	0(0)	2(1.4)	2(1.4)	
Blood pressure	Hypotensive	22(15.4)	120(83.9)	142(99.3)	0.669
	Normotensive	0(0)	1(0.7)	1(0.7)	
Anemia	Present	11(7.7)	82(57.3)	93(65)	0.108
	Absent	11(7.7)	39(27.3)	50(35)	
Jaundice	Present	1(0.7)	2(1.4)	3(2.1)	0.384
	Absent	21(14.7)	119(83.2)	140(97.9)	
Dehydration	Present	20(14)	99(69.2)	119(83.2)	0.294
	Absent	2(1.4)	22(15.4)	24(16.8)	
Hepatomegaly	Present	17(11.9)	111(77.6)	128(89.5)	0.042
	Absent	5(3.5)	10(7)	15(10.5)	
Splenomegaly	Present	2(1.4)	51(35.7)	53(37.1)	0.003
	Absent	20(14)	70(49)	90(62.9)	
CNS findings	Present	0(0)	2(1.4)	2(1.4)	0.544
	Absent	22(15.4)	119(83.2)	141(98.6)	
Day of defervescence	Less than 4 days	1(0.7)	2(1.4)	3(2.1)	0.384
	More than 4 days	21(14.7)	119(83.2)	140(97.9)	

Legends- CNS: central nervous system, C/S: culture and sensitivity

Table 4: Association of laboratory and radiological findings drug sensitive enteric fever and drug resistant enteric fever.

Variables	Type of Enteric Fever		Total n(%)	p-value
	Drug Sensitive n(%)	Drug Resistant n(%)		
Hemoglobin				
less than 7gm/dl	0 (0.0)	3 (2.1)	3 (2.1)	0.571
7.1-12gm/dl	20 (14.0)	112 (78.3)	132 (92.3)	
>12gm/dl	2 (1.4)	6 (4.2)	8 (5.6)	
TLC				
less than 4000/cumm	8 (5.6)	45 (31.5)	53 (37.1)	0.756
4000-11000/cumm	13 (9.1)	65 (45.5)	78 (54.5)	
more than 11000 cumm	1 (0.7)	11 (7.7)	12 (8.4)	
Neutrophil				
30-50%	17 (11.9)	76 (53.1)	93(65.0)	0.160
51-70%	2 (1.4)	34 (23.8)	36(25.2)	
>70%	3 (2.1)	11 (7.7)	14(9.8)	
Lymphocyte				
<40%	3 (2.1)	38 (26.6)	41 (28.7)	0.136
41-60%	19 (13.3)	79 (55.2)	98 (68.5)	
>60%	0 (0.0)	4 (2.8)	4 (2.8)	
Platelets				
Less than 50000zcumm	0 (0.0)	1 (0.7)	1 (0.7)	0.577
50000-100000/cumm	1 (0.7)	18 (12.6)	19 (13.3)	
100000-150000 /cumm	6 (4.2)	31 (21.7)	37 (25.9)	
More than 150000	15 (10.5)	71 (49.7)	86 (60.1)	
Stool antigen				
Positive	0 (0.0)	10 (7.0)	10 (7.0)	0.162
Negative	22 (15.4)	111 (77.6)	133 (93.0)	
Size of mesenteric lymph nodes on ultrasound				
Less than 1cm	22 (15.4)	93 (65.0)	115 (80.4)	0.012
More than 1 cm	0 (0.0)	28 (19.6)	28 (19.6)	

Legends- TLC-Total leukocyte count, Stool DR- stool detailed report

The size of mesenteric lymph nodes on ultrasound exhibited a statistically significant relationship with drug resistance (p=0.012). Specifically, none of the patients with mesenteric lymph nodes measuring less than 1 cm were classified as drug-resistant, while 28 (19.6%) patients with nodes larger than 1 cm were categorized as drug-resistant. Other laboratory parameters, such as hemoglobin levels, total leukocyte count (TLC), neutrophil percentages, lymphocyte percentages, platelet counts, and stool drug resistance results, did not demonstrate statistically significant differences between the drug-sensitive and drug-resistant groups, with p-values exceeding 0.05, as presented in Table **4**.

DISCUSSION

Enteric fever is endemic to tropical countries like Pakistan [8]. Traditionally, enteric fever was considered a relatively mild illness that could be managed in an outpatient setting. However, with the rising levels of antibiotic resistance, there has been a growing necessity for hospitalization. This is primarily because the disease

has become more severe, leading to prolonged illness, the development of complications, and the requirement for intravenous antibiotics [9]. The province of Sindh witnessed a significant surge in cases when an extensive outbreak of extensively drug-resistant (XDR) typhoid emerged in Hyderabad in 2016, leading to a substantial increase in the number of cases throughout Pakistan [10]. This novel strain made the traditional therapies redundant and newer stronger drugs like azithromycin had to be used [5].

In the current study, 76(53.1%) patients were male, similar findings have been reported by other studies done in Pakistan and Uganda [11, 12]. This predisposition lacks a biological explanation, but it becomes clearer when we consider the higher exposure of male children to external environments with elevated contamination rates. The mean age in our study was 6.23±3.20 years, which is similar to research done in Karachi [13]. According to blood culture and sensitivity 121 (84.6%) had Drug Resistant (MDR and XDR) enteric fever with 27 (18.9%) MDR and 94 (65.7%) XDR. Another researcher from Lahore has reported that the majority were XDR S. Typhi (n = 276, 46.1%), followed by MDR S. Typhi (n = 147, 24.5%) [14]. We noted that a very large number of children were not vaccinated for S. Typhi. These findings are consistent with another study by Vighio A *et al.* [13]. The limited adoption of vaccination is linked to both the high cost of the vaccine and its exclusion from the Expanded Programme on Immunization. The most commonly used antibiotic before blood C/S report was IV Ceftriaxone in 79 (55.2%) of cases because it is known to have maximum effectiveness and the least amount of side effects [15].

