

## Analisis Rasio Neutrofil-Limfosit dan Rasio Trombosit-Limfosit pada Pasien Terinfeksi Dengue

### *Analysis of Neutrophil-Lymphocyte Ratio and Platelet-Lymphocyte Ratio in Dengue-Infected Patients*

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#### *Abstract*

*Dengue infection, caused by the dengue virus and transmitted by Aedes mosquitoes, remains a significant public health issue in Indonesia. The ability to identify reliable biomarkers for assessing disease severity is critical for improving clinical management. This study aimed to evaluate the relationship between the Neutrophil-to-Lymphocyte Ratio (NLR) and Platelet-to-Lymphocyte Ratio (PLR) as potential biomarkers of severity in dengue infection. An observational cross-sectional design was employed, analyzing 76 dengue cases at RSAU dr. Dody Sardjoto. Data were collected from medical records of patients during the critical fever period (days 4-7). The majority of patients were male and adult, with a higher incidence of Dengue Hemorrhagic Fever (DHF). Statistical analysis showed no significant correlation between NLR and PLR with disease severity ( $p$ -value  $>0,05$ ), although a positive correlation between NLR and PLR was observed. However, neither NLR nor PLR effectively predicted hospitalization duration. These results suggest that while NLR and PLR reflect immune responses in dengue infection, they are not suitable biomarkers for assessing disease severity. Further research is needed to identify more reliable biomarkers for better management of dengue infection.*

**Keywords:** biomarkers, dengue infection, neutrophil-to-lymphocyte ratio

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### Abstrak

menjadi masalah kesehatan masyarakat yang signifikan di Indonesia. Kemampuan untuk mengidentifikasi biomarker yang andal dalam menilai tingkat keparahan penyakit sangat penting untuk meningkatkan pengelolaan klinis. Penelitian ini bertujuan untuk mengevaluasi hubungan antara Rasio Neutrofil-Limfosit (NLR) dan Rasio Trombosit-Limfosit (PLR) sebagai biomarker potensial keparahan pada infeksi demam berdarah. Desain observasional potong lintang digunakan, menganalisis 76 kasus demam berdarah di RSAU dr. Dody Sardjoto. Data dikumpulkan dari catatan medis pasien selama periode demam kritis (hari ke-4 hingga ke-7). Mayoritas pasien adalah laki-laki dan dewasa, dengan insidensi yang lebih tinggi pada Demam Berdarah Dengue (DBD). Analisis statistik menunjukkan tidak ada korelasi signifikan antara NLR dan PLR dengan tingkat keparahan penyakit ( $p\text{-value} > 0,05$ ), meskipun korelasi positif antara NLR dan PLR diamati. Namun, baik NLR maupun PLR tidak efektif dalam memprediksi lama rawat inap. Hasil ini menunjukkan bahwa meskipun NLR dan PLR mencerminkan respon imun dalam infeksi demam berdarah, keduanya tidak cocok sebagai biomarker untuk menilai keparahan penyakit. Penelitian lebih lanjut diperlukan untuk mengidentifikasi biomarker yang lebih andal guna pengelolaan infeksi demam berdarah yang lebih baik.

**Kata Kunci:** biomarker, infeksi dengue, rasio neutrofil-limfosit

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#### Highlight:

- The study found no significant correlation between the Neutrophil-Lymphocyte Ratio (NLR) or Platelet-Lymphocyte Ratio (PLR) and the severity of dengue infection ( $p > 0.05$ ).
- Both markers showed no significant relationship with the duration of hospital stay, indicating they are not useful prognostic indicators for clinical outcomes.
- Despite their limited predictive value, the study observed a strong positive correlation between NLR and PLR, reflecting interconnected immune responses in dengue infection.

### INTRODUCTION

Dengue infection, caused by the dengue virus and transmitted by *Aedes* mosquitoes (specifically *Aedes aegypti* and *Aedes albopictus*), is one of the fastest spreading vector-borne diseases globally. It is the second most serious after malaria (Jing and Wang, 2019). In Southeast Asia, Indonesia has the highest incidence and mortality rates from dengue (Salim et al., 2021). In 2021, Indonesia's national incidence rate (IR) for dengue hemorrhagic fever (DHF) was 27 per 100,000 population, with South Sulawesi having a higher IR of 40 per 100,000 (Kemenkes, 2022). Dengue infection presents in two forms: Dengue Fever (DF) and DHF, with DHF classified into four levels. Levels 3 and 4 are associated with severe complications such as Dengue Shock Syndrome (DSS) (Kemenkes, 2017; Jing and Wang, 2019). Dengue has a broad spectrum of clinical manifestations, making early recognition and timely intervention challenging. While many cases resolve without complications, severe infections with plasma leakage and bleeding can be fatal (Kemenkes, 2017).

Given the difficulty in predicting disease progression, reliable biomarkers are needed to assess the severity of dengue infection. The *Neutrophil-Lymphocyte Ratio* (NLR) is a promising candidate. It reflects both the innate immune response (neutrophils) and adaptive immunity (*lymphocytes*). NLR has been shown to have prognostic value and is associated with mortality in various infectious diseases, including sepsis, pneumonia, and COVID-19 (Asidik et al., 2021; Buonacera et al., 2022). Similarly, the *Platelet-Lymphocyte Ratio* (PLR) can be used to evaluate dengue severity. PLR reflects acute inflammation and coagulation activation, which are important in dengue's pathophysiology. Changes in PLR have been linked to systemic inflammation in several diseases (Gasparyan et al., 2019).

At RSAU dr. Dody Sardjoto, analyzing NLR and PLR in dengue patients from 2022 to 2024 aims to explore the relationship between these ratios and disease severity. Understanding these associations can improve the predictive power of laboratory tests, aiding in better patient stratification for treatment (Ren et al., 2022; Prado and Adiao, 2024). This study could contribute to a deeper understanding of dengue pathogenesis and help guide more targeted therapeutic interventions (Birhman dan Mogha, 2022; Santos dan Azeredo, 2022). In summary, analyzing NLR and PLR in dengue patients at RSAU dr. Dody Sardjoto is a crucial step in understanding the interplay between immune responses and disease severity. By examining these hematological parameters, the study aims to determine their diagnostic value as easily obtainable biomarkers, potentially facilitating rapid diagnosis and timely treatment (Gasparyan et al., 2019).

## METHODS

This study employed a quantitative, analytical observational design with a cross-sectional approach (Agnesia et al., 2023; Liberty, 2024). It was conducted at the RSAU dr. Dody Sardjoto Air Force Hospital, Maros Regency, South Sulawesi Province, between August and October 2024. The study population consisted of all patients diagnosed with dengue infection at the hospital from May 2022 to July 2024.

A total sampling technique was applied, where all eligible patients who met the inclusion criteria were included in the study. The inclusion criteria were: (1) patients diagnosed with dengue infection, confirmed by laboratory tests such as the detection of dengue-specific IgM and/or IgG antibodies or dengue RNA by PCR, and (2) patients presenting with fever on days 4 to 7 of illness, as this period is critical for assessing disease severity. Exclusion criteria included: (1) patients with other concurrent infectious diseases or conditions (such as bacterial infections, chronic inflammatory disorders, or malignancies) that could influence neutrophil, lymphocyte, and platelet counts; (2) patients who did not have complete medical records, including missing hematological data. The sample size was determined based on the total number of eligible patients who met the inclusion and exclusion criteria during the study period.

Data were collected from the medical records of patients who were treated at RSAU dr. Dody Sardjoto between May 2022 and July 2024. Hematological parameters, including neutrophil, lymphocyte, and platelet counts, were obtained from laboratory reports. The Neutrophil-Lymphocyte Ratio (NLR) was calculated as the ratio of neutrophil count to lymphocyte count ( $NLR = \text{Neutrophil count} / \text{Lymphocyte count}$ ), and the Platelet-Lymphocyte Ratio (PLR) was calculated as the ratio of platelet count to lymphocyte count ( $PLR = \text{Platelet count} / \text{Lymphocyte count}$ ). All laboratory tests were performed using standard automated hematology analyzers.

Data were analyzed using Microsoft Excel and SPSS version 26 (Sujarweni,

2015). Univariate analysis was used to summarize the data and present it in frequency distribution tables. Bivariate analysis was conducted using the Mann-Whitney U test to assess the relationship between NLR, PLR, and dengue severity (Jing and Wang, 2019). Nonparametric tests were chosen because the data were not normally distributed, as confirmed by the Shapiro-Wilk test. A Spearman rank correlation test was used to evaluate the association between NLR, PLR, and length of hospitalization. A p-value of less than 0,05 was considered statistically significant for all tests (Ghozali, 2018). This research has complied with the research code of ethics number 251/A.1/KEP-UMI/VII/2024.

## RESULTS AND DISCUSSION

### Analysis of the distribution of characteristics in patients with dengue infection

Table 1 presents the characteristics of the 76 patients with dengue infection. The majority of patients were male (60,5%) and adults (50,0%). Most patients reported a fever duration of 4 days upon admission (42,1%) and were treated for 4 days (35,5%). The majority were diagnosed with Dengue Hemorrhagic Fever (DHF) (72,4%).

**Table 1. Characteristics of patients with dengue infection**

Characteristics		n	%
Gender (Sex)	