Section: Pediatrics

Original Research Article

EVALUATION OF NEUTROPHIL–LYMPHOCYTE RATIO AND PLATELET–LYMPHOCYTE RATIO IN CHILDREN WITH TYPHOID FEVER

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Received : 27/02/2024
Received in revised form : 22/04/2024
Accepted : 06/05/2024

Keywords:
Typhoid fever, Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, diagnostic biomarkers.

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DOI: 10.47009/jamp.2024.6.3.9

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (3); 38-44

Abstract

Background: Typhoid fever is one of the significant public health challenges in developing regions, particularly in areas lacking proper sanitation and clean water. The infection, caused by Salmonella enterica serotype Typhi, is prevalent among children in India. This study explores the Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) as inflammatory markers, offering rapid, cost-effective, and non-invasive alternatives for early diagnosis and monitoring of typhoid fever. **Materials and Methods:** Conducted at GMERS Medical College & Civil Hospital, Gandhinagar, Gujarat, this comparative cross sectional study included 110 participants, split equally between subjects (diagnosed with typhoid fever confirmed by positive serum Widal test) and healthy controls. Data collected encompassed demographic details, clinical symptoms, and complete blood counts to calculate NLR and PLR. Statistical analyses such as unpaired Student's t-test and Pearson's correlation test were employed for comparison and correlation respectively. **Result:** The study found significant decreased NLR and PLR among typhoid subjects compared to controls. Mean NLR in the subject group was 1.42 ± 1.19 compared to 2.15 ± 0.6 in controls, and the mean PLR in the subjects was 60.9 ± 53.09 versus 89.75 ± 37.55 in controls, both with p-value<0.001. Additionally, typhoid subjects displayed statistically significant lower hemoglobin level (mean Hb 8.95 ± 2.0 gm/dl), lower neutrophil count (mean 3.34 ± 1.85x10^9/L) and lower platelet count (mean 129.02 ± 63.84x10^9/L) compared to controls, all with p-value<0.001. Further, NLR and PLR both are negatively correlated with CRP (r = -0.62, p-value<0.001 and r = -0.4, p-value = 0.002 respectively) in the subject group. Anemia was seen in 69.09% and thrombocytopenia in 58.18% of the subjects. Socioeconomic data indicated a higher typhoid incidence in children from lower socioeconomic background. **Conclusion:** NLR and PLR are substantiated as simple and effective biomarkers for diagnosing and monitoring children with typhoid fever. Use of these hematological indices facilitates early diagnosis and can significantly improve clinical outcomes in typhoid management, especially in resource-constrained environments.

INTRODUCTION

Typhoid fever remains a significant public health challenge in developing countries, particularly in regions with limited access to clean water and adequate sanitation facilities.[1] Caused by Salmonella enterica serotype Typhi, this systemic infection presents a substantial burden, especially among children in endemic areas.[2] In typhoid fever presenting features are fever with chills, persistent headache, abdominal discomfort, diarrhoea, weakness, dizziness, nausea and vomiting. Late diagnosis or failure to respond to treatment may cause serious complications which include cerebral dysfunction, perforation of the gut wall, gastrointestinal haemorrhage and shock. Terminal ileal perforation is the most common complication of enteric fevers.[3]The disease's impact is profoundly felt in South Asia, including India, where the incidence of typhoid fever is notably high.[4] Gandhinagar, Gujarat, with its diverse population dynamics and varying public health

