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ORIGINAL ARTICLE

PREDICTION OF TYPHOID FEVER ON THE BASIS OF BLOOD PARAMETERS, A COMPARATIVE STUDY

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ABSTRACT

Background: Salmonella Typhi is highly prevalent in this part of the world and calls for research into accurately predicting the infection on the basis of various blood parameters while awaiting the blood culture reports.

Materials & Methods: This cross sectional study was conducted in the Department of Internal Medicine, Hayatabad Medical Complex, Peshawar from 1st August, 2021 to 30 July, 2022. A total of 400 adult patients of either sex, between 18 to 70 years of age, with history of fever, and symptoms suggestive of typhoid fever for the past 07 days were included. The patients were categorized into cases and control groups on the basis of the blood culture reports. The stratification of the general variables against the eosinopenia and leukopenia was analyzed followed by further application of logistic regression to allow true estimation of the association.

Results: The age distribution amongst the control and the cases group was 46.14±17.3SD and 47.03±16.7SD respectively. Leukopenia was observed statistically more (p value .000) in the cases as compared to the control group whereas no such statistically significant association was observed in case of eosinopenia. Further stratification with respect to age and gender didn't show any association in cases of eosinopenia and leukopenia. Logistic regression showed presence of leukopenia was seven times and eosinopenia was twice more in culture positive patients with culture positivity increase with unit increase in the leukopenia.

Conclusion: In an appropriate clinical scenario, with history of ongoing fever for 1 week with associated unexplained gastrointestinal symptoms and evidence of leukopenia on the initial blood film, the diagnosis of typhoid fever is highly likely.

Key Words: Salmonella Typhi; Leukopenia; Eosinopenia; Blood Culture.

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INTRODUCTION

In developing world, Enteric fever triggered by Salmonella Typhi and Salmonella Paratyphi remain a prominent cause of morbidity and mortality with over 22 million cases and subsequent 200000 deaths in South Asia in year 2000. The WHO has reported that the incidence of typhoid continues to escalate in parts of South Asia with sadly the highest incidence in parts of Pakistan with 451.7 per 1, 00,000 individuals/year, trailed by India with 214.2 per 1, 00,000 individuals/year.[1] The blood cultures continue to remain gold standard but the facilities remain inadequate especially in the endemic regions primarily due to poor antibiotic stewardship programs. This leaves the treating physicians to retort upon the clinical signs and rapid bacteriological isolation methods which also have its inherent flaws. This approach calls for finding the most frequently hematological abnormalities at the time of initial interaction in confirmed cases of typhoid fever and then using the subset to initiate the appropriate antibiotics while awaiting the blood culture reports. The potential wait for bacterial isolation comes with inherent problems of protracted hospital stay with amplified morbidity and mortality besides the poor positive and negative predictive value of the commonly used serological tests.[2]

The hematological abnormalities have been studied to a varied influence in helping the diagnosis of typhoid fever. It has been observed that WBC counts are normal in most of the cases and seeing evidence of leukocytosis without any clinical evidence of associated complications makes the diagnosis less likely. In a study concerning the assessment of risk

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factors in cases of enteric perforation in India, it was observed that leukopenia was seen in 54% in cases without and 22% in cases of enteric perforation. (P< 0.05).[3] Tashfeen S et al observed the presence of leucopenia to be 14% in cases with non-resistant typhoid whereas 6.3% in the resistant cases whereas the remaining had normal white cells counts.[4]

On analysis of the available literature, we witnessed that the clinicians across the globe employ various strategies with regard to the presumptive diagnosis of typhoid fever on the basis of particular subset symptoms and the varied haematological parameters with varying success while awaiting the blood culture results. Despite the fact that infectious diseases are rampant in this part of the world and more so typhoid fever, such evidence in our local population seems lacking and hence leaves the treating physicians with less chances of accurately predicting typhoid fever. We wanted to undertake this comparative cross sectional study to know the predictive value of accurately diagnosing typhoid fever in suspected patients on the basis of the initial haematological parameters while awaiting the blood culture reports.

