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Original Article

Pathology Section

Navigating the Haematological Maze: Unraveling the Role of NLR and PLR as Predictors of Dengue Severity- A Cross-sectional Study from Southern India

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ABSTRACT

Introduction: Dengue Fever (DF) poses a critical public health threat in tropical regions, displaying a spectrum of manifestations without distinct diagnostic hallmarks. Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) are useful biomarkers of inflammation and prognostic markers in various diseases. The inflammation that occurs in dengue is due to the exaggerated response of the immune system.

Aim: To assess the utility value of NLR and PLR as prognostic markers for dengue severity.

Materials and Methods: A cross-sectional study was conducted on 99 admitted Dengue patients. Patients were grouped into three categories: DF, Dengue Haemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). Various parameters of Complete Blood Count (CBC), NLR, and PLR were compared among the groups using Analysis of Variance (ANOVA) test (p-value <0.05 considered significant). Sensitivity, specificity, and accuracy were calculated using Receiver Operating Characteristic (ROC) curve.

Results: Among the 99 patients, 63.6% exhibited thrombocytopenia (platelet count <1.5 lac/dL), and 7% of patients had a platelet count <20,000/dL. All DHF and DSS patients had thrombocytopenia. Leucopenia was evident in 45.45% of patients, with 6% having a Total Leukocyte Count (TLC) <2000/dL. TLC remained stable across these stages. The mean NLR in DF was 2.47 (range 0.1-15.4), in DHF it was 1.013 (range 0.2-3.2), and in DSS it was 0.41 (range 0.08-0.65.17) with a p-value of 0.02. The PLR displayed substantial differences, with mean values of 134.4 (range 10.1-273.8) for DF, 50.57 (range 7.1-96.1) for DHF, and 10.39 (range 3.1-38.8) for DSS with a p-value of 0.003. NLR had 63% accuracy, 77.8% sensitivity, and 94.4% specificity. PLR had 81.5% accuracy, 93.3% sensitivity and 33.3% specificity.

Conclusion: The specificity of NLR was higher, while PLR exhibited superior accuracy and sensitivity in detecting severe cases.

Keywords: Dengue haemorrhagic fever, Mosquito-borne, Prognosis, Shock syndrome

INTRODUCTION

The DF is a tropical emergency for the public health sector worldwide [1-3]. In parts of Southern India such as Tamil Nadu, Andhra Pradesh, Karnataka, and Kerala, Dengue is a major cause of mortality and morbidity [4-6]. Dengue is a mosquito-borne virus disease transmitted to human beings from the bite of an infected *Aedes aegypti* and *Aedes albopictus* mosquito. The dengue virus belongs to the family *Flaviviridae* [7,8]. Dengue virus causes headache, fever, functional dyspepsia, anorexia, arthralgia, rash, nausea, and emesis [6-8]. Mostly, dengue is treated symptomatically by rural physicians. Complications such as an increase in mortality arise when dengue is not properly treated [7,8]. According to the World Health Organisation (WHO) (2011) "Comprehensive Guidelines for Prevention and Control of Dengue and Dengue Haemorrhagic Fever," haematological parameters, platelet count, and haematocrit are important biological indicators for diagnosing dengue infection [9].

A recent study has shown that NLR is a prognostic biomarker in cardiovascular diseases, infections, inflammatory diseases, and various types of cancers. Its application in the context of dengue has not been comprehensively explored. The PLR is another marker of inflammation used in predicting inflammation as well as mortality [10]. A lower PLR has been associated with DF, with thrombocytopenia being a crucial finding in DF [11]. Despite extensive research on dengue, there is a notable gap in the literature regarding specific prognostic markers that can facilitate early identification and management of severe cases, especially in resource-limited rural healthcare settings. While current diagnostic and management practices mainly rely on symptomatic treatment, there is a need for more targeted and reliable indicators to assess disease severity and guide therapeutic interventions. Thus, this study aims to address this gap by investigating the potential of NLR and PLR as novel prognostic markers for DF. This investigation holds potential implications for refining clinical strategies, particularly in regions where dengue is endemic, and may pave the way for a more targeted approach to DF management.

MATERIALS AND METHODS

A cross-sectional study was conducted on 99 dengue patients who were admitted to the Department of General Medicine and Emergency at Chettinad Hospital and Research Institute, a tertiary care centre, Kelambakkam, Tamil Nadu, India, between May 2023 and November 2023 with ethical committee approval (IHEC-I/1480/22).