ISSN (O): 2687-5365; ISSN (P): 2753-6556

standards, provides a unique setting to study this infectious disease, particularly among pediatric populations. Many hematological changes are common in typhoid fever which includes anemia, leucopenia, eosinophilia, thrombocytopenia, elevated ESR and subclinical disseminated intravascular coagulation with elevated prothrombin time (PT), and Activated Partial Thromboplastin time (APTT).[5,6,7] Current diagnosis for typhoid is still via the method of culture and antibody detection by means of the Widal test. Isolation of Salmonella typhi has remained as the gold standard, with culture of the bone marrow aspirate or a combination of specimens from blood, stool or urine. However, it is well recognised that facilities for culture are not readily available or are limited in many areas. Even though, the culture method may show specificity, it lacks sensitivity and speed.[8] In endemic areas where culture facilities are lacking or limited, the Widal test remains among the few tests available to differentiate enteric infection from other illnesses.[9] Normally, salmonella typhi O antibodies appear on day 6-8 and H antibodies on days 10-12 after the onset of disease.[10] But this test also shows many drawbacks. Antibodies against Salmonella typhi have been detected among nontyphoid Salmonella infections and sometimes the disease itself caused by another pathogen.[11,12] The available diagnostic methods have many shortcomings which demands the detailed analysis of CBC in typhoid fever. Recent advances in diagnostic methodologies have highlighted the potential of hematological indices as tools for the early diagnosis and monitoring of typhoid fever. Among these, the Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) have emerged as significant biomarkers. These indices, derived from simple complete blood count tests, offer a rapid, cost-effective, and non-invasive diagnostic alternative. This is particularly crucial in resource-limited settings where traditional culture methods are costly, time-consuming, and require sophisticated laboratory infrastructure.[13,14]

The role of NLR and PLR as inflammatory markers has been well documented in various systemic infections and inflammatory conditions. Inflammation plays a pivotal role in the pathophysiology of typhoid fever, influencing the course and severity of the disease. Neutrophils and lymphocytes are key players in the inflammatory response, with their relative proportions providing insights into the immune response against infections. Similarly, platelets are not only involved in hemostasis but also in immune modulation and inflammation.[15.16] Therefore, studying these ratios could provide valuable insights into the inflammatory dynamics specific to typhoid fever in children. The Department of Pediatrics at GMERS Medical College & Civil Hospital, Gandhinagar, offers an excellent platform for such an investigation. The department is well-equipped and staffed with experienced professionals capable of conducting robust epidemiological and clinical research. Additionally, the hospital's high volume of pediatric admissions for typhoid fever ensures a sufficient sample size for statistical analysis, thereby enhancing the study's validity. This study aims to evaluate the diagnostic value of NLR and PLR in children diagnosed with typhoid fever. By establishing reference thresholds and understanding the variations in these indices among typhoid-affected children, the research seeks to contribute to the existing diagnostic protocols and potentially guide treatment strategies. Thus, this study not only aims to enhance the scientific understanding of hematological responses in typhoid fever but also to improve clinical outcomes through more informed decision-making in pediatric care settings.

MATERIALS AND METHODS

Study Design and Setting

This study employed a comparative cross sectional design and was conducted at the Department of Pediatrics, GMERS Medical College & Civil Hospital, Gandhinagar, Gujarat (from april 2019 to September 2019). The hospital serves a large pediatric population, making it an ideal location for conducting such research.

Study Participants

The study included a total of 110 participants, divided into two groups: subjects and controls, with 55 children in each group. The subjects consisted of children diagnosed with typhoid fever, confirmed by a positive serum Widal test, which is widely used for detecting Salmonella enterica serotype Typhi infection. The control group included 55 children visiting the outpatient department for routine check-ups or minor non-infectious conditions, who had no history of typhoid fever or other significant acute or chronic illnesses.

Inclusion and Exclusion Criteria

Subjects:

- **Included:** Children aged 5-15 years diagnosed with typhoid fever confirmed by a positive serum Widal test.
- **Excluded:** Children with co-existing chronic diseases, such as hematological disorders like thalassemia and sickle cell anemia, tuberculosis, HIV, severe acute malnutrition, autoimmune diseases, or those on treatments that affect white blood cells or platelet counts (e.g., steroids or chemotherapy).

Controls:

- **Included:** Healthy children aged 5-15 years with no recent history (within the past month) of any infectious or inflammatory conditions.
- **Excluded:** Children with any history of typhoid fever or vaccination against typhoid fever in the past year, or those presenting any signs of acute or chronic illness.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Data Collection

Data were collected from both subjects and controls. For all participants, demographic information (age, gender, socioeconomic status) and clinical data (history of present illness, duration of symptoms) were recorded. A complete blood count (CBC) was performed to determine the hemoglobin neutrophil, lymphocyte, and platelet counts. The NLR and PLR were calculated by dividing the absolute neutrophil count by the absolute lymphocyte count and the absolute platelet count by the absolute lymphocyte count, respectively.