MATERIAL AND METHODS

This cross sectional study was conducted in the Department of Internal Medicine, Hayatabad Medical Complex, Peshawar, Pakistan for a period of one year from 1st August, 2021 till 30 July, 2022. Ethical approval from the hospital ethical committee was obtained. All adult patients of either sex, belonging to the province of Khyber Pakhtunkhwa, Pakistan, between 18 to 70 years of age, whether admitted through casualty or the outpatients, having a history of fever, and symptoms suggestive of typhoid fever (Nausea, Vomiting, Diarrhoea or Constipation) for the past 07 days and no prior history of admission or use of antibiotics in past one month were included.

At the time of admission, 5 ml of blood was sent for peripheral smear to the hospital laboratory. A further 15 ml of blood was drawn and sent immediately to hospital main laboratory for culture and sensitivity. The blood samples were incubated on MacConkey agar followed by gram staining and morphology besides identification of the strain using the poly-valent sera (BD Difco TM Salmonella). The results of the isolated Salmonella Typhi or otherwise along with peripheral smear results of all the included patients were uploaded on the hospital automated Health-system Management and Information System (HMIS). A total of 200 patients during the study period whose blood culture showed the growth of Salmonella Typhi were recruited as the cases while the other 200 patients with the same set of symptoms but culture failed to show the growth were included in the control group. The cases of eosinopenia were defined as absolute eosinophil count less than 0.40 X 109/L whereas Leukopenia as total white cells count less than 4.00 X 109/L on the initial smear results.

All the data was entered into a proforma made for the study and analyzed using SPSS version 22. Mean and standard deviation were calculated for numerical variables like age, total leukocytes count and the eosinophil's count. Frequency and percentages were calculated for categorical variables like gender. The stratification of the general variable against the eosinopenia and leukopenia was analyzed and p value of 0.05 was considered statistically significant. Further application of logistic regression allowed true estimation of the association between the variables. All the results were presented in the form of tables.

RESULTS

The distribution of patients amongst the control and the cases group was nearly uniform 46.14±SD17.3 and 47.03±SD16.7 respectively as shown in table 1. The presence of leukopenia was observed statistically more with a p value of .000 in the cases as compared to the control group whereas no such statistically significant association was observed in case of eosinopenia.

Table 1: Distribution of age, Total Leucocytes Count and Eosinophil Counts

Variable	Group	N	Mean	SD	P-Value
Age(in years)	Control	200	46.1450	17.31888	.601
	Cases	200	47.0350	16.70055	
Total Leucocyte count (x10/L)	Control	200	7.6780	3.31766	.000
	Cases	200	4.4400	2.11776	
Eosinophil count (x10/L)	Control	200	.7465	.73947	.941
	Cases	200	.7415	.61655	

Table 2: Stratification of the Eosinopenia with respect to age and gender

Variable		Eosinopenia		P- Value
Yes		No		
Group	Control	53.5%(107)	46.5%(93)	0.421
	Cases	57.5%(115)	42.5%(85)	
Gender	Male	55.2%(111)	44.8%(90)	0.911
	Female	55.8%(111)	44.2%(88)	
Age	≤40 years	57.2%(91)	42.8%(68)	0.571
	More than 40 years	54.4%(131)	45.6%(110)	

Table 3: Stratification of Leukopenia with respect to age and gender amongst the cases and control groups:

Variable		Leukopenia		P- Value
Yes		No		
Group	Control	12.2% (6)	55.3% (194)	0.000
	Cases	87.8%(43)	44.7%(157)	
Gender	Male	51.0%(25)	50.1%(176)	0.908
	Female	49.0%(24)	49.9%(175)	
Age	≤40 years	49.0%(24)	38.5%(135)	0.159
	More than 40 years	51.0%(25)	61.5%(216)	

Table 4: Logistic Regression with respect to Gender, Age, Leukopenia and Eosinoipenia.

Variables	B	S.E.	Wald	Df	Sig.	Exp(B)	95.0% C.I.for EXP(B)	
							Lower	Upper
Gender	.025	.236	.011	1	.917	1.025	.645	1.628
Age	.395	.244	2.619	1	.106	.674	.418	1.087
Leukopenia	2.052	.478	18.421	1	.000	7.785	3.050	19.872
Eosinopenia	.060	.237	.064	1	.800	1.062	.667	1.689

The presence of eosinopenia and further stratification with respect to the age and gender in both the cases and the control group failed to show any statistically significant association as shown in table 2.

