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Jimenez, AMD, Tiu, JM. Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as Early Predictive Markers of Dengue Severity in Pediatric Patients: A Retrospective Analysis
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ORIGINAL ARTICLE

NEUTROPHIL-TO-LYMPHOCYTE RATIO (NLR) AND PLATELET-TO-LYMPHOCYTE RATIO (PLR) AS EARLY PREDICTIVE MARKERS OF DENGUE SEVERITY IN PEDIATRIC PATIENTS: A RETROSPECTIVE ANALYSIS

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ABSTRACT

Objective: To determine whether neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) within the first three days of dengue illness are independent predictors of dengue severity among pediatric patients.

Methodology: A cross-sectional analytical retrospective study was conducted among pediatric dengue patients admitted to The Medical City, Pasig from September 2021 to August 2024. Data collection was done through electronic chart review. Baseline characteristics were analyzed using the Kruskal-Wallis test, Chi-Square test, and Fisher's exact test. Receiver Operating Characteristic (ROC) and Area Under the Curve (AUC) analyses, along with diagnostic performance metrics, were used to evaluate daily ratio cut-offs differentiating dengue classifications. Multivariable logistic regression was performed to assess NLR and PLR as independent predictors of warning signs or severe dengue development.

Results: Among the 316 subjects included in the analysis, 40.5% had dengue fever without warning signs, 57.3% had dengue fever with warning signs, and 2.2% had severe dengue. Differentiating patients without warning signs from those with warning signs, the NLR cut-offs were 4.73, 2.07, and 2.5 on days 1-3, respectively, whereas from those with severe dengue, the cut-offs were 1.27, 0.68, and 0.47 on the same days. For this pairwise analysis, PLR cut-offs were 170, 233.92, and 208.79 for the first comparison; and 209.24, 244.12, and 187.5 for the second, respectively. Statistical analysis showed poor discrimination and diagnostic performance for all cut-offs. Likewise, multivariable linear regression revealed no significant correlation between either ratio and dengue severity.

Conclusion: NLR and PLR within the first three days of dengue illness revealed poor performance in predicting the development of warning signs or progression to severe dengue among pediatric patients.

KEYWORDS: *Dengue fever; Dengue warning signs; Dengue severity; Neutrophil-to-lymphocyte ratio (NLR); Platelet-to-lymphocyte ratio (PLR)*

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The authors declare that the data presented are original material and has not been previously published, accepted or considered for publication elsewhere; that the manuscript has been approved by all authors, and that the authors have met the requirements for authorship.

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INTRODUCTION

Dengue fever remains a significant global health challenge, especially in endemic areas such as the Philippines. While most cases are self-limiting, some patients develop warning signs and progress to severe dengue. According to international and local guidelines, the presence of any warning sign warrants the need for hospitalization.[1-3] Furthermore, although warning signs usually precede clinical deterioration, cases without warning signs may abruptly lead to severe dengue, albeit rarely. Therefore, early recognition of dengue severity that allows for timely appropriate interventions is crucial in preventing morbidity and mortality.

The disease presents with a wide spectrum of clinical manifestations.[1] This undeniably presents a significant challenge in underdeveloped areas that lack adequately trained healthcare workers and accessible tertiary care facilities. These settings could benefit from early predictive markers of dengue outcomes that will aid in decision-making regarding the need for urgent hospitalization. These markers should be simple, cost-effective, and widely accessible to maximize their benefits, especially in these areas. Conversely, in settings where resources are readily available, triaging dengue patients at the time of presentation poses a different challenge. While dengue is relatively simple to diagnose, early identification of patients who are likely to progress to severe disease is not always an easy task. Ideally, based on guidelines, dengue patients who do not exhibit any warning signs may be managed at home.[1-2] However, some clinicians prefer to admit patients without warning signs on a case-to-case basis for closer monitoring of possible severe outcomes. Seeing this dilemma, clinicians could benefit from early markers of dengue severity to guide them to a more rational approach to management at the early stages of the disease. Ultimately, these could help decrease the number of unnecessary hospitalizations, thereby improving resource allocation not only for the patient and his family but for healthcare institutions as well.

With such benefits of an early predictive marker of dengue severity, studies investigating laboratory parameters that serve this purpose prove to be significant. Traditionally, the complete blood count (CBC) has been a widely available and cost-effective diagnostic tool that is used along with clinical manifestations to determine the progression and severity of dengue illness. Particularly, trends in hematocrit, white blood cell count, and platelet count have been correlated with disease progression.[1-3] In recent studies, the roles of novel inflammatory markers in predicting dengue severity have emerged. Among these are the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which are both readily available given a simple CBC. Recent literature on the utility of these markers, however, lacks studies in the local setting as well as those specifically among the pediatric population. In line with this, the objective of this research is to determine whether early NLR and PLR derived from CBC taken within the first three days of dengue illness are independent predictors of dengue severity among pediatric patients.

MATERIALS AND METHODS

Research Design

This research is a cross-sectional analytical retrospective study conducted among pediatric dengue patients in The Medical City, Ortigas, Pasig City.

Study Population

The study population consisted of inpatient pediatric patients (i.e., below 19 years of age) with discharge diagnosis of any of the following dengue classifications: (1) dengue fever without warning signs; (2) dengue fever with warning signs; or (3) severe dengue.

Inclusion Criteria

All pediatric patients who were admitted to The Medical City, Ortigas, Pasig City from September 2021 to August 2024 and subsequently discharged with a diagnosis of dengue fever were initially screened for inclusion. Only those with laboratory-confirmed diagnosis through a positive dengue NS1 or IgM test, and at least one CBC taken by day 3 of fever onset, were eventually included in the study.