Statistical Analysis

Data were entered into an Excel spreadsheet and analyzed using Epi Info™ 7.2 software. Continuous variables were described using means and standard deviations or medians and ranges, as appropriate. Unpaired student's t-test and the Mann-Whitney U test were used for normally and non-normally distributed data, respectively. Pearson's correlation test was used to find out correlation between hematological indices in typhoid fever. The chi-square test was employed for categorical data. A p-value of less than 0.05 was considered statistically significant.

RESULTS

The present study investigated the effect of inflammatory response in children with typhoid fever on various hematological parameters emphasizing on Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR).

[Table 1] details the demographic characteristics of the study participants, categorizing them into subjects (children diagnosed with typhoid fever) and controls (healthy children). Both groups are comparable in age and gender distribution, with the mean age for subjects was 9.4 ± 2.6 years and for controls 10.4 ± 3.0 years , and gender distribution showing 41.81% males in subjects and 50.9% in controls, evidenced by p-values of 0.31 and 0.33 respectively, indicating no significant differences. However, a notable variance is observed in socioeconomic status; 61.8% of subjects are from low socioeconomic backgrounds compared to 36.4% of controls, with a statistically significant p-value of 0.014. This suggests a potential link between lower socioeconomic status and higher prevalence of typhoid fever, possibly due to reduced access to clean water and adequate healthcare, highlighting the importance of addressing social determinants in managing and understanding the spread of typhoid fever.

[Table 2] highlights the clinical features at presentation of the subjects (children diagnosed with typhoid fever). All the children in the subject group exhibited fever (100%), vomiting (72.7%) and abdominal pain (76.3%), while 65.4% children among subjects were suffering from diarrhea and only 4 children out of all 55 subjects (7.2%) were having symptoms of encephalitis. Anemia was observed in 38 (69.09%) children, 18 (32.7%) children were having leucopenia and thrombocytopenia was seen in 32 (58.18%) children out of 55 subjects.

[Table 3] provides a comparative analysis of Laboratory parameters between the subjects (children diagnosed with typhoid fever) and the controls (healthy children). Mean level of hemoglobin in subjects was 8.95 gm/dl with standard deviation of 2.0, which is significantly lower than the control group where mean hemoglobin is 10.8 gm/dl with standard deviation of 1.8 (p-value<0.001). Subjects also showed statistically significant lower total WBC count with mean 7.01 x 10^9/L and standard deviation of 4.0 than the control group (10.08 ± 1.79 x 10^9/L) with p-value < 0.001. The neutrophil counts for subjects averaged at 3.34 x 10^9/L with a standard deviation of 1.85, which is significantly lower compared to 6.47 x 10^9/L with a standard deviation of 1.46 in controls, indicating a significant inflammatory response in typhoid fever with bone marrow suppression (p-value < 0.001). Platelet counts also followed this trend, with subjects showing lower mean 129.02 x 10^9/L (SD = 63.84) compared to controls at 262.65 x 10^9/L (SD = 70.9), which is highly significant with p-value < 0.001. Conversely, there is no significant difference found in lymphocyte counts in subjects (3.27 x 10^9/L, SD = 2.49) than in controls (3.18 x 10^9/L, SD = 0.85). CRP level showed significant increment in subjects with mean 154.62 mg/L and standard deviation 105.3 compared to the controls (25.85±15.07). These findings highlight the hematological changes associated with typhoid fever, including anemia, leucopenia, neutropenia and thrombocytopenia providing critical insights into the disease's impact on blood parameters.

