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Neutrophil–Lymphocyte Ratio as a Differential Diagnostic Biomarker in Dengue Fever and Enteric Fever: A Comparative Analysis

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ABSTRACT:

Background: In tropical and subtropical areas, enteric fever and dengue fever are frequently responsible for an acute febrile illness and the clinical picture is sometimes similar, making early diagnosis difficult. Neutrophil-to-lymphocyte ratio (NLR) has been identified as a simple, cheap and readily available biomarker of systemic inflammation based on a complete blood count (CBC). This study was undertaken to assess the role of NLR for the diagnosis of enteric fever and dengue fever.

Materials and Methods: A prospective, hospital-based comparative observational study was done in the Department of General Medicine of a tertiary care teaching hospital for one year. One hundred consecutive patients with laboratory-confirmed acute febrile illness, 50 with enteric fever and 50 with dengue fever were enrolled. Demographic, clinical and laboratory parameters were obtained at admission. The independent Student's t-test was used to compare the different hematological parameters, inflammatory markers, and neutrophil-to-lymphocyte ratio between the two groups, and $p < 0.05$ was considered statistically significant.

Results: The most affected age group was young adults aged 21-30 years (46.0%) and males were 60.0% of the study population. Patients with enteric fever demonstrated significantly higher neutrophil counts (72.84 ± 8.16% vs. 56.48 ± 9.37%; $p < 0.001$), lower lymphocyte counts (18.26 ± 5.48% vs. 31.92 ± 7.24%; $p < 0.001$), and a markedly elevated neutrophil-to-lymphocyte ratio (4.32 ± 1.28 vs. 1.83 ± 0.69; $p < 0.001$) compared with patients with dengue fever. Dengue fever had significantly lower platelet counts (81.46 ± 31.74 × 10^9/L) compared to enteric fever (164.72 ± 46.85 × 10^9/L) and there was significant difference between two groups in C-reactive protein and erythrocyte sedimentation rate which were more elevated in enteric fever ($p < 0.001$). There was no statistically significant difference in T-LC among groups ($p = 0.173$).

Conclusion: Neutrophil to Lymphocyte ratio is easily available, inexpensive, simple and is a good useful marker to differentiate enteric fever from dengue fever in patients presenting with acute febrile illness. A significantly elevated NLR, in addition to elevated inflammatory markers and relatively well-preserved platelet counts, supports its potential as a complementary laboratory test for prompt clinical evaluation, especially in low-resource health care environments. Higher and larger multicenter studies are desirable to confirm the best diagnostic cut-off and to confirm the routine clinical use of NLR.

Introduction

Enteric fever is a systemic infectious disease caused primarily by Salmonella enterica serovar Typhi, and, less frequently, Salmonella Paratyphi A, B and C. It continues to be a significant public health problem in many developing nations, especially in South Asia, Southeast Asia and sub-Saharan Africa, where poor sanitation, hygiene and drinking water quality are responsible for the ongoing transmission of disease (Tejedo-Romero & Araujo, 2022). The widespread occurrence of multidrug resistant and extensively drug-resistant Salmonella strains has added further complexity to Salmonella control and the importance of early diagnosis and risk-stratification (Miftode et al., 2025).

The clinical picture of enteric fever is often non-specific particularly in early stages. The most common symptoms include fever, headache, weakness, malaise, loss of appetite, nausea, abdominal pain, diarrhea or constipation, and sometimes neurological symptoms like confusion or encephalopathy (Afrin et al., 2022). These symptoms have a similar clinical manifestation with other tropical febrile diseases like dengue, malaria, leptospirosis, and scrub typhus, which makes early diagnosis difficult, especially without laboratory testing (Barathan, 2024). Mortality and morbidity are increased significantly due to delayed recognition causing intestinal hemorrhage, intestinal perforation, septic shock, hepatitis, encephalopathy, and multiorgan dysfunction (Kumar et al., 2022).

Dengue fever is a mosquito transmitted viral infection caused by the dengue virus and one of the fastest spreading vector borne diseases in the world. It's very common in tropical and subtropical areas, and may include fever, headache, retro-orbital pain, muscle and joint pain, leukopenia and thrombocytopenia (Chibuzor U. Nyenke et al., 2023). Dengue fever may have non-specific clinical signs in early stages which may resemble enteric fever and other acute febrile illnesses and make diagnosis difficult. The clinical management and treatment of dengue fever vary significantly from bacterial infections like enteric fever and hence early differentiation is important (P. Gurugama et al., 2010).