Exclusion Criteria

All patients with secondary diagnoses during admission, any clinically significant pre-existing illness (e.g., currently on maintenance medications, such as steroids), and/or any antibiotic use within the past three months of admission were excluded from the study.

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Data Collection

The list of all patients who satisfied the population description was retrieved from the census of the Institute of Pediatrics and the Medical Records department of The Medical City. Retrieval of data was conducted within the hospital through its electronic medical record system.

The data on demographics, medical history, and laboratory results were collected. The age, sex, weight, height, body mass index (BMI), comorbidities, previous dengue infection, and dengue vaccination status were recorded for analysis of baseline characteristics.

The CBC of each subject on day 1, day 2, and day 3 of fever onset were recorded, and the NLR and PLR values were calculated for each available CBC. For any subject with more than one CBC taken within the same day of illness, only the earliest CBC for that day was recorded.

For this study, the subjects were grouped under their respective dengue severity classification based on their discharge diagnosis, regardless of the admitting assessment. As an example, those who were admitted as dengue fever without warning signs, but later progressed to severe dengue, were classified under the severe dengue group.

Statistical Analysis

Descriptive statistics were used to summarize the clinico-demographic characteristics of the study sample. The Kolmogorov-Smirnov normality test was used to determine normally distributed variables. Mean and standard deviation were to be utilized for normally distributed interval/ratio variables, and median and interquartile range (IQR) for non-normally distributed interval/ratio variables. Frequency and proportion were used for categorical variables (nominal/ordinal).

To compare the baseline characteristics across the three dengue severity classifications, the Kruskal-Wallis test was used for continuous data. For categorical variables, analysis was done using the Chi-Square test, or Fisher's exact test when Chi-Square assumptions were not met.

To further evaluate the utility of NLR and PLR, the Receiver Operating Characteristic (ROC) curve analysis for day 1, day 2, and day 3 of dengue illness was utilized. This analysis was used to determine the Area Under the Curve (AUC), reflecting the overall diagnostic accuracy of NLR and PLR in predicting dengue severity. Optimal cut-off points were identified based on the Youden Index. ROC analysis was done in RStudio using the 'cutpointr' function.

The diagnostic performance of the determined NLR and PLR cut-off points was assessed based on the following metrics: sensitivity, specificity, positive and negative predictive values (PPV and NPV), positive and negative likelihood ratios (+LR and -LR), and overall accuracy. These metrics were calculated using the cross-tabulations derived from R version 4.4.1 (R Foundation for Statistical Computing, Vienna, Austria) and MedCalc version 23.0.5 (MedCalc Software Ltd., Ostend, Belgium) calculators for diagnostics.

Multivariable logistic regression was utilized to confirm NLR and PLR as an independent predictor of more severe dengue outcomes (i.e., dengue fever with warning signs, and severe dengue). Logistic regression was presented for crude and adjusted odds ratios (OR). Daily NLR and PLR were each used as the main exposure per model and were adjusted with the baseline clinico-demographic characteristics. This analysis was done using IBM SPSS for Windows version 29 (IBM Corp., Armonk, NY, USA).

All valid data were included in the analysis. Missing variables were neither replaced nor estimated, hence different variables had different sample sizes.

Ethical Considerations

Upon approval of the research protocol by the Institutional Review Board (IRB), permission to access the patients' electronic medical records was obtained from the chief information officer of The Medical City. Research data was encoded in a password-encrypted file using Microsoft Excel for Mac, version 16.96 (Microsoft 365, Microsoft Corp., Washington, USA), with all identifiable information given a code number, made accessible only to the authors and statistician. A master list linking the code numbers and subject identities is kept separately and is only accessible to the primary investigator. No identifying data shall appear in any report or publication of this study. The research records will be stored for at least three years following completion of this research. These measures are strictly implemented to protect data confidentiality in adherence to the Data Privacy Act of 2012.

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RESULTS

Subject Selection

A total of 525 pediatric patients were admitted from September 2021 to August 2024 and were subsequently discharged with a diagnosis of dengue fever. Those with no laboratory confirmation of dengue, no CBC taken by day 3 of fever, and/or with undocumented temperature on the onset of fever were not included in the subsequent charts review. Out of the remaining 407 subjects, 91 were excluded as they had at least one of the following: a secondary diagnosis during admission; any clinically significant pre-existing illness (e.g., currently on maintenance medications, such as steroids); or any antibiotic use within the past three months. After applying the inclusion and exclusion criteria, a total of 316 subjects remained for analysis. These included 128 (40.5%) patients diagnosed with dengue fever without warning signs, 181 (57.3%) with dengue fever with warning signs, and 7 (2.2%) with severe dengue (Figure 1).