[Table 4] presents the Neutrophil-Lymphocyte Ratio (NLR), a key inflammatory marker, comparing the subjects (children with typhoid fever) to the controls (healthy children). The mean NLR for the subjects is substantially lower at 1.42, with a standard deviation of 1.19, compared to 2.15 (SD = 0.6) for the controls. The median values further emphasize this difference, with subjects at 0.94 and controls at 2.1, and the range for subjects spans from 0.47 to 6.46, indicating a broader variability than in controls, which ranged from 1.0 to 3.8. This pronounced decrease in NLR among the subjects, yielding a statistically significant p-value of less than 0.001, underscores the enhanced inflammatory response in children suffering from typhoid fever, reinforcing the utility of NLR as a potential diagnostic biomarker for distinguishing between affected and healthy pediatric populations.

[Table 5] shows the Platelet-Lymphocyte Ratio (PLR) across both the groups in the study, reflecting differences in blood parameters in typhoid fever. The mean PLR in the subject group is significantly lower at 60.9, with a standard deviation of 53.09,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

compared to 89.75 (SD = 37.55) in the control group. This variation is also reflected in the median values, with subjects showing a median PLR of 36.4 and controls at 81.63. The range for subjects, spanning from 15 to 265, demonstrates greater variability than in controls, which ranged from 28 to 192. The decreased PLR among the subjects, which is statistically significant with p-value <0.001, illustrates an altered thrombocytic and lymphocytic response in typhoid fever. These findings emphasize PLR's potential as an informative biomarker for detecting inflammatory changes and immune responses specific to typhoid fever in children.

[Table 6] shows correlation of NLR and PLR with CRP. Significant large negative correlation is seen between NLR and CRP, r = -0.62 with P-value <0.001. Significant medium negative correlation is seen between PLR and CRP, r = -0.4 with p = 0.002. Above findings showed higher CRP levels are associated with decrease neutrophil and platelet count in typhoid fever as a result of inflammation and bone marrow suppression effect.

Table 1: Demographic Characteristics of Participants

Characteristic	Subjects (n=55)	Controls (n=55)	P-value
Age (years)			
Mean ± SD	9.4 ± 2.6	10.04 ± 3.0	0.31
Gender			
Male	23(41.81%)	28(50.90%)	0.33
Female	32(58.18%)	27(49.09%)	
Socioeconomic Status			
Low	34 (61.8%)	20 (36.4%)	0.014
Medium	16 (29.1%)	25 (45.5%)	
High	5 (9.1%)	10 (18.2%)	

Table 2: Clinical and laboratory Profile of Subject

Symptoms		Number of participants	Percentage(%)(n=55)
Fever		55	100%
Vomiting		40	72.7%
Abdominal pain		42	76.3%
Diarrhea		36	65.4%
Encephalitis		4	7.2%
Laboraory parameters			
Hemoglobin	Anemia(Hb<11gm/dl)	38	69.09%
Total WBC Count(x10^9/L)	Leucopenia (WBC<4.0x10^9/L)	18	32.7%
Platelet Count (pc)(x10^9/L)	Thrombocytopenia (pc <150 x10^9/L)	32	58.18%

Table 3: Comparison of Laboratory Parameters between subjects and controls

Parameter	Subjects (Mean ± SD)	Controls (Mean ± SD)	P-value
Hemoglobin(gm/dl)	8.95 ±2.0	10.8 ±1.8	<0.001
Total WBC Count(x10^9/L)	7.01±4.0	10.08±1.79	<0.001
Neutrophil Count (x10^9/L)	3.34 ± 1.85	6.47 ± 1.46	<0.001
Lymphocyte Count (x10^9/L)	3.27 ± 2.49	3.18± 0.85	0.79
Platelet Count (x10^9/L)	129.02 ± 63.84	262.65 ± 70.9	<0.001
CRP(mg/L)	154.62±105.30	25.85±15.07	<0.001

Table 4: Neutrophil-Lymphocyte Ratio (NLR)

Group	Mean NLR	Standard Deviation	Median NLR	Range	P-value
Subjects	1.42	1.19	0.94	0.47 – 6.46	<0.001
Controls	2.15	0.6	2.1	1.0 – 3.8	

Table 5: Platelet-Lymphocyte Ratio (PLR)

