DOI: 10.7860/JCDR/2023/65292.18658

Original Article

Internal Medicine Section

Significance of Neutrophil-lymphocyte Ratio, Neutrophil-platelet Ratio, and Neutrophil-to-lymphocyte and Platelet Ratio in Predicting Outcomes in Dengue Patients on Admission in Wardha, Maharashtra, India: A Retrospective Cohort Study

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ABSTRACT

Introduction: Dengue is an important viral infectious disease, mostly seen in tropical countries during the rainy season, and is emerging as a public health hazard for healthcare facilities. The most common parameters used to assess the severity of dengue are platelet count and haematocrit. However, new haematological parameters have emerged to predict the severity of dengue fever and assist clinicians, especially in resource-limited settings.

Aim: To highlight the significance of Neutrophil-Lymphocyte Ratio (NLR), Neutrophil-Platelet Ratio (NPR), and Neutrophil-to-Lymphocyte and Platelet Ratio (NLPR) in predicting outcomes in patients with dengue infection.

Materials and Methods: A retrospective observational study was conducted in rural central India in the Department of Medicine at Jawaharlal Nehru Medical College, Wardha, Maharashtra, India. A total of 540 patients infected with the dengue virus between June 2021 and December 2021. Data analysis was conducted from January to April 2022. Neutrophil, platelet, and lymphocyte counts were used to calculate NLR, NPR, and NLPR, and their roles in predicting the final outcome were studied. The final analysis was performed using the Statistical Package for Social Sciences (SPSS) software, version 21.0. The p-value <0.05 than 0.05 was considered statistically significant.

Results: The mean age of the patients was 29.85±13.40 years, ranging from 18 to 85 years, with a median age of 25 years. A total of 331 (61.7%) patients below 30 years of age were significantly higher than patients aged 30 years or older (38.3%) (Z=3.39; p=0.0007). The Area Under Curve (AUC) for NLR (0.852) was higher than that for NLPR (0.828) and NPR (0.708). Therefore, NLR was more effective in predicting adverse outcomes compared to NLPR and NPR. However, the efficacies of NLR and NLPR seemed to be more or less equal.

Conclusion: The NLR was a better predictor of outcome or severity in dengue fever when compared to NPR and NLPR. Hence, it can be a cost-effective tool used by physicians working in rural hospitals with limited resources.

Keywords: Complete blood count, Coronavirus disease-2019, Dengue fever, Differential count, Haemogram, Severity

INTRODUCTION

Dengue has emerged as one of the most important vector-borne diseases globally, with increasing incidence throughout the world. It is estimated that more than two-fifths of the world's population resides in areas endemic for dengue, and approximately 2% are infected annually [1]. Previously, dengue was thought to be a disease primarily affecting urban areas. However, with unplanned urbanisation, exponential population growth, and improved transportation, favourable environments for the dengue fever vector Aedes aegypti have developed [2]. Dengue has also become a matter of concern in rural areas of India, posing challenges for healthcare providers who need to manage this condition in resource-limited areas, where the at-risk population is often unaware of the warning signs and potential complications of dengue [3].

To mitigate the mortality and morbidity associated with dengue infection, it is important to understand the clinical profile of the disease, along with the laboratory parameters of dengue fever. An important indicator of dengue infection is the complete blood count. World Health Organisation (WHO) criteria (2011) define that certain components of the complete blood count, such as leukocytes, platelets, and haematocrit, are important for determining the clinical development of dengue [4]. Platelet count and haematocrit are commonly used as indicators of dengue infection, while leukocyte count is less commonly used [5]. Neutrophils and lymphocytes make up 80% of the leukocytes and play an active role in the body's response to inflammation and infection, allowing for an immune response to be inferred from the proportion of these two cell types [6]. NLR is also an important marker of inflammation that may be used in dengue fever; however, there are limited studies regarding its use in dengue fever [7]. The platelet-to-lymphocyte ratio is another marker of inflammation that has been used in predicting inflammation as well as mortality [8]. A lower platelet-to-lymphocyte ratio has been linked to dengue fever, with thrombocytopenia being an important finding in dengue fever.