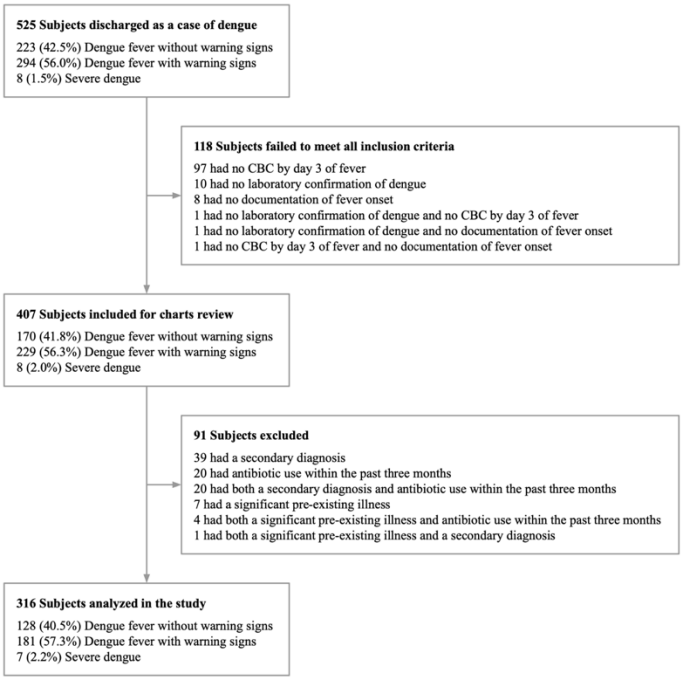

Figure 1. Subject selection flow

Comparing the baseline characteristics, the patient demographics (age, weight, height, BMI, and sex) were statistically similar across the dengue classification groups (Table 1; Table 2). Grossly looking at the distribution of patients with comorbidities, previous dengue infection, and dengue vaccination, all groups recorded the same trend. That is, the majority of each dengue classification group did not have any of these parameters on medical history. Statistically, the actual percentages of patients under each category did not show any significant difference (Table 2).

Table 1. Baseline characteristics across dengue classification groups for continuous variables

Characteristic	DF without WS (n=128; 40.5%)		DF with WS (n=181; 57.3%)		Severe Dengue (n=7; 2.2%)		p-value*
	Median	IQR	Median	IQR	Median	IQR	
Age (years)	11	8.0 - 14.0	12	9.0 - 15.0	12	9.0 - 16.0	0.148
Weight (kg)	45.45	26.0 - 59.5	47	33.8 - 61.2	41.5	25.3 - 58.0	0.237
Height (cm)	151	128.0 - 161.0	151	137.0 - 163.5	158.5	132.0 - 167.0	0.389
BMI (kg/m^2)	20	16.1 - 24.6	20.55	16.9 - 24.4	16.5	14.5 - 20.8	0.238

DF: Dengue fever; WS: Warning signs; IQR: Interquartile range; BMI: body mass index
* Reported from Kruskal-Wallis Test

Table 2. Baseline characteristics across dengue classification groups for categorical variables

Characteristic	Category	DF without WS		DF with WS		Severe Dengue		p-value*
		Count	%	Count	%	Count	%	
Sex	Male	76	59.4	101	55.8	3	42.9	0.572‡
	Female	52	40.6	80	44.2	4	57.1	
Comorbidities	No	101	78.9	127	70.2	6	85.7	0.175†
	Yes	27	21.1	54	29.8	1	14.3	
Previous dengue infection	No	115	89.8	158	87.3	7	100	0.496†
	Yes	13	10.2	23	12.7	0	0	
Dengue vaccination	No	127	99.2	178	98.3	7	100	0.675‡
	Yes	1	0.8	3	1.7	0	0	

DF: Dengue fever; WS: Warning signs
* p-values were based on Chi-Square Tests (†) or Fisher's Exact Test (‡)

Determination and Diagnostic Performance of NLR and PLR Cut-offs

NLR and PLR cut-off points were determined per day of CBC collection, for each pairwise group of dengue classification: dengue fever without versus with warning signs; and dengue fever without warning signs versus severe dengue. ROC analysis was done for each cut-off.

The NLR cut-offs for dengue fever without versus with warning signs were 4.73, 2.07, and 2.5 for days 1 to 3, respectively. Looking at the AUC, day 2 recorded the highest value of 0.603. Nonetheless, this still falls below the acceptable discrimination value of at least 0.70. For dengue fever without warning signs versus severe dengue, the day 1 to 3 cut-offs were 1.27, 0.68, and 0.47, respectively. The AUC values for these cut-offs showed a lower range at 0.3605 to 0.4414, suggesting poor discrimination (Table 3).

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Table 3. Optimal cut-off determination for NLR

Statistic	DF without WS vs. DF with WS			DF without WS vs. Severe Dengue		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Sample	115	205	286	45	92	125
Optimal cut-off	4.73	2.07	2.5	1.27	0.68	0.47
Youden	0.2025	0.1734	0.1323	0.1395	0.092	0.0847
AUC	0.5945	0.603	0.5773	0.3605	0.4414	0.3608
True Positives	33	72	45	2	5	7
False Negatives	39	46	123	0	0	0
False Positives	11	38	16	37	79	108
True Negatives	32	49	102	6	8	10

NLR: Neutrophil-to-lymphocyte ratio; DF: Dengue fever; WS: Warning signs; AUC: Area under the curve

For PLR, the daily cut-offs for dengue fever without warning signs versus dengue fever with warning signs were 170, 233.92, and 208.79. The AUC values were close to each other, ranging from 0.56 to 0.58. Likewise, all the values fall below acceptable discrimination. For dengue fever without warning signs versus severe dengue, the respective cut-offs were 209.24, 244.12, and 187.5 for days 1 to 3. Day 1 recorded the highest AUC at 0.6279 but is still below acceptable discrimination values (Table 4).