Group	Mean PLR	Standard Deviation	Median PLR	Range	P-value
Subjects	60.9	53.09	36.4	15 – 265	<0.001
Controls	89.75	37.55	81.63	28 – 192	

Table 6: Correlation of Laboratory Markers in typhoid fever

Laboratory Marker	Pearson Correlation coefficient	P-value
NLR and CRP	-0.62	< 0.001
PLR and CRP	-0.40	0.002

ISSN (O): 2687-5365; ISSN (P): 2753-6556

DISCUSSION

Our study demonstrates various haematological effects as a result of systemic inflammation and bone marrow suppression with special reference to Neutrophil-lymphocyte ratio and platelet-lymphocyte ratio in the children with typhoid fever.

In this study total 55 subjects with 55 controls were enrolled. Mean age of children in subjects was 9.4 ± 2.6 and in control 10.04 ± 3.0 .There were 32 (58.18%) female and 23(41.81%) male in subject group while 27 (49.09%) female and 28 (50.9%) male in control group. Out of 55 subjects 34 (61.8%) children were from lower socioeconomic class compared to 20 (36.4%) children from control group and the difference is statistically significant with p – value<0.05. Similar findings have been shown in the study by Devaranavadagi et al.,where 51% children with typhoid fever were from lower socioeconomic class.[17] This supports the previous work, who found that poor sanitation and limited access to clean water are strong predictors of typhoid prevalence in low-income populations.[18] Our study underscores the need for improved public health infrastructure and access to clean water in these communities to reduce the burden of typhoid fever.

Our study reported fever was present in all the children (100%) followed by abdominal pain (76.3%), vomiting (72.7%), diarrhea (65.4%) and only 4 (7.2%) children suffered from encephalitis in the subject group. A study by Kapoor JP et al. also reported almost similar results, in their study most common presentation was fever (100%), followed by vomiting(47%), abdominal pain(38%),loose motion (13%) and headache(5%).[19] Our study observed anemia in 38 (69.09%), leucopenia in 18 (32.7%) and thrombocytopenia in 32 (58.18%) children. Nearly similar findings have been reported in the study by Devaranavadagi et al.,they reported anemia 16%, leucopenia 34%, neutropenia 40% and thrombocytopenia 15% among study participants.[17]

Typhoid fever is a disease, if left untreated can lead to serious complications. Bone marrow evaluation in typhoid patients often shows granulocytic hyperplasia with hemaphagocytosis, it's severity correlates with peripheral blood cytopenia followed by hemaphagocytosis.[20]. Bone marrow suppression and hemophagocytosis are considered to be an important mechanism in producing hematological changes.[6] In our study we found statistically significant lower mean hemoglobin level in subjects than the controls. Mean haemoglobin in subjects was 8.95 ± 2.0 gm/dl and in the control was 10.8 ± 1.8 gm/dl. We also observed leucopenia (mean total WBC count 7.01 ± 4.0 x 10^9/L), neutropenia (mean neutrophil count 3.34 ± 1.85 x 10^9/L), and thrombocytopenia (mean platelet count 129.02 ± 63.84 x 10^9/L) in subject group when compared to mean total WBC count 10.08 ±1.79 x 10^9/L , mean neutrophil count 6.47 ± 1.46 x 10^9/L and mean platelet count 262.65 ± 70.9 x 10^9/L in control group respectively, the difference is statistically significant with p-value<0.001. Mean CRP is also increased in the subject group (154.62 ± 105.3 mg/L) compared to the controls (25.85 ± 15.07 mg/L) with p-value<0.001. Similarly, in a study by Yap et al.showed anemia in 13%, leucopenia in 16% & thrombocytopenia in 32% of the participants in their study.[21] According to Yaramis A et al., they observed leucopenia in 18% & thrombocytopenia in 10% of subjects.[22] Another study by Malik et al. showed thrombocytopenia in 26% of typhoid fever subjects in Malasian children[23]. Likewise, Ifeanyi et al. also reported reduced PCV, reduced neutrophil count and relatively raised lymphocyte count in typhoid patients.[6] Same as our study Choo et al. observed higher CRP level with mean 43 mg/L in culture positive typhoid patients.[24] These results are consistent with our study indicates the response to systemic infection and inflammation in typhoid fever.