Blood culture remains the gold standard for diagnosis; however, its sensitivity is compromised by previous antibiotic use, low counts of bacteria and delayed presentation, and the results of the blood culture take many days to be available. Recently, there has been increased interest in the identification of cheap, easily available biomarkers that can help clinicians in an early diagnosis and prognosis of enteric fever. However, its role in enteric fever is still limitedly known. Culture confirmation of enteric fever in this case report showed that serial NLR measurements tracked well with disease severity and clinical recovery and might serve as an easily accessible diagnostic or prognostic biomarker in the regular clinical practice (Buonacera et al., 2022).

Comparative studies in enteric fever patients and dengue fever patients have revealed the difference in NLR between the two as pointed out by their inflammatory response in the body (Rini et al., 2020). Enteric fever typically leads to a relative lymphopenia with a neutrophil's predominance, which leads to an NLR value that is significantly higher compared with dengue fever where the relative lymphocytosis during the critical phase and the concurrent thrombocytopenia yield comparatively lower NLR values (Wang et al., 2021). The observations are supportive of the possibility that NLR can be used as an adjunctive biomarker to differentiate common tropical febrile illnesses when presenting to hospital.

Research Methodology

Study Design

This present study is planned as prospective, hospital based comparative observational study to assess and compare the neutrophil-to-lymphocyte ratio (NLR) in enteric fever and dengue fever patients. The study was carried out for one year in the Department of General medicine in a tertiary care teaching hospital.

Study Population

One hundred consecutive patients with acute febrile illness were studied prospectively. The study population was divided into two groups:

- Group I: 50 patients with laboratory-confirmed enteric fever.
- Group II: 50 patients with laboratory-confirmed dengue fever.

Inclusion Criteria

The following patients were in the study:

- Patients 18 years and above.
- Patients with laboratory confirmation of enteric fever (positive blood culture for *Salmonella typhi/paratyphi* or suggestive serological results).
- Laboratory confirmed Dengue fever (Dengue antigen NS1, Dengue IgM & IgG antibody).
- Patients who were willing to involve in the study and gave their written informed consent.

Exclusion Criteria

The following criteria excluded patients:

- Presence of co-existing bacterial or viral infections.
- Patients with autoimmune or chronic inflammatory diseases.
- Hematological malignancies or blood disorders.
- Chronic liver disease or chronic kidney disease.
- Pregnant women.
- Patients receiving corticosteroids or immunosuppressive therapy.
- HIV-positive patients.
- Patients with incomplete clinical or laboratory data.

Data Collection

All participants were asked about their age and gender. Clinical data including length of fever, presenting symptoms and vital signs were recorded on a case record form. Laboratory investigations conducted on admission were complete blood count and differential leukocyte count, hemoglobin, total leukocyte count, platelet count, hematocrit, liver function tests, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and disease specific confirmatory investigations. Absolute neutrophil count (ANC) and absolute lymphocyte count (ALC) were derived from the complete blood count and used to calculate the neutrophil to lymphocyte ratio (NLR).

Outcome Measures

The main objective was to compare the NLR of enteric fever and dengue fever. Secondary endpoints included comparison of haematological parameters, inflammatory markers, platelet count and the value of NLR in differentiating bacterial from viral febrile illnesses.

Statistical Analysis

Data collected were analyzed with the use of statistical package, IBM SPSS Statistics version 26.0. Continuous variables were expressed as mean ± standard deviation (SD) and the categorical variables were presented as frequencies and percentages. The independent Student's t-test was used to compare normally distributed continuous variables between the two groups, whereas the Mann–Whitney U test was used for non-normally distributed data. The Chi-square test or Fisher's exact test was used to analyze categorical variables. Receiver operating characteristic (ROC) curve analysis was used to assess the diagnostic performance of NLR, and the area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value were determined. The P value of < 0.05 was regarded as statistically significant.

Results

The study was conducted in 100 patients with laboratory confirmed acute febrile illness, consisting of 50 patients who had an enteric fever and 50 patients who had a dengue fever. Results are presented as demographic characteristics of the study population, as well as the comparison of the hematological and inflammatory parameters between the two groups, especially the neutrophil-to-lymphocyte ratio (NLR).