Table 4. Optimal cut-off determination for PLR

Statistic	DF without WS vs. DF with WS			DF without WS vs. Severe Dengue		
	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Sample	115	205	286	45	92	125
Optimal cut-off	170	233.92	208.79	209.24	244.12	187.5
Youden	0.1731	0.1394	0.137	0.4884	0.1586	0.1985
AUC	0.5575	0.5777	0.5673	0.6279	0.5218	0.5036
True Positives	56	49	70	2	2	4
False Negatives	16	69	98	0	3	3
False Positives	26	24	33	22	21	44
True Negatives	17	63	85	21	66	74

PLR: Platelet-to-lymphocyte ratio; DF: Dengue fever; WS: Warning signs; AUC: Area under the curve

The optimal cut-offs for NLR and PLR were then analyzed in terms of their diagnostic ability to differentiate dengue fever without warning signs from the more severe dengue classifications – versus with warning signs, and versus severe dengue (Table 5; Table 6).

Using the NLR cut-offs, only 56.52% on day 1, 59.02% on day 2, and 51.4% on day 3 were accurately identified as either dengue fever without or with warning signs. Sensitivity is highest on day 2 at 61.02% and lowest on day 3 at 26.79%. These were below the commonly accepted value of 80%, altogether reflecting a low probability that dengue patients with warning signs will test positive (i.e., NLR above the cut-off). Meanwhile, specificity is highest on day 3, where there is a probability of 86.44% that dengue patients without warning signs will test negative (i.e., NLR below the cut-off). Specificity was lower on days 1 and 2 at 74.42% and 56.32%, respectively, and both were below the commonly accepted value of 80%. The PPV from days 1 to 3 remained relatively consistent, ranging from 65.45% to 75%. These values indicate the percentage of dengue patients with an NLR above the cut-off who actually had warning signs. In essence, around one-fourth were determined to be false positives. The NPV remained low across all days, ranging from 45.07% to 51.58%. This means that more than half of the patients with an NLR below the cut-off actually had warning signs, classifying them as false negatives. The +LR values of 1.4 to 1.99 suggest a minimal impact on increasing the probability of having warning signs when the NLR is above the cut-off. Similarly, the -LR values of 0.69 to 0.85 indicate a negligible decrease in the odds of having warning signs when the NLR is below the cut-off (Table 5).

Moreover, looking at the diagnostic performance of the NLR cut-offs in discriminating between dengue fever without warning signs from severe dengue, the overall accuracy on days 1 to 3 was only 13.6% to 17.78%. All three days recorded 100% sensitivity. However, the wide CI indicates a lack of precision in estimating this statistic. This can be attributed to the noticeably small subgroup of patients diagnosed with severe dengue in this study. While the NLR cut-offs had very high sensitivity, their specificity conversely showed very poor performance at 8.47% to 13.95%. Given the low specificity, low PPV at 5.13% to 6.09% was expected. On the other hand, the high sensitivity relates to high NPV, which was also at 100% on all days. It should be noted, however, that PPV and NPV are dependent on the prevalence of the outcome. Therefore, having only 7 patients with severe dengue (versus 128 cases of dengue fever without warning signs), the PPV and NPV are not reliable indicators of diagnostic performance in predicting severe dengue. In terms of likelihood ratios, the +LR values at 1.09 to 1.16 again reflect negligible odds of increasing the probability of detecting the outcome of severe dengue. The -LR values are 0 on all days, given the 100% sensitivity (Table 5).

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Table 5. Diagnostic performance of NLR in differentiating dengue fever without warning signs vs. (A) dengue fever with warning signs, and (B) severe dengue

Statistic	Day 1		Day 2		Day 3	
	Value	95% CI	Value	95% CI	Value	95% CI
(A) NLR for DF without WS vs. DF with WS						
Sensitivity	45.83	34.02 - 58.00	61.02	51.61 - 69.86	26.79	20.26 - 34.15
Specificity	74.42	58.83 - 86.48	56.32	45.26 - 66.94	86.44	78.92 - 92.05
PPV	75	62.96 - 84.12	65.45	58.91 - 71.46	73.77	62.58 - 82.55
NPV	45.07	38.38 - 51.94	51.58	44.31 - 58.78	45.33	42.48 - 48.22
+LR	1.79	1.01 - 3.16	1.4	1.06 - 1.85	1.98	1.17 - 3.32
-LR	0.73	0.55 - 0.96	0.69	0.52 - 0.93	0.85	0.75 - 0.95
Accuracy	56.52	46.96 - 65.74	59.02	51.96 - 65.83	51.4	45.44 - 57.33
(B) NLR for DF without WS vs. Severe Dengue						
Sensitivity	100	15.81 - 100.00	100	47.82 - 100.00	100	59.04 - 100.00
Specificity	13.95	5.30 - 27.93	9.2	4.05 - 17.32	8.47	4.14 - 15.03
PPV	5.13	4.57 - 5.75	5.95	5.59 - 6.34	6.09	5.78 - 6.41
NPV	100	54.07 - 100.00	100	63.06 - 100.00	100	69.15 - 100.00
+LR	1.16	1.03 - 1.31	1.1	1.03 - 1.18	1.09	1.03 - 1.15
-LR	0	-	0	-	0	-
Accuracy	17.78	8.00 - 32.05	14.13	7.74 - 22.95	13.6	8.13 - 20.88

NLR: Neutrophil-to-lymphocyte ratio; DF: Dengue fever; WS: Warning signs; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio

The diagnostic performance of PLR cut-offs was analyzed likewise. In differentiating dengue without warning signs versus with warning signs, the accuracy level of PLR cut-off showed a decreasing trend from day 1 at 63.48% to day 3 at 54.2%. Day 1 also had the highest sensitivity at 77.78%, but specificity was lowest on this day at 39.53%. On the contrary, days 2 and 3 had lower sensitivity at 41.53% and 41.67%, and higher specificity at 72.41% and 72.03%, respectively. The PPV levels were close to each other with a range of 67.12% to 68.29%, suggesting a substantial percentage of false positives. Meanwhile, the NPV levels at 46.45% to 51.52% indicate that around half of the sample were false negatives. Likelihood ratios, with +LR ranging from 1.29 to 1.51, and -LR from 0.56 to 0.81, all imply a negligible effect on increasing or decreasing the probability of having warning signs (Table 6).