Our findings indicate that both NLR and PLR are significantly decreased in children with typhoid fever compared to healthy controls. The pathomechanism of neutropenia in typhoid fever is complex and includes the presence of endotoxins, cytokines including tumor necrosis factor (TNF), interleukin 6 (IL-6), and interferon γ (IFN-γ) contributing to increased hemophagocytosis. All these inflammatory mediators lead to upregulation of endothelial adhesion molecules and a shift of peripheral granulocytes to endothelium.[25,26] These mechanism is responsible for bone marrow suppression and cytopenia in typhoid fever. In this study mean NLR (1.42 ± 1.19) is significantly lower in subjects than the controls (2.15 ± 0.6), p–value<0.001. PLR also showed significant decline in subjects with mean 60.9 ± 53.09 than the controls (mean 89.75 ± 37.55), p–value<0.001. Contrary to our findings other studies showed increased NLR and PLR in various other non-salmonella bacterial infection. They argued that NLR elevation reflects an acute immune response where neutrophils are elevated due to their role in fighting infection, while lymphocytes are relatively decreased due to physiological stress. Further increased PLR in their study indicates the role of platelets in the body's response to infection and inflammation, as platelets are not only involved in hemostasis but also play a part in the body's immune response.[15,16] Thus decreased NLR and PLR in typhoid subjects in this study further verify the mechanism of bone marrow suppression and hemophagocytosis in children specific to typhoid fever.

We also observed decreased NLR values were associated with increased CRP value. Strong negative correlation was seen between NLR and CRP{r = -0.62, p<0.001}, and moderate negative correlation is seen between PLR and CRP {r = -0.40 , p=0.002} in the subject group, suggestive of increased level of inflammation in typhoid patients

ISSN (O): 2687-5365; ISSN (P): 2753-6556

leads to bone marrow suppression and cytopenia which can lead to further complications.

The statistical significance of the differences in NLR and PLR between subjects and controls in our study provides a robust argument for the use of these markers in the early diagnosis of typhoid fever. Furthermore, the implications of our findings for clinical practice are significant. It can be suggested that routine blood tests, which include complete blood counts, could be utilized more effectively along with clinical features for the preliminary screening of typhoid fever in endemic regions before confirmatory testing. This approach could facilitate earlier intervention and management, can significantly improve outcome in affected children.

Our study adds to the growing body of evidence that supports the use of hematological indices such as NLR and PLR as valuable tools in the diagnosis and management of typhoid fever in pediatric populations. Future research should focus on longitudinal studies to track the variations in these indices over the course of the illness and their potential role in monitoring treatment efficacy.

CONCLUSION

This study underscores the potential of Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) as effective hematological indices for diagnosing typhoid fever in children. The significant differences in these ratios between subjects of typhoid fever and healthy controls highlight their utility as non-invasive, cost-effective, and readily available diagnostic tools. The findings also emphasize the need for considering socio-economic factors in the management and prevention strategies of typhoid fever, particularly in resource-limited settings. While, the current results are encouraging for the use of NLR and PLR in early diagnostic protocols, potentially leading to timely and improved patient management and outcomes, future studies should be conducted with longitudinal designs and larger, more diverse populations to fully establish the diagnostic and prognostic value of these hematological markers in typhoid fever.

Limitations

While the findings of this study are promising, there are several limitations that must be acknowledged. First, the reliance on the Widal test for diagnosing typhoid fever in subjects presents a challenge due to its variable sensitivity and specificity, which can lead to potential misclassification of subjects and controls. Second, the study's cross-sectional design limits the ability to establish causality between hematological indices and typhoid fever progression or outcome. Additionally, the sample size, although sufficient for initial investigations, may not fully capture the variability and potential outliers in a broader population. Furthermore, the study did not account for the duration of illness prior to hospital presentation, which could influence the hematological parameters significantly. Finally, as the study was conducted in a single geographical area, the findings may not be generalizable to other settings with different epidemiological profiles of typhoid fever.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556