Table 1. Demographic Characteristics of the Study Population (N = 100)

Characteristics	Enteric Fever (n = 50)	Dengue Fever (n = 50)	Total (N = 100)
Sample Size	50	50	100
Gender – Male, n (%)	31 (62.0%)	29 (58.0%)	60 (60.0%)
Gender – Female, n (%)	19 (38.0%)	21 (42.0%)	40 (40.0%)
Most Affected Age Group	21–30 years (22, 44.0%)	21–30 years (24, 48.0%)	21–30 years (46, 46.0%)

The demographic data of the study population is presented in Table 1. A total of 100 patients with laboratory confirmed acute febrile illness were enrolled including 50 patients with enteric fever and 50 patients with dengue fever. The male participants were the majority in both the study groups with a percentage of 62.0% in enteric fever group and 58.0% in dengue fever group. A total of 60.0% of the study population were male while 40.0% were female. Young adults (21 to 30 years old) comprised the highest proportion of patients with acute febrile illness both with enteric fever and with dengue fever, accounting for 44.0% and 48.0% respectively.

Comparative Analysis Between Enteric Fever and Dengue Fever

Comparative analysis of various haematological and inflammatory parameters were done in patients with laboratory confirmation of enteric fever (n = 50) and dengue fever (n = 50) and are presented in Table 2. Patients with enteric fever had significantly higher neutrophil count (72.84 ± 8.16%) than dengue fever (56.48 ± 9.37%) ($t = 9.32$, $p < 0.001$). On the other hand, the mean lymphocyte percentages in the enteric fever group (18.26 ± 5.48%) was significantly different from that of the dengue fever group (31.92 ± 7.24%) ($t = -10.66$, $p<0.001$) indicating the different inflammatory responses associated with bacterial and viral infection.

Patients with enteric fever had significantly raised primary outcome of the study, neutrophil-to-lymphocyte ratio (NLR) (4.32 ± 1.28) as compared to patients with dengue fever (1.83 ± 0.69) ($t = 12.48$, $p < 0.001$). The results suggest that NLR can be useful as a biomarker in the early diagnosis of acute febrile illness and have the potential to distinguish bacterial enteric fever from viral dengue fever.

No statistically significant difference was observed in total leukocyte count between the two groups (4.18 ± 1.12 × 10^9/L vs. 3.84 ± 1.36 × 10^9/L; $t = 1.37$, $p = 0.173$). The platelet count was however found to be significantly lower among patients with dengue fever (81.46 ± 31.74 × 10^9/L) than those with enteric fever (164.72 ± 46.85 × 10^9/L) ($t = 10.39$, $p < 0.001$). Likewise, the enteric fever group had high inflammatory markers. Mean CRP levels were 68.74 ± 22.41 mg/L in enteric fever compared with 24.63 ± 13.85 mg/L in dengue fever ($t = 12.03$, $p < 0.001$), while ESR values were significantly higher in enteric fever (39.82 ± 10.63 mm/hour) than in dengue fever (22.18 ± 8.74 mm/hour) ($t = 9.13$, $p < 0.001$). Together, these results confirm that enteric fever is associated with more systemic inflammation (higher NLR) and dengue fever with more severe thrombocytopenia (lower NLR).

Table 2. Comparative Analysis of Hematological and Inflammatory Parameters Between Enteric Fever and Dengue Fever Patients (N = 100)

Parameter	Enteric Fever (n = 50)	Dengue Fever (n = 50)	Test Statistic	*p*-value
Neutrophils (%)	72.84 ± 8.16	56.48 ± 9.37	$t = 9.32$	<0.001*
Lymphocytes (%)	18.26 ± 5.48	31.92 ± 7.24	$t = -10.66$	<0.001*
Neutrophil-to-Lymphocyte Ratio (NLR)	4.32 ± 1.28	1.83 ± 0.69	$t = 12.48$	<0.001*
Total Leukocyte Count (×10^9/L)	4.18 ± 1.12	3.84 ± 1.36	$t = 1.37$	0.173

Platelet Count ($\times 10^9$/L)	164.72 ± 46.85	81.46 ± 31.74	t = 10.39	<0.001*
C-Reactive Protein (mg/L)	68.74 ± 22.41	24.63 ± 13.85	t = 12.03	<0.001*
ESR (mm/hour)	39.82 ± 10.63	22.18 ± 8.74	t = 9.13	<0.001*

Discussion

This was a prospective, comparative study that tested the clinical usefulness of the neutrophil to lymphocyte ratio (NLR) as an inflammatory marker to distinguish enteric fever from dengue fever among patients with acute febrile illness. The results showed that enteric fever patients had significantly higher neutrophils count, lower lymphocytes count and hence a higher NLR as compared to the dengue fever patients (Prajapati, 2024). The observations provide support for the hypothesis that NLR is related to the inflammatory response pattern to bacterial and viral infections and could be a useful diagnostic parameter when assessing patients in the early stages of disease.