The accuracy of PLR cut-offs in differentiating dengue fever without warning signs from severe dengue ranges from 51.11% to 73.91% with day 2 recording the highest. Day 1 has 100% sensitivity, whereas days 2 and 3 have low sensitivity at 40% and 57.14%, respectively. All days, however, had wide CIs, showing a lack of precision. Specificity ranged from 48.84% to 75.86%, all below the acceptable value of 80%. PPV levels were very low at 8.33% to 8.7%, in contrast to the high NPV at 95.65% to 100%. Similar to the previous likelihood ratios, none of the +LR and -LR values approached acceptable levels, indicating minimal impact on the probability of detecting severe dengue (Table 6).

Table 6. Diagnostic performance of PLR in differentiating dengue fever without warning signs vs. (A) dengue fever with warning signs, and (B) severe dengue

Statistic	Day 1		Day 2		Day 3	
	Value	95% CI	Value	95% CI	Value	95% CI
(A) PLR for DF without WS vs. DF with WS						
Sensitivity	77.78	66.44 - 86.73	41.53	32.53 - 50.96	41.67	34.12 - 49.51
Specificity	39.53	24.98 - 55.59	72.41	61.79 - 81.46	72.03	63.02 - 79.90
PPV	68.29	62.15 - 73.86	67.12	57.73 - 75.32	67.96	60.15 - 74.88
NPV	51.52	37.57 - 65.23	47.73	42.78 - 52.72	46.45	42.25 - 50.70
+LR	1.29	0.98 - 1.69	1.51	1.01 - 2.25	1.49	1.06 - 2.09
-LR	0.56	0.32 - 0.99	0.81	0.66 - 0.99	0.81	0.68 - 0.96
Accuracy	63.48	53.99 - 72.26	54.63	47.55 - 61.58	54.2	48.23 - 60.07
(B) PLR for DF without WS vs. Severe Dengue						
Sensitivity	100	15.81 - 100.00	40	5.27 - 85.34	57.14	18.41 - 90.10
Specificity	48.84	33.31 - 64.54	75.86	65.50 - 84.40	62.71	53.33 - 71.44
PPV	8.33	6.36 - 10.85	8.7	2.97 - 22.88	8.33	4.39 - 15.25
NPV	100	83.89 - 100.00	95.65	91.42 - 97.85	96.1	91.20 - 98.32
+LR	1.95	1.46 - 2.62	1.66	0.53 - 5.16	1.53	0.77 - 3.03
-LR	0	-	0.79	0.38 - 1.63	0.68	0.29 - 1.63
Accuracy	51.11	35.77 - 66.30	73.91	63.71 - 82.52	62.4	53.30 - 70.90

PLR: Platelet-to-lymphocyte ratio; DF: Dengue fever; WS: Warning signs; CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; +LR: Positive likelihood ratio; -LR: Negative likelihood ratio

NLR and PLR Prediction Models for Dengue Severity

The crude OR of NLR as a predictor of dengue fever with warning signs is significant for days 2 and 3. Their corresponding crude OR values suggest a 25% increase in the odds of having warning signs for day 2 and a 31% increase for day 3. Although also significant on days 2 and 3, the crude OR of PLR taken on these days suggests a much smaller effect, with only a 0.03% increase in odds of dengue fever with warning signs. Furthermore, taking into consideration the individual effect of each clinico-demographic characteristic, their crude ORs suggest that an increase in either age or height also led to a minimal increase in the odds of dengue fever with warning signs. The rest of the baseline variables had no statistical significance (Table 7).

With regards to predicting severe dengue, neither NLR nor PLR on any of the three days showed a statistically significant crude OR. Similarly, none of the baseline characteristics had an impact on the odds of severe dengue (Table 7). Due to the small number of severe dengue cases (n=7), the prediction models may be underpowered, and results should be interpreted with caution.

When evaluating NLR and PLR as independent predictors of dengue fever with warning signs, after adjusting for baseline characteristics, the adjusted ORs for both ratios on days 2 and 3 were no longer significant. A similar trend was observed for age and height, which also yielded statistically insignificant adjusted ORs (Table 8; Table 9).

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Moreover, due to a sparse sample for the severe dengue group, the prediction models per day were unable to yield adjusted ORs for both ratios and for baseline characteristics.

Table 7. NLR, PLR, and baseline clinico-demographic characteristics as predictors of (A) dengue fever with warning signs, and of (B) severe dengue

Variable	(A) Dengue fever with warning signs				(B) Severe dengue			
	Crude OR	95% CI		Sig.	Crude OR	95% CI		Sig.
		Lower	Upper			Lower	Upper	
NLR								
Day 1	1.072	0.952	1.208	0.251	0.768	0.35	1.683	0.51
Day 2	1.247	1.04	1.494	0.017*	0.84	0.398	1.772	0.648
Day 3	1.311	1.063	1.616	0.011*	0.511	0.17	1.532	0.231
PLR								
Day 1	1.001	0.998	1.004	0.383	1.001	0.99	1.011	0.912
Day 2	1.003	1	1.006	0.047*	1	0.991	1.01	0.958
Day 3	1.003	1	1.005	0.042*	0.999	0.99	1.008	0.796
Baseline Characteristics								
Age	1.057	1.005	1.112	0.031*	1.038	0.875	1.232	0.668
Sex	1.158	0.732	1.832	0.532	1.949	0.419	9.071	0.395
Weight	1.009	0.998	1.019	0.116	0.996	0.963	1.031	0.824
Height	1.01	1	1.02	0.047*	1.008	0.976	1.041	0.625
BMI	1.021	0.985	1.059	0.247	0.928	0.795	1.084	0.347
Comorbidities	1.591	0.936	2.704	0.087	0.623	0.072	5.402	0.668
Prev. dengue infection	1.288	0.626	2.649	0.492	0	0	.	0.999
Dengue vaccination	2.14	0.22	20.814	0.512	0	0	.	1