In our study largest number of cases were less than 5 years, however, the pattern of drug susceptibility or resistance was not affected by age. This finding is also confirmed by another researcher [14] The duration of hospital stay was up to 7 days in 94(65.7%), in the drug-resistant group 43(30.1%) had hospital stays between 8-10 days. The length of stay was significantly associated with drug-resistant enteric fever. Reasons for longer stays include a higher incidence of complications and the need for parenteral antibiotic treatment. The present study finding coincides with the previously published data [16, 17].

Single-drug therapy with augmentin and ceftriaxone was preferred in drug-susceptible cases of enteric fever, while a combination of IV imipenem/ meropenem + IV azithromycin was used for the treatment of drug-resistant enteric fever. In a study assessing treatment approaches for patients with extensively drug-resistant (XDR) Salmonella in Pakistan, 27% of patients were treated with azithromycin alone, 25% received meropenem monotherapy, and 48% were administered a combination of both drugs [18]. Gastrointestinal bleeding was found to be the most common complication in the drug-resistant group, while no complications were noted in the drug-susceptible enteric fever group. There is no significant difference in complications between drug-susceptible and resistant strains of typhoid. Our study's findings are inconsistent with those of another study which had no GI bleeding complication in their set of study population [19].

No significant difference was found in clinical findings of pulse rates, blood pressure, anemia, jaundice, dehydration, C/S findings, and day of defervescence between drug-susceptible and drug-resistant cases. The present study's finding coincides with the previously published research by Fida *et al.* [20]. Interestingly, splenomegaly was observed in 35.7% of drug-resistant cases. A similar high incidence of splenomegaly has been reported in India [21]. Finally, central nervous system (CNS) findings were limited, with 1.4% of drug-resistant patients demonstrating such symptoms. These findings underscore the multifaceted clinical disparities between drug-susceptible and drug-resistant enteric fever patients, shedding light on the complexity of the disease presentation and its implications.

The examination of laboratory in drug-sensitive and drug-resistant enteric fever patients showed that hemoglobin levels within the range of 7.1-12 gm/dl were commonly observed, 78.3% of the drug-resistant cases fell within this range, compared to only 14.0% of the drug-sensitive cases. Neutrophil counts within the range of 30-50% were observed in 53.1% of patients with drug-resistant enteric fever. Additionally, lymphocyte counts between 41-60% were prevalent in 55.2% of these drug-resistant cases. Furthermore, platelet counts exceeding 150,000/cumm was more frequently encountered in the drug-resistant group, accounting for 49.7% of the cases. Lastly, positive stool antigen results were identified in 7.0% of patients with drug-resistant enteric fever. Non-significant association was found between hemoglobin levels (p=0.571), total leukocyte counts (TLC) (p=0.756), neutrophil count (p=0.160), lymphocyte count (p=0.136), and platelet counts (p=0.577), as well as stool DR (Vi antigen) (p=0.162). Larger mesenteric lymph nodes (more than 1 cm) on ultrasound were associated with drug-resistant enteric fever (19.6%) with a significant p-value of 0.012, signifying a statistically significant difference between the two groups. Mesenteric lymphadenitis is reported to be associated with drug-resistant enteric fever [22, 23].

CONCLUSION

The findings of this study highlight the high prevalence of drug-resistant enteric fever, especially XDR strains, in children. Those with drug-resistant enteric fever had longer fever durations, extended hospital stays, and required more aggressive antibiotic therapies. Significant associations with hepatomegaly and splenomegaly were noted in the drug-resistant group.

Given the substantial burden of drug-resistant enteric fever and its clinical implications, there is an urgent need

for improved preventive measures, such as widespread typhoid vaccination and stricter antibiotic stewardship. Moreover, the findings point to the need for enhanced diagnostic tools to identify drug-resistant cases early, allowing for timely and effective treatment interventions. Future studies should explore long-term outcomes and the role of socio-economic and environmental factors in driving resistance patterns. Addressing these challenges requires a multi-faceted approach, including public health initiatives and continued surveillance of antimicrobial resistance trends.

ETHICS APPROVAL

This study was approved by the ethics review committee of The Sambros Hospital, Karachi, Pakistan. All procedures performed in studies involving human participants were following the ethical standards of the institutional and/ or national research committee and the Helsinki Declaration.

CONSENT FOR PUBLICATION

The study was conducted after formal written consent from the patient's parents/ guardians.

AVAILABILITY OF DATA

Authors confirm that data supporting the results of this study are available in the article. Data can be provided on request.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORS' CONTRIBUTION

All authors have contributed to the manuscript in accordance with the authorship criteria outlined by the Committee on Publication Ethics (COPE). The specific contributions of each author are detailed below:

Study Design and Final Approval: SH

Writing and Editing Article: MHM, FS

Data Collection and Entry: ES, FA

Writing and Statistical Analysis: MA

All authors have read and approved the final version of the manuscript.

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