The presence of leukopenia showed statistically significant association amongst the controls and cases but further stratification with regard to age and gender failed to show any association as shown in table 3.

Further application of logistic regression revealed that the presence of leukopenia was seven times and eosinopenia was twice more in culture positive as that of culture negative patients as shown in table 4. Culture positivity significantly increased with the unit increase in the leukopenia.

DISCUSSION

The clinical diagnosis of Typhoid fever on the basis of clinical features remains of extraordinary value particularly in the endemic regions of the world where the prevalence remains high and the diagnostic facilities remain scarce. In endemic areas, the presence of fever for more than seven days complemented by chills with absence of cough is exceedingly suggestive of typhoid fever.[5] The blood and the bone marrow culture positivity in typhoid fever has remained dismal with a study reporting 54% isolates of salmonella typhi showing the Multiple Drug Resistance patterns in Pakistan.[6] These findings are particularly worrisome in developing countries like Pakistan where the health care facilities are always under immense pressure, the inability to pay for the treatment cost coupled with lack of any universal health insurance makes the situation complicated. The use of various blood parameters in a good clinical setting in accurately predicting the diagnosis of typhoid fever remains pivotal in developing countries. This provides a valuable chance to the treating doctors to empirically start the appropriate treatment while awaiting the culture results with resultant decrease morbidity and mortality.[7]

Our results revealed that the presence of leukopenia

was documented statistically more in the cases in contrast to the control group where the blood cultures failed to show the growth of Salmonella Typhi. However in the case of eosinopenia, we didn't identify any differences in the occurrence amid both the groups. The stratification of both the blood parameters with respect to the age and gender amongst the cases and the control groups failed to show any differences. Application of logistic regression allowed us to predict that the presence of leukopenia on the initial blood smear of the suspected typhoid fever patients is nearly seven times more likely as compared to culture negative subset of the patients. No such correlation was observed in case of eosinopenia amongst both the groups. Eosinophil provide a valuable protection apparatus by residing at the mucosal surfaces of the gut epithelium and it is postulated that the upsurge marginalization of them following infection may account for early and significant decline, however the complete understanding of the mechanisms remain unclear, and warrants further research.[8] The presence of eosinopenia has been observed in varied infectious diseases and sepsis syndrome but its specific presence in patients suffering from typhoid fever still remains unclear.[9] Waddington and coworkers reported "anesionphilia" as a much better tool to predict the evidence of typhoid fever.[10] There was no statistically significant difference observed in the monocytes and eosinophil values between patients with typhoid and non-typhoid fevers.[11] These findings are in total agreement with our study results, where similarly no statistically significant differences observed between the two groups with regard to eosinophil count. Lokhandwala et al recounted absolute eosinopenia in 73% cases of enteric fever.[12] These findings are at odds with our study results where we couldn't find any evidence of increased prevalence of eosinopenia in the cases and control groups. The differences might be because of the dissimilarity in the varied characteristics of the study population besides the varied genomic sequences of salmonella and the resultant virulence patterns.

The frequency of leukopenia has been reported as 35.4% whereas leukocytosis being rare has been seen in 14.55% by Arya et al.[13] Ndako JA et al also reported a statistically substantial occurrence of leukopenia in the patients with typhoid fever when equated with the normal healthy adults.[14]

Our study results seem in total agreement with these findings where we observed statistically more prevalence of leukopenia in the cases as compared to the control groups with fever where the blood cultures failed to show growth of gram negative rods.

The magnitude of the problem of infectious diseases calls for wider population based studies to ensure that before the availability of the results of the blood cultures, the treating doctors can have some blood parameters coupled with the appropriate scenario to accurately predict the occurrence of typhoid fever. The appropriately pointed clues should allow initiation of the treatment with resultant decrease in morbidity and mortality. The literature review shows that the results in one study population cannot be generalized and have regional variance, probably because of the differences in the characteristics of the study population and the isolated causative bacteria.

Conclusion:

Following the results of our study, we gathered that in our population, in appropriate clinical scenario, where there is a history of ongoing fever for a week along the associated unexplained gastrointestinal symptoms and evidence of leukopenia on the initial blood film, the diagnosis of typhoid fever is highly likely. Nonetheless, this is a single center study on the adult population only, so there is a need of broader scale multicenter trials enrolling patients from all age groups for better generalization of the results.