There have been only a few studies conducted on the use of the neutrophil-to-lymphocyte and platelet ratios as indirect markers of inflammation and sepsis, particularly in viral infections [5-7]. Recently, some readily available parameters from routine complete blood counts, such as NLR, NPR, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, and mean platelet volume-to-platelet count ratio, have been investigated as potential biomarkers in bacterial sepsis. However, the results have been mixed, and there is no consensus yet regarding their accuracy and clinical usefulness [8-10].

Therefore, these ratios can potentially serve as potent markers of inflammation in both bacterial and viral infections, indicating more severe infection or adverse outcomes. The present study was conducted to highlight the significance of NLR, NPR, and NLPR in predicting outcomes in patients with dengue infection.

MATERIALS AND METHODS

A retrospective observational study was conducted in rural central India in the Department of Medicine at Jawaharlal Nehru Medical College in Wardha, Maharashtra, India, from June 2021 to December 2021. All analysis and study compilation were conducted during the period from January to April 2022. The study was conducted after receiving approval from the Institutional Ethics Committee (IEC), with certificate number DMIMS(DU)/IEC/2021/1230. All the patients enrolled for dengue infection were diagnosed using the BIOLINE dengue duo rapid test (Non-structural antigen 1 and immunoglobulin IgM/IgG). The data used for the present study was retrieved from the medical records of all the patients who were admitted during that period for dengue fever and fulfilled the inclusion criteria.

Inclusion criteria: The study population consisted of adult patients (18 years old and above) infected with the dengue virus, confirmed by Nonstructural protein 1 (NS1) antigen or IgM antibody positive for dengue, from June 2021 to December 2021 were included in the study.

Exclusion criteria: Patients with a past history of dengue or any other arbovirus infection, paediatric patients, pregnant patients, patients with chronic renal failure, malignancy, chronic liver diseases such as cirrhosis, immunodeficient states such as long-term corticosteroid therapy/organ transplantation or acquired immune deficiency, and other autoimmune and inflammatory diseases were excluded from the study.

Study Procedure

The complete data for the patients' complete blood counts who met the inclusion criteria was extracted from the Coulter reports. The parameters included in the study were Haemoglobin (Hb), Red Blood Cell (RBC), White Blood Cells (WBC), and its components such as neutrophil, lymphocyte, platelet, Mean Corpuscular Volume (MCV), haematocrit, Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), and Red Cell Distribution Width (RDW).

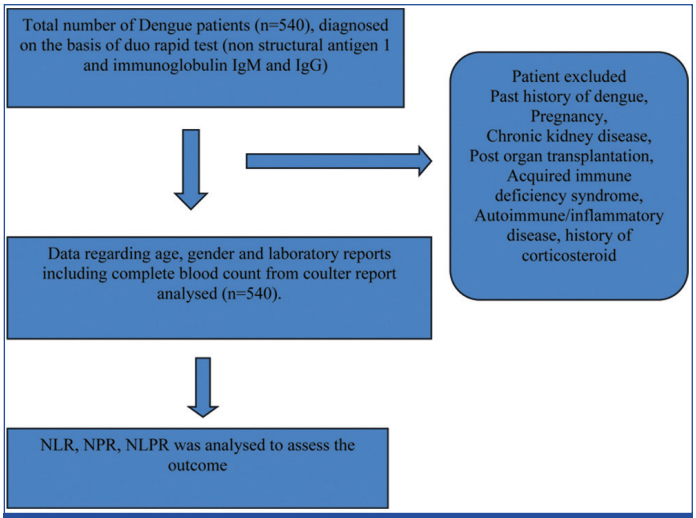
Clinical parameters, including age, sex, symptoms, and laboratory results collected upon admission, were retrieved.

Sample size calculation: The NLR was calculated by dividing the absolute count for neutrophils by the absolute count for lymphocytes. NPR was calculated as neutrophil count ($\times 10^9$ L)×1000/platelet count ($\times 10^9$/L). Finally, NLPR was calculated using the following formula: NLPR: (Neutrophil count×100)/(Lymphocyte count×Platelet count) [11]. The flow diagram of the study is highlighted in [Table/Fig-1].

The primary outcome of the study was to assess the severity or final outcome (death and discharge) in dengue patients based on NLR, NPR, and NLPR. The secondary outcome was to assess the diagnostic accuracy, sensitivity, and specificity of these parameters in dengue patients.