Inclusion criteria: People over the age of 18 with a history of fever and patients who had a positive dengue NS1Ag/IgG/IgM antibody were included in the study.

Exclusion criteria: Patients with pancytopenia secondary to causes such as chronic liver disease, blood component transfusion, administration of immunosuppressive drugs, steroids, and haematological disease and patients aged below 18 years were excluded from the study.

Sample size estimation: Cross-sectional study

n=1.96 ^ 2* (0.10) (1-0.10)/0.06 ^ 2=97~100,

Where, z=1.96 (i.e.,) 95% confidence interval.

Population proportion=0.10 [12] and

E (Precision)=06%

Methodology: This study was conducted on 99 dengue patients admitted to the General Medicine or Emergency department. Both oral and written consent were obtained from the patients. Other information regarding demographic parameters like age, gender, and relevant clinical history was collected. About 2 mL of blood was collected in a plain vacutainer (red topped) for the serological tests and 3 mL in an EDTA vacutainer for CBC. The serum was separated by centrifugation from a plain vacutainer and was used for the rapid card and ELISA. The serum samples were aliquoted into Eppendorf vials and stored in the deep freezer at -20°C in case they could not be processed on the same day. The samples were subjected to Immunochromatography (ICT) and ELISA to detect NS1 antigen, IgM, and IgG antibodies. The ICT cards used were SD Biosensor, Cassette Duo Rapid Card Test, and for ELISA, Micro Lisa J Mithra testing was used. The procedures were followed according to the manufacturer's instructions. Blood samples in the EDTA vacutainer were run in Beckman Coulter LH 780 for obtaining complete blood counts, and samples with critical counts were smeared and examined. Patients with positive dengue serology were grouped into three groups: DF, DHF, and DSS based on the clinical history using the WHO criteria [13].

NLR and PLR were estimated for each subject as per the formulas given below:

NLR=Neutrophil%/Lymphocyte%

PLR=Platelet Count/Absolute Lymphocyte Count

Various parameters such as complete blood count, NLR, and PLR were compared among the groups.

STATISTICAL ANALYSIS

Mean±SD were calculated for continuous variables and frequency tables for categorical variables. After confirming the normality check, parametric tests were used. ANOVA was used to assess the differences in continuous variables across the different severity groups. Chi-square was used to analyse associations between categorical variables and severity grade. Sensitivity and specificity were calculated using ROC curve analysis with Statistical Package for Social Sciences (SPSS) software, version 27.0.

RESULTS

After applying the predefined criteria for inclusion and exclusion, the study encompassed a cohort of 99 patients whose ages ranged from 18 to 60 years [Table/Fig-1], comprising 46 males and 53 females. The distribution of dengue severity among the patients is shown in [Table/Fig-2].

Age group (years)	n (%)
18-25	48 (48.49)
26-35	20 (20.20)
36-45	19 (19.19)
46-55	7 (7.07)
56-60	5 (5.05)

[Table/Fig-1]: Patient distribution based on age group.

Severity grade of dengue	n (%)
Dengue Fever (DF)	72 (72.72)
Dengue Haemorrhagic Fever (DHF)	18 (18.18)
Dengue Shock Syndrome (DSS)	9 (9.10)

[Table/Fig-2]: Patient distribution based on severity.

Among the 99 patients, 63.6% exhibited thrombocytopenia (platelet count <1.5 lac/dL), and 7% of patients had a platelet count <20,000/dL. Notably, all patients diagnosed with DHF and DSS presented with thrombocytopenia, underscoring its consistent prevalence in these severe stages of dengue infection. Leucopenia (TLC less than 4000/dL) was evident in 45.45% of patients. A 6% of patients had TLC <2000/dL. Among these, 33 patients with DF, 10 with DHF, and two with DSS demonstrated leucopenia [Table/Fig-3].