REFERENCES

1. World Health Organization. Typhoid Vaccines: WHO Position Paper - March 2018.Weekly Epidemiological Record 2018; 13:153-172.
2. Enany SA, El-Ghreb MS, Zaghloul MH, Fatouh AA. Validation of Polymerase chain reaction for diagnosis of typhoid fever In Egyptian Patients. J of Card Dis Res. 2021;12(3):609-25.
3. Mali D, Jakhar M. Assessment of risk factors for enteric perforation in cases of typhoid fever patients of west zone of Rajasthan. European Journal of Molecular & Clinical Medicine. 2022;9(6):1049-52.
4. Tashfeen S, Asif N, Farooq M. Haematological profile derangements in patients due to non-resistant and resistant typhoid fever. Pak Armed Forces Med J 2021; 71(5): 1615-1618. https://doi.org/10.51253/pafmj.v71i5.4359
5. Neupane DP, Dulal HP, Song J. Enteric fever diagnosis: Current challenges and future directions. Pathogens. 2021;10(4):410. https://doi.org/10.3390/pathogens10040410
6. Ingle DJ, Nair S, Hartman H, Ashton PM, Dyson ZA, Day M, et al. Informal genomic surveillance of regional distribution of Salmonella Typhi genotypes and antimicrobial resistance via returning travellers. PLoS neglected tropical diseases. 2019;13(9):e0007620. https://doi.org/10.1371/journal.pntd.0007620
7. Mali D, Jakhar M. Assessment of risk factors for enteric perforation in cases of typhoid fever patients of west zone of Rajasthan. European Journal of Molecular & Clinical Medicine. 2022;9(6):1049-52.
8. Brewer SM, Twittenhoff C, Kortmann J, Brubaker SW, Honeycutt J, Massis LM, et al. A salmonella typhi rna thermosensor regulates virulence factors and innate immune evasion in response to host temperature. PLoS Pathog. 2021;17: e1009345. https://doi.org/10.1371/journal.ppat.1009345

9. Holubar M. Antimicrobial resistance: a global public health emergency further exacerbated by international travel. Journal of travel medicine. 2020;27(1):taz095. https://doi.org/10.1093/jtm/taz095

10. Waddington CS, Darton TC, Jones C, et al. An outpatient, ambulant-design, controlled human infection model using escalating doses of Salmonella Typhi challenge delivered in sodium bicarbonate solution. Clin Infect Dis 2014; 58: 1230 -40. https://doi.org/10.1093/cid/ciu078

11. Ifeanyi OE. Changes in some haematological parameters in typhoid patients attending University Health Services Department of Michael Okpara University of Agriculture, Nigeria. Int J Curr Microbiol. App Sci 2014;3(1):670-4.

12. Lokhandwala A, Athar S, Turrin NP. Role of Absolute Eosinopenia as Marker of Enteric Fever: Experience from a Tertiary Care Hospital in the United Arab Emirates. Ibnosina Journal of Medicine and Biomedical Sciences 2012;4(6):249-253. https://doi.org/10.4103/1947-489X.210782

13. Arya V, Gehlawat VK, Mittal K. Evaluation of clinico-demographic and laboratory profile of children admitted with enteric fever: A retrospective observational study. Headache.;13:11-82.25.

14. Raj C. Clinical profile and antibiotic sensitivity pattern of typhoid fever in patients admitted to pediatric ward in a rural teaching hospital. Int J Med Res Health Sci 2014;3(2):245-8. https://doi.org/10.5958/j.2319-5886.3.2.054

15. Ndako JA, Olisa JA, Ifeanyichukwu IC, Ojo SK, Okolie CE. Evaluation of diagnostic assay of patients with enteric fever by the box-plot distribution method. New Microbes and New Infections 2020;38(1):100795. https://doi.org/10.1016/j.nmni.2020.100795

CONFLICT OF INTEREST
Authors declare no conflict of interest.
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	MTM, MI
Acquisition, Analysis or Interpretation of Data:	MTM, MI, GF, AQJ
Manuscript Writing & Approval:	MTM, MI, GF, AQJ

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.