STATISTICAL ANALYSIS

Descriptive statistical analysis was performed to calculate the means with corresponding Standard Deviations (SD). A test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference in proportions, and a Chi-square test was performed to find associations. The Receiver Operating Characteristic (ROC) curve was used to find the Area Under the Curve (AUC), followed by the Youden method to determine the cut-off value of different parameters for outcomes. A p-value of <0.05 was considered statistically significant. The statistical analysis was conducted using



[Table/Fig-1]: Flow diagram of the study.

SPSS software, version 21.0, manufactured by International Business Machine (IBM), Chicago, United States of America (USA).

RESULTS

A total of 540 patients with dengue fever were included in the present observational study. The mean age of the patients was 29.85±13.40 years, with a range of 18-85 years and a median age of 25 years. There were significantly more patients below the age of 30 years (331 patients, 61.7%) compared to patients aged 30 and above (209 patients, 38.3%) (Z=3.39, p=0.0007). The mean age of male patients was 29±12.4 years, while that of female patients was 31.6±14.9 years. The proportion of male patients (330 patients, 61.1%) was significantly higher than that of female patients (210 patients, 38.9%) (Z=3.11, p=0.0018). Other baseline parameters of patients with dengue fever are highlighted in [Table/Fig-2].

Parameters	Mean±SD	Median	Range
Age (in years)	29.85±13.40	25	18-85
Male	330 (61.1%)		(Z=3.11; p=0.0018*)
Female	210 (38.9%)		
Hb (gm%)	13.20±2.16	13.4	4.5-18.9
RBC (mL/cumm)	4.72±0.83	4.78	1.3-7.1
WBC (cmm)	5379.70±4558.31	4400	240-50500
MCV (g/dL)	84.22±27.36	83	3.3-663.0
MCH (g/dL)	28.85±11.09	28.3	16.3-266.0
MCHC (g/dL)	33.91±2.62	33.9	26.2-82.9
RDW (fL)	14.40±2.14	14	3.1-33.7
Neutrophil (%)	64.86±13.40	65	11-92
Lymphocyte (%)	28.48±13.46	29.4	3.9-80.0
Platelet (lac/cumm)	1.26±0.96	1.11	0.1-9.6
NLR (%)	0.33±0.28	0.22	0.0-2.4
NPR (%)	110.59±136.23	57.36	4.7-937.5
NLPR (%)	533±765.8	259.5	4.5-6412

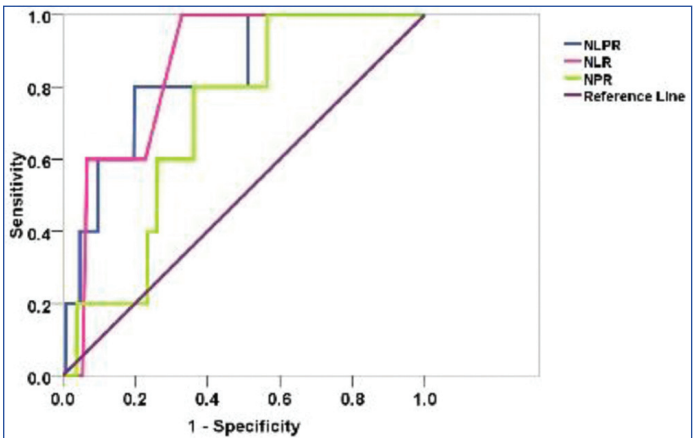
[Table/Fig-2]: Parameters of the patients with dengue fever.
Hb: Haemoglobin; RBC: Red blood cell; WBC: White blood cells; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; RDW: Red cell distribution width; NLR: Neutrophil-lymphocyte ratio; the NPR: Neutrophil-Platelet ratio; and NLPR: Neutrophil-to-lymphocyte and platelet ratio. Test of proportion was used to find the Standard Normal Deviate (Z) to compare the difference proportions and p-value was calculated to find the significance

Neutrophil count, lymphocyte count, and NLR were significantly associated with the outcome (p<0.001). However, the association of platelet count and NPR with the outcome was statistically insignificant (p=0.10, p=0.044, respectively). A comparison of various parameters among patients who died during treatment versus discharged patients is highlighted in [Table/Fig-3]. The AUC for NLR was higher than the AUC for NLPR and NPR, indicating that NLR was more

effective in predicting adverse outcomes. However, the efficacies of NLR and NLPR were similar. The area under the ROC curve for NLR in predicting adverse outcomes (death) was 0.852, while it was 0.828 for NLPR and 0.708 for NPR, as shown in [Table/Fig-4]. NLR had the highest diagnostic accuracy of 90.93% with a sensitivity of 60% and specificity of 91.2%. NLPR had the lowest diagnostic accuracy of 53.15% with a sensitivity of 80% and specificity of 52.90%, as shown in [Table/Fig-5].