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index
* p-value < 0.05

Table 8. NLR as a predictor of dengue fever with warning signs, after adjusting for baseline clinico-demographic characteristics

Variable	Day 1				Day 2				Day 3			
	Adj. OR	95% CI		Sig.	Adj. OR	95% CI		Sig.	Adj. OR	95% CI		Sig.
		Lower	Upper			Lower	Upper			Lower	Upper	
NLR	1.078	0.945	1.229	0.263	1.205	1	1.452	0.050	1.182	0.947	1.475	0.138
Age	0.973	0.814	1.163	0.766	0.962	0.841	1.1	0.569	0.986	0.889	1.094	0.788
Sex	1.947	0.764	4.957	0.162	1.339	0.711	2.522	0.366	1.344	0.79	2.289	0.276
Weight	0.965	0.887	1.05	0.409	0.964	0.896	1.038	0.335	0.953	0.889	1.021	0.173
Height	1.051	0.986	1.121	0.129	1.037	0.989	1.087	0.132	1.038	0.998	1.08	0.064
BMI	1.08	0.905	1.289	0.391	1.086	0.902	1.308	0.381	1.109	0.931	1.321	0.245
Comorbidities	3.638	1.342	9.866	0.011	1.578	0.803	3.1	0.185	1.574	0.875	2.829	0.130
Prev. dengue infection	1.587	0.433	5.81	0.486	1.063	0.431	2.623	0.895	1.291	0.595	2.801	0.518
Dengue vaccination	0.694	0.036	13.191	0.808	1.653	0.139	19.612	0.690	1.898	0.185	19.419	0.589

NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index

Table 9. PLR as a predictor of dengue fever with warning signs, after adjusting for baseline clinico-demographic characteristics

Variable	Day 1				Day 2				Day 3			
	Adj. OR	95% CI		Sig.	Adj. OR	95% CI		Sig.	Adj. OR	95% CI		Sig.
		Lower	Upper			Lower	Upper			Lower	Upper	
PLR	1.001	0.998	1.004	0.626	1.002	0.999	1.005	0.254	1.001	0.998	1.004	0.481
Age	0.978	0.819	1.168	0.803	0.976	0.855	1.115	0.722	0.997	0.9	1.104	0.947
Sex	1.91	0.747	4.883	0.177	1.342	0.715	2.521	0.360	1.349	0.792	2.298	0.270
Weight	0.97	0.896	1.05	0.452	0.972	0.909	1.038	0.392	0.956	0.892	1.024	0.201
Height	1.046	0.983	1.114	0.159	1.031	0.986	1.078	0.183	1.036	0.995	1.078	0.085
BMI	1.074	0.912	1.264	0.394	1.069	0.909	1.257	0.420	1.103	0.926	1.313	0.272
Comorbidities	3.667	1.359	9.895	0.010	1.587	0.812	3.101	0.177	1.653	0.925	2.953	0.089
Prev. dengue infection	1.642	0.451	5.974	0.452	1.136	0.463	2.787	0.781	1.297	0.599	2.807	0.510
Dengue vaccination	0.677	0.035	12.895	0.795	1.526	0.128	18.254	0.739	2.027	0.199	20.64	0.551

PLR: Platelet-to-lymphocyte ratio; OR: Odds ratio; CI: Confidence interval; BMI: Body mass index

DISCUSSION

Dengue fever presents with a wide clinical spectrum, ranging from self-limiting symptoms to severe, life-threatening illness. The disease is classified into the following, based on severity: dengue fever without warning signs, dengue fever with warning signs, and severe dengue.[1-3]

Aside from clinical findings, an important and widely available diagnostic tool used to assess the progression and severity of the illness is the CBC. According to the World Health Organization (WHO) [1], CBC components such as leukocytes, platelets, and hematocrit levels play a crucial role in assessing the clinical progression of dengue. While trends in these parameters have traditionally been correlated with the course of dengue illness, other CBC indices have emerged as predictors of dengue severity. This study aimed to investigate whether a simple CBC can provide more information on whether a patient with dengue fever will develop warning signs or progress to severe dengue.

NLR as a Predictor of Dengue Severity

The NLR is a well-established inflammatory marker that has been studied as a potential prognostic marker in various inflammatory conditions, including both infectious and non-infectious diseases. Typically, elevated NLR reflects systemic inflammation and immune dysregulation, ultimately contributing to the pathogenesis of severe infection.

In this retrospective study, the NLR of pediatric patients with dengue fever without warning signs was compared to that of patients who developed warning signs. The daily NLR cut-offs for differentiating the two groups were 4.73, 2.07, and 2.5 on days 1 to 3, respectively. However, all these cut-offs demonstrated poor discrimination accuracy and diagnostic performance. The NLR cut-off on day 3 had the highest specificity at 86.44%, but all other metrics were below acceptable levels. The NLR cut-offs differentiating dengue fever without warning signs from severe dengue were 1.27, 0.68, and 0.47 on days 1 to 3, respectively. Similarly, these had poor discrimination and overall diagnostic performance.