Parameters	DF (72), n (%)	DHF (18), n (%)	DSS (9), n (%)
White Blood Cell (WBC) count			
2000-4000/dL	30 (41.66)	7 (38.88)	2 (22.22)
<2000/dL	3 (4.16)	3 (16.66)	0
Total	33 (45.8)	10 (55.5)	2 (22.2)
Platelet count			
50000-1.5 lac/dL	30 (41.67)	15 (83.33)	1 (1.11)
21000-50000/dL	4 (5.55)	2 (11.11)	4 (44.44)
<20000/dL	2 (2.78)	1 (5.55)	4 (44.44)
Total	36 (50)	18 (100)	9 (100)

[Table/Fig-3]: Incidence of leucopenia and thrombocytopenia in dengue patients.

The TLC remained stable across these stages, with mean values of 4755 cells/dL ranging from 1900 to 10500 cells/dL for DF, 4533.3 cells/dL ranging from 1600 to 9600 cells/dL for DHF, and 5733 cells/dL ranging from 2800 to 11400 cells/dL for DSS [Table/Fig-4].

Parameters	DF (72) Mean±SD	DHF (18) Mean±SD	DSS (9) Mean±SD	p-value
Haemoglobin (gm/dL)	12.8±2.1	11.9±3.4	14.2±1.9	0.16
Haematocrit (%)	38.7±6.1	37.6±5.4	42.2±5.6	0.17
Total Leukocyte Count (TLC) (cells/dL)	4755±2295	4533.3±2461	5733±2825	0.87
Neutrophil (%)	51.45±19.3	37.7±15.7	26.5±9.6	0
Eosinophil (%)	1.8±0.9	1.3±0.8	0.7±0.4	0.33
Basophil (%)	0.3±0.2	0.2±0.2	0.2±0.2	0.33
Lymphocyte (%)	38.9±19.1	51.75±19.6	67.6±11.3	0
Monocyte (%)	7.8±3.6	8.9±4.0	4.3±2.4	0.33
Platelet (cells/dL)	1.56±0.76	0.71±0.26	0.33±0.21	0
Neutrophil to Lymphocyte Ratio (NLR)	2.47±1.32	1.013±0.8	0.41±0.18	0.02
Platelet to Lymphocyte Ratio (PLR)	134.94±95.6	50.57±20.1	10.39±3.1	0.003

[Table/Fig-4]: CBC values among the dengue groups.

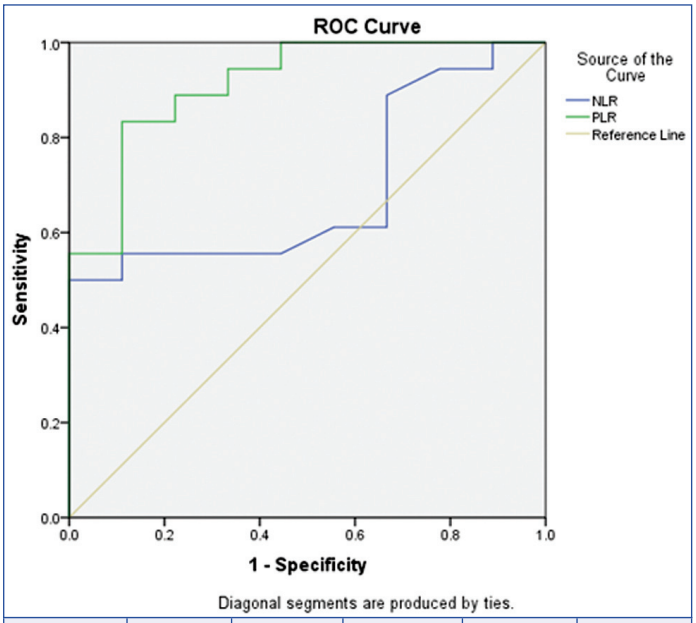
Notably, the percentages of neutrophils exhibited significant differences, with DF showing a higher mean of 51.45% (9-88%) compared to DHF at 37.7% (16-63%) and DSS at 26.5% (8-38%). Distinct variations were also observed in the percentages of lymphocytes with means of 38.9% (9-90%) for DF, 51.75% (19-78%) for DHF, and notably higher at 67.6% (56-91%) for DSS [Table/Fig-4]. The mean NLR in DF was 2.47, ranging from 0.1 to 15.4; in DHF, it was 1.013, ranging from 0.2 to 3.2; and in DSS, it was 0.41, ranging from 0.08 to 0.65. The distribution of NLR among the groups is depicted in [Table/Fig-5].