Parameters	Outcome	Mean±SD	t-value	p-value
Age	Died during treatment (n=5)	27.40±7.30	0.75	0.50 NS
	Discharged alive (n=535)	29.87±13.44		
Hb	Died during treatment (n=5)	11.84±2.92	1.05	0.35 NS
	Discharged alive (n=535)	13.21±2.15		
RBC	Died during treatment (n=5)	3.97±0.97	1.76	0.15 NS
	Discharged alive (n=535)	4.73±0.83		
WBC	Died during treatment (n=5)	6180.00±5373.73	0.34	0.75 NS
	Discharged alive (n=535)	5372.22±4555.26		
MCV	Died during treatment (n=5)	87.90±13.45	0.61	0.58 NS
	Discharged alive (n=535)	84.19±27.46		
MCH	Died during treatment (n=5)	30.14±5.19	0.55	0.61 NS
	Discharged alive (n=535)	28.84±11.14		
MCHC	Died during treatment (n=5)	34.22±1.38	0.50	0.65 NS
	Discharged alive (n=535)	33.91±2.62		
RDW	Died during treatment (n=5)	15.46±2.96	0.81	0.46 NS
	Discharged alive (n=535)	14.39±2.14		
Neutrophil	Died during treatment (n=5)	81.00±5.48	6.47	<0.001 S
	Discharged alive (n=535)	64.71±13.36		
Lymphocyte	Died during treatment (n=5)	14.00±5.48	5.81	<0.001 S
	Discharged alive (n=535)	28.62±13.45		
Platelet	Died during treatment (n=5)	0.81±0.47	2.13	0.10 NS
	Discharged alive (n=535)	1.26±0.96		
NLR (%)	Died during treatment (n=5)	0.66±0.26	2.92	0.04 S
	Discharged alive (n=535)	0.33±0.28		
NPR (%)	Died during treatment (n=5)	162.93±161.35	0.73	0.51 NS
	Discharged alive (n=535)	110.10±136.05		
NLPR (%)	Died during treatment (n=5)	507.5±259	0.02	0.04 S
	Discharged alive (n=535)	533.4±769		

[Table/Fig-3]: Comparison of parameters of the patients died during treatment versus discharged patients.
S: Statistically significant; NS: Statistically not significant; Hb: Haemoglobin; RBC: Red blood cell; WBC: White blood cells; MCV: Mean corpuscular volume; MCH: Mean corpuscular haemoglobin; MCHC: Mean corpuscular haemoglobin concentration; RDW: Red cell distribution width; NLR, the NPR, and the NLPR: Neutrophil-to-lymphocyte and platelet ratio



[Table/Fig-4]: Sensitivity and specificity.

DISCUSSION

According to estimates by the WHO, the rates of dengue infection have increased significantly by thirtyfold in the last five decades.

Parameter	Diagnostic accuracy (%)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
NLR	90.93	60.00	91.21	6.00	99.59
NPR	75.19	40.00	75.51	1.50	99.26
NLPR	53.15	80.00	52.90	1.56	99.65

[Table/Fig-5]: Different parameters with their diagnostic accuracy, sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV).

This increase can be attributed to its complex pathophysiology, ecological problems, and economic issues [12].

In the present study, the proportion of males (330, 61.1%) was found to be significantly higher than that of females (210, 38.9%). This difference may be due to male members of rural families engaging more in outdoor activities, thus being more exposed to the mosquito vector for dengue. Similar findings were also reported by Patil PS et al., where 59.3% of dengue patients were male, and by Gupta E et al., where the frequency of dengue fever was higher in males than females in Delhi, India [13,14]. In the present study, the mean age of the patients was 29.85±13.40 years, with a median age of 25 years. A total of 331 (61.7%) patients were below the age of 30, significantly higher than the patients aged 30 and above (38.3%). Different findings were reported by Patil PS et al., where the majority of dengue patients belonged to the age group of 31-40 years, and by Yuditya D and Sudirgo I, where the majority of dengue patients belonged to the age group of 17 to 25 years [13,15].