Further analysis was done to determine the association between NLR and dengue severity. Results showed that higher NLR on days 2 and 3 increases the

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probability of developing warning signs, although only by 25% and 31%, respectively. However, after adjusting for baseline clinico-demographic variables, the association is no longer significant. Moreover, NLR also did not show any significant changes on the probability of progressing to severe dengue. These analyses therefore show that NLR does not have a statistically significant correlation with dengue severity.

In a recent study by Agrawal et al. (2023), a higher NLR on admission was determined to be a statistically significant predictor of adverse outcomes, particularly of mortality. While trends were congruent with this previous study,[4] the associations in our study were not statistically significant. Hasanah et al. (2023) likewise examined the correlation between NLR and dengue severity, specifically in dengue hemorrhagic fever (DHF).[5] The group of DHF with shock had a statistically significant lower NLR compared to DHF without shock. The study also showed that those with shock had an NLR below the cut-off, which was established at 0.39. An earlier study by Yuditya & Sudirgo et al. (2020) likewise correlated a lower NLR with a more severe grade of DHF.[6] In their study, the authors cited another cross-sectional study by Yuntoharjo et al. (2018) where NLR was found to be lower in patients who developed DHF than those with dengue fever. Moreover, a study by Bhati, Meena, & Sharma (2022) showed that among dengue patients, the groups who manifested with adverse outcomes such as hemorrhage and shock had a statistically significant lower NLR compared to those without severe outcomes.[7] Of note, their study analyzed NLR on day 7 of illness, in contrast to the early NLR taken on days 1 to 3 in this present study. In another retrospective study by Sadgir et al. (2023), the NLR cut-off was arbitrarily set at 2 and an NLR below the cut-off showed a strong correlation with decreased platelet count (<40,000 per µL), which was interpreted as a clinical marker of dengue severity.[8] Similar to this present study, a local study by Prayon & Oncog (2022) utilized CBC taken during the first 72 hours of illness to prognosticate dengue in pediatric patients.[9] In their study, NLR also had no significant association with dengue severity.

PLR as a Predictor of Dengue Severity

The PLR is another emerging inflammatory marker that has been gaining attention. On the background of recent studies exploring its utility in prognosticating illnesses, the study included PLR particularly since platelet trends have already been established in dengue.

In this study, PLR cut-offs to differentiate dengue fever without warning signs from more severe dengue classifications. With relation to dengue fever with warning signs, the PLR cut-offs were determined at 170, 233.92, and 208.79 on days 1 to 3, respectively. On the other hand, compared to severe dengue, the daily cut-offs were at 209.24, 244.12, and 187.5, respectively. In both pairwise analyses, the PLR cut-offs were shown to have poor discrimination and diagnostic performance across all days.

Furthermore, linear regression analysis showed that PLR on days 2 to 3 of illness had negligible impact as it increased the odds of developing warning signs by only 0.03% on both days. Upon adjusting for baseline clinico-demographic variables, the effect was no longer significant, as with day 1 PLR as well. Likewise, PLR had no significant effect on increasing the probability of severe dengue, both before and after baseline characteristics have been factored in.

In contrast to this study, Verliyani et al. (2023) showed that PLR is significantly lower in DHF patients with more severe disease, with mortality vs recovery as the primary outcome in their study.[10] In a more recent study by Navya et al. (2024), NLR and PLR, along with individual CBC parameters, were each correlated with the severity of dengue in terms of the traditional classification (i.e., dengue fever, dengue hemorrhagic fever, dengue shock syndrome).[11] In their study, a lower NLR and PLR were individually found to correlate with more severe dengue classification. Between the two ratios, PLR demonstrated a higher overall accuracy and sensitivity, although lower specificity.

CONCLUSION

This study explored the diagnostic utility of early NLR and PLR taken on days 1 to 3 of dengue fever, in predicting more severe dengue outcomes. Although previous studies have shown a correlation between these ratios and dengue severity, our findings suggest that NLR and PLR lack adequate correlation with dengue classification when applied early in the disease course. Daily cut-offs were determined for each ratio, all showing poor diagnostic performance in differentiating patients

who eventually developed warning signs, as well as those who progressed to severe dengue. Further analysis showed no statistically significant difference in the NLR or PLR of dengue patients without warning signs when analyzed pairwise against those with warning signs and those with severe dengue.

This study then underscores the need for further investigation of early markers that could aid clinicians in predicting the development of severe dengue outcomes, ultimately contributing to a more efficient healthcare resource allocation.

RECOMMENDATIONS

Overall, the results of this study failed to demonstrate the utility of NLR or PLR as an early predictive marker of more severe dengue classifications. Seeing that prior similar studies have successfully shown a correlation between these ratios and dengue severity, it must be noted that most of these studies utilized either the adult population or a combination of adults and children. Furthermore, the ratios analyzed in most of these other studies were taken later in the course of the illness, whereas this study only analyzed CBC on the first three days of dengue illness. Given these findings, a future direction for this research is to analyze the trend in these ratios throughout the course of dengue illness. Ratios measured on the later stages may offer prognostic utility. Several studies have explored this trend. Chaloemwong et al. (2018) reported that NLR is typically higher in the early stages of dengue fever and reverses after an average of 6-9 days.[12] In a more recent cross-sectional study, Ishaque et al. (2022) observed that this NLR reversal occurred slightly earlier, within 3-5 days, in the majority (85%) of the subjects.[13] In this latter study, dengue patients were classified into early-reversal and late-reversal groups based on whether their NLR reversed within or after 5 days, respectively. The late-reversal group had a higher percentage of patients who developed DHF and experienced prolonged hospital stays, suggesting persistent elevation of NLR later in the disease course may be associated with more severe outcomes.

Another limitation of this study is the small sample size of patients with severe dengue, at only 2.2% of the total sample. Thus, future studies should consider increasing the sample size, particularly ensuring that each dengue classification is well represented. Given that the study was done retrospectively in a single tertiary institution, it is recommended that future research be conducted over a longer time frame retrospectively or prospectively, and in multiple institutions, to adequately represent cases with more severe outcomes.

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CONFLICT OF INTEREST

None declared.

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REFERENCES

1. World Health Organization (WHO). Dengue: Guidelines for diagnosis, treatment, prevention and control. 2009. Available from: https://www.who.int/publications/i/item/9789241547871
2. Philippine Pediatric Society (PPS), Philippine Infectious Disease Society of the Philippines (PIDSP). Clinical practice guidelines on dengue in children. 2017. Available from: http://www.pidsphil.org/home/wp-content/uploads/2017/06/2017_Dengue_CPG_Final.pdf
3. Halstead SB. Dengue fever, dengue hemorrhagic fever, and severe dengue. In: Kliegman RM, St Geme JW, Blum NJ, Shah SS, Tasker RC, Wilson KM, editors. Nelson textbook of pediatrics. 21st ed. Philadelphia (PA): Elsevier, Inc.
4. Agrawal S, Kumar S, Talwar D, Patel M, Reddy H. 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. J Clin of Diagn Res [Internet]. 2023 Nov [cited 2024 Nov 8];17(11):OC01-OC04. Available from: https://doi.org/10.7860/JCDR/2023/65292.18658
5. Hasanah AN, Esa T, Bahrun U. Comparison of neutrophil-lymphocyte ratio in patients with COVID-19 and dengue hemorrhagic fever. Indonesian J Clin Pathol Med Lab

[Internet]. 2023 Nov [cited 2024 Nov 8];30(1):60-65. Available from: https://doi.org/10.24293/ijcpml.v30i1.2056

6. Yuditya DC, Sudirgo I. The relation between neutrophil lymphocyte count ratio (NLCR) and dengue infection grade of severity in adult patients in RS Muhammadiyah Ahmad Dahlan Kediri in January 2019. STRADA Jurnal Ilmiah Kesehatan [Internet]. 2020 May [cited 2024 Nov 8];9(1):20-25. Available from: https://doi.org/10.30994/sjik.v9i1.265
7. Bhati MR, Meena H, Sharma AK. Neutrophil to lymphocyte ratio as the predictor of severity of dengue viral fever: a cross sectional study at a tertiary care centre in Central Rajasthan. Int J Pharm Clin Res [Internet]. 2022 [cited 2024 Nov 8];14(10):7-12. Available from: https://impactfactor.org/PDF/IJPCR/14/IJPCR,Vol14,Issue 10,Article2.pdf
8. Sadgir A, Durge K, Masavkar S. Neutrophil-lymphocyte ratio as a prognostic indicator in dengue fever patients at tertiary care hospital in Northwest-Maharashtra. Int J Adv Res [Internet]. 2023 Jan [cited 2024 Nov 8];11(01):1198-1202. Available from: https://www.journalijar.com/article/43600/ DOI: 10.21474/IJAR01/16137
9. Prayon KM, Oncog AS. Absolute neutrophil counts and neutrophil to lymphocyte ratio as early predictive markers of dengue severity among children admitted in Governor Celestino Gallares Memorial Hospital: a 5-year retrospective study. Acta Sci Paediatr [Internet]. 2022 Jul [cited 2024 Nov 8];5(7):37-45. Available from: https://actascientific.com/ASPE/pdf/ASPE-05-0537.pdf DOI: 10.31080/ASPE.2022.05.0537
10. Verliyanti V, Esa T, Nurulita A. Analysis of platelet lymphocyte ratio on severe COVID-19 and dengue hemorrhagic fever grade IV. Indonesian J Clin Pathol Med Lab [Internet]. 2023 Nov [cited 2024 Nov 8];30(1):78-82. Available from: https://doi.org/10.24293/ijcpml.v30i1.2053
11. Navya PT, Begum R, Thajudeen AS, Hussain MA, Vijayashree R (2024). Navigating the haematological maze: Unraveling the role of NLR and PLR as predictors of dengue severity- a cross-sectional study from Southern India. J Clin of Diagn Res [Internet]. 2024 Mar [cited 2024 Nov 8];18(3):EC23-EC26. Available from: https://doi.org/10.7860/JCDR/2024/68904.19162
12. Chaloemwong J, Tantiworawit A, Rattanathammethee T, Hantrakool S, Chai-Adisaksopha C, Rattarittamrong E, Norasetthada L. Useful clinical features and hematological parameters for the diagnosis of dengue infection in patients with acute febrile illness: a retrospective study. BMC Hematol [Internet]. 2018 Aug [cited 2024 Nov 8];18(20):1-10. Available from: https://doi.org/10.1186/s12878-018-0116-1
13. Ishaque N, Siddique MU, Imran A, Malik NA. Utilization of neutrophil to lymphocyte ratio to assess recovery in patients with dengue. J Haematol Stem Cell Res [Internet]. 2022 Oct [cited 2024 Nov 8];2(2):77-80. Available from: https://jhscr.org/index.php/JHSCR/article/view/52