NLR	DF	DHF	DSS
<0.4	7 (9.7%)	7 (38.8%)	3 (33.3%)
0.4-0.79	16 (22.2%)	2 (11.1%)	6 (66.7%)
0.8-1.19	8 (11.1%)	4 (22.2%)	0
1.2-1.59	8 (11.1%)	3 (16.6%)	0
1.6-1.99	7 (9.7%)	1 (5.5%)	0
2 or more	26 (36.1%)	1 (5.5%)	0
Total	72	18	9

[Table/Fig-5]: Distribution of NLR in DF, DHF, and DSS.

The observed differences in NLR among the groups are statistically significant with a p-value of 0.001. The AUC for NLR is 0.69. NLR

had higher specificity and lower sensitivity compared to PLR. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of NLR are depicted in [Table/Fig-6].



Parameters	Accuracy (%)	Sensitivity	Specificity	Positive predictive value	Negative predictive value
NLR	63	77.8	94.4	77.8	33.3
PLR	81.5	93.3	33.3	77.8	88.9

[Table/Fig-6]: ROC and comparison of NLR with PLR.
AUC for NLR-0.69 and for PLR-0.91

Haemoglobin levels demonstrated slight variances, with mean values of 12.8 g/dL (7.7-15.1 g/dL) for DF, 11.9 g/dL (8-15 g/dL) for DHF, and a slightly elevated value of 14.2 g/dL (11.1-16 g/dL) for DSS. Similar trends were evident in Haematocrit percentages with mean values of 38.7% (23.5-48.5%) for DF, 37.6% (26.7-50.1%) for DHF, and a somewhat higher mean of 42.2% (36-49%) for DSS [Table/Fig-4]. Eosinophil percentages remained relatively consistent across the stages, with mean values of 1.8% (0-9%) for DF, 1.3% (0-6%) for DHF, and 0.7% (0-3%) for DSS [Table/Fig-4]. Furthermore, the PLR displayed substantial differences, with mean values of 134.94 (10.1-273.8) for DF, 50.57 (7.1-96.1) for DHF, and notably lower at 10.39 (3.1-38.8) for DSS. The distribution of PLR among the groups is depicted in [Table/Fig-7]. The observed differences in PLR among the groups are statistically significant with a p-value of 0.00001. The AUC for PLR is 0.91. PLR had higher accuracy, sensitivity, and negative predictive value compared to NLR. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of PLR are depicted in [Table/Fig-6].

PLR	DF	DHF	DSS
<20	7 (9.7%)	7 (38.9%)	8 (88.9%)
21-40	7 (9.7%)	1 (5.5%)	1 (11.1%)
41-60	3 (4.2%)	5 (27.8%)	0
61-80	10 (13.9%)	1 (5.5%)	0
>81	45 (62.5%)	4 (22.3%)	0

[Table/Fig-7]: Distribution of PLR in DF, DHF, and DSS.

DISCUSSION

The DF, a viral illness transmitted by *Aedes* mosquitoes, is known for its diverse clinical presentations, making its diagnosis a complex task. It is an emergency for the public health sector around the tropical part of the world [1-3], especially in southern parts of India, where dengue is one of the major causes of mortality and morbidity [4-6]. The disease can manifest in various forms, ranging from mild to severe, without distinct hallmarks that facilitate immediate diagnosis. The severity of dengue is traditionally classified into three categories: DF, DHF, and DSS.

In this study, the male-to-female ratio is 0.86:1 with a slight female preponderance. However, in most studies, a male preponderance was observed [14-16]. The majority of the patients were between 18-25 years (48.5%), which correlates with the study done by Yuditya DC and Sudirgo I who had the majority of patients between 17 and 25 years [12].

Platelet count: In this study, it has been observed that a substantial proportion of dengue patients (63%) experienced thrombocytopenia. Castilho BM et al., found thrombocytopenia in 40% of cases in their study [17]. Notably, all patients diagnosed with DHF and DSS exhibited thrombocytopenia, aligning with the findings of Agrawal VK et al., which independently associated low platelet counts with severe dengue (p-value <0.0001) [7]. Thrombocytopenia may result from the destruction of peripheral platelets or bone marrow megakaryocytes by viruses, consequently reducing platelet production [18].

Total leucocyte count: Dengue infection is commonly associated with leukopenia, which is a potent marker of the critical phase of illness. In the critical phase of DF, there is a decline in leukocyte count [19]. This study revealed that 46% of patients experienced leukopenia. This finding was consistent with the research conducted by Gitika G et al., who reported leukopenia in 43% of patients, and Patel MK and Patel HJ who found a similar condition in 25% of their cases [6,20]. However, the total white blood cell count did not demonstrate any statistically significant differences among the three study groups, mirroring the pattern observed in platelet counts. The leukopenia observed in cases of dengue infection was hypothesised to be a result of the destruction or inhibition of myeloid progenitor cells. This hypothesis was based on findings from bone marrow examinations, which indicated mild hypocellularity during the initial seven days of fever, followed by a return to normal cellularity in the convalescent phase [21].

Neutrophil to Lymphocyte Ratio (NLR): An interesting facet of the study is the significant decline in the NLR as the severity of dengue increased. This observation parallels the results of Modampuri AK et al., study, where a statistically significant correlation was established between bleeding and shock occurrences and a decrease in NLR among dengue patients [22]. Furthermore, Sadgir A et al., research concluded that NLR bears a substantial relationship with the severity of DF in adult patients. Their findings suggested that monitoring NLR could provide insights into disease prognosis and severity [23]. Neutropenia arises from viral infection, prompting neutrophils to undergo apoptosis. The positive correlation between the apoptosis rate of neutrophils and the severity grade of the disease supports the protective role of neutrophils in the antiviral response, as noted by Galani IE and Andreakos E [24]. In the critical phase of dengue infection, there is a decrease in neutrophils more than lymphocytes, changing the NLR. This indicates an upcoming critical phase of DF, which is associated with plasma leakage. This is a relatively early change that precedes the changes in platelet count and haematocrit [15]. A relative increase in lymphocyte count, along with atypical lymphocytes, is usually observed in the later febrile stage or during the recovery phase of dengue [15]. This observation was further reinforced by Candra A, showing a relationship between dengue severity grade and heightened inflammation due to an excessive immune response [25]. In essence, a lower NLR ratio corresponds to a more severe disease. Hence, NLR can serve as a valuable prognostic indicator for dengue patients. The NLR shows high specificity (94.4%), suggesting that when the NLR is high, it is good at correctly identifying non-severe cases. The observed sensitivity was 77.8%, indicating that it is moderately effective in correctly identifying severe cases. The observed accuracy was 63%, suggesting that the overall performance may be limited, and there may be some false positives and false negatives.

Platelet to Lymphocyte Ratio (PLR): In the present study, it was observed that PLR exhibited a noteworthy reduction in cases of DHF and DSS. This reduction was attributed to a significant decrease in platelet count, a common feature in severe dengue, along with an increased percentage of lymphocytes compared to neutrophils. PLR has been studied extensively in Coronavirus Disease-2019 (COVID-19) patients, and not many studies have been published in dengue patients. In a meta-analysis on COVID-19 patients by Simadibrata DM et al., high PLR levels on admission were associated with severe COVID-19 cases [26]. In the present study, PLR has a higher accuracy (81.5%) compared to NLR. The sensitivity (93.3%) was high, indicating that it is effective in correctly identifying severe cases. However, the specificity (33.3%) is low, suggesting that it may also generate a significant number of false positives. The high NPV (88.9%) indicates that when PLR is high, it is reliable in ruling out severe cases. However, in a study by Agrawal S et al., NLR and Neutrophil to Lymphocyte and Platelet ratio were compared in dengue patients for assessing the severity. They found NLR was a better predictor of outcome compared to neutrophil to lymphocyte and platelet ratio [11].

Limitation(s)

The study was conducted at a single tertiary care centre with a modest sample size of 99 patients, underscoring the need for larger-scale investigations. Collaborative efforts across multiple centres would enhance the robustness and generalisability of these findings. The study predominantly focuses on inpatients within the Department of General Medicine and Emergency. Future research should strive for a more comprehensive representation of both inpatient and outpatient populations.

CONCLUSION(S)

NLR exhibited high specificity for identifying non severe dengue cases. Its moderate sensitivity and overall accuracy suggest limitations with potential false results. On the other hand, PLR displayed superior overall accuracy and sensitivity, making it effective in identifying severe cases. These insights could contribute to the timely identification and management of severe dengue cases if used in correlation with the clinical condition, ultimately improving patient outcomes in resource-limited settings.

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