Dengue infection is commonly associated with leukopenia, which in turn is a potent marker of the critical phase of illness. In the critical phase of dengue fever, there is a decline in leukocyte count, generally below 5000 cells/mm^3 [15]. This is also associated with a change in the neutrophil count, such that the neutrophil count decreases more than lymphocytes, further changing the NLR [15]. This indicates an upcoming critical phase of dengue fever, 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]. The decrease in neutrophil count or neutropenia results from viral infection leading to apoptosis of neutrophils. Another theory suggests that neutrophils encapsulate platelets positive for dengue viral antigen through neutrophil extracellular traps, signifying that neutropenia seen in dengue patients may be a defense mechanism of the host against the dengue virus [16].

Thrombocytopenia is a common laboratory finding in dengue fever. It usually reaches its peak in the critical phase of dengue fever and then resolves in the recovery phase. Thrombocytopenia seen in dengue fever can result from increased destruction of platelets or a decrease in the production of platelets by the bone marrow. Another mechanism of thrombocytopenia can be immune-mediated destruction of platelets coated with antibodies. This is due to the cross-reactivity among antibodies formed against NS1 antigen and platelets [17]. One of the other postulated mechanisms is complement-mediated platelet clearance [18].

The NLR, NPR, and neutrophil-lymphocyte-platelet ratio calculated in the present study were 0.33±0.28, 110.59±136.23, and 533±765.8, respectively. The AUC was highest for NLR, making it the best marker out of the three for predicting the outcome in dengue fever. It had a diagnostic accuracy of 90.93%, sensitivity of 60%, and specificity of 91.21%. The findings of the present study were similar to the study conducted by Yuditya D and Sudirgo I, where NLR was significantly associated with dengue severity (p-value=0.000, p<0.05) [15]. However, different findings were reported by Athira PP et al., where there was no significant difference in NLR between dengue and non dengue patients [19].

In a study conducted by Osuna-Ramos JF et al., it was concluded that NLPR had low diagnostic accuracy in Coronavirus Disease-2019 (COVID-19) and dengue fever (57.14%). Their study revealed

that NLPR was independently associated with COVID-19 with a good fit predictive value (p=0.1041). The NLR (AUC=0.88, 95% CI=0.84-0.91) was able to discriminate COVID-19 from dengue with high sensitivity and specificity values (above 80%) [20]. In the present study as well, a high diagnostic accuracy of NLR (90.93%) and NPR (75.19%) but low diagnostic accuracy of NLPR (53.15%) was seen in predicting the outcome of dengue fever.

Another important aspect of the present study was the increased NLR (0.66±0.26; p<0.04 significant) seen in adverse outcomes compared to discharged patients. This contrasts the findings of Yuditya D and Sudirgo I, where it was reported that a lower NLR is associated with higher severity of dengue fever [15]. The present might be explained by the fact that neutropenia occurs around the fifth day of admission [21], and the complete blood count in the present study was taken upon admission. Therefore, initially, a high NLR is seen in dengue fever, which eventually gets reversed. This study signifies that an initial high NLR on admission is also associated with adverse outcomes in dengue fever. Further studies conducted on a large scale can help verify the findings of the present study, thereby establishing NLR as an early marker of adverse outcomes in dengue fever.

Limitation(s)

The sample size of the current study was relatively small, requiring further studies with a larger sample size to validate the findings. Additionally, the complete blood count could not be repeated serially due to the retrospective observational study design.

CONCLUSION(S)

The NLR is an important early predictor of outcome in dengue fever, which can be used by physicians in rural set-ups to decide upon admission criteria or for the decision of referral to equipped centres, as changes in white blood cells precede changes in platelet counts and haematocrit.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: May 08, 2023
- Manual Googling: Aug 03, 2023
- iThenticate Software: Aug 30, 2023 (9%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **May 07, 2023**
Date of Peer Review: **Aug 02, 2023**
Date of Acceptance: **Sep 02, 2023**
Date of Publishing: **Nov 01, 2023**