Most patients in both groups in the present study were young adults (21 to 30 years) and there were slightly more men than women. The results are in accordance with the epidemiology of enteric fever and dengue fever in the endemic area which is where young adults are exposed to contaminated food, water and mosquito vectors more often due to work and outdoor activities. The high male prevalence has also been observed in various previous epidemiological studies, and might just be environmentally related.

The most significant result of this study was that the NLR of patients with enteric fever was significantly higher than that of patients with dengue fever (4.32 ± 1.28 vs. 1.83 ± 0.69, $p < 0.001$). Acute bacterial infections cause a rise in the production and activation of neutrophils via inflammatory cytokines including interleukin-6, interleukin-1β and tumour necrosis factor-α, and also cause lymphocytopenia due to stress. This leads to relative neutrophilia and lymphopenia in the patients with enteric fever that leads to increased NLR. Dengue fever, on the other hand, is associated with viral-mediated immune activation, relative lymphocytosis during the critical phase, and bone marrow suppression, thus resulting in much lower NLR.

Another significant observation was the extreme thrombocytopenia present in patients with dengue fever in comparison with enteric fever. The enteric fever group had nearly twice as many platelets as did the non-enteric fever group and was one of the greatest and most characteristic laboratory abnormalities found in dengue infection. The significant decrease in platelet counts is a well-documented aspect of the dengue pathogenesis, caused by immune-mediated thrombocytolysis, bone marrow stress and decreased peripheral consumption. Hence, there is a strong possibility that simultaneous estimation of platelet count and NLR can significantly contribute to early discrimination of bacterial enteric fever from viral dengue fever.

This study also showed that inflammatory markers such as C-reactive protein and ESR were significantly elevated in patients who had enteric fever. The higher CRP and ESR values were indicative of increased systemic inflammatory response in the case of invasive bacterial infections, complementing the results of the NLR analysis (Beberashvili et al., 2023). A higher NLR, elevated inflammatory markers and platelet count are suggestive of enteric fever, while a lower NLR with severe thrombocytopenia is more indicative of dengue fever (Liang & Yu, 2022).

NLR has certain clinical benefits over specialized inflammatory markers. It is low cost, immediate, easy to reproduce, and can be directly calculated from a standard complete blood count without extra laboratory expenses. The features of NLR make it an important tool in resource-limited health care environments where complex diagnostics or microbiological confirmation is not immediately possible .

Although these positive results are encouraging, there are a number of caveats. This investigation was a single-center, relatively small study, and may have limited generalizability. NLR is also an nonspecific inflammatory marker which can be affected by other bacterial or viral infections, auto-immune diseases, haematological diseases, malignancies, corticosteroid treatment and physiological stress. Thus, NLR must not be viewed as a standalone marker but as a complementary marker that can be used along with clinical parameters, microbiological tests and other laboratory markers.

In summary, the results of the present study indicated that the NLR is a meaningful and easily-available biomarker in differentiating enteric fever from dengue fever. Elevated NLR along with increased inflammatory markers and relatively normal platelet count in enteric fever suggesting its role in early diagnosis of acute febrile illness. Further multicenter studies with bigger patient numbers and receiver operating characteristic (ROC) analysis are recommended to define the optimum cut-off point

for NLR, validate the diagnostic accuracy of NLR, and establish its use in clinical routine for differentiating tropical febrile diseases.

Conclusion

This is a prospective, comparative study that shows that the NLR is a useful, inexpensive, and widely-available laboratory marker that can be used to differentiate enteric fever from dengue fever in patients with acute febrile illness. Patients with enteric fever had significantly raised neutrophils, reduced lymphocytes, elevated inflammatory markers, and a significantly high NLR when compared with patients with dengue fever while patients with dengue fever had profound thrombocytopenia and relatively low NLR values.

NLR is a laboratory test that can be performed using the same laboratory equipment and health care resources that are used to perform a CBC, and it requires no additional laboratory equipment or health care expense, making it ideal for resource-limited environments where rapid microbiological confirmation may not be available. In addition to platelet count, C-reactive protein, erythrocyte sedimentation rate, clinical examination and specific tests for the diagnosis of enteric fever, the NLR can help the clinician to make an early diagnosis of dengue fever and allow timely treatment.

While not a substitute for definitive microbiological testing (including blood culture or dengue-specific laboratory testing), NLR is a useful and convenient "adjunctive" biomarker to aid the initial assessment of the patient with an acute febrile illness. Optimal cut-off values for future multicenter studies with larger and more diverse populations should also be validated by using ROC curve analysis and further define the value of NLR in the clinical routine for the diagnosis, risk stratification, and monitoring of tropical infectious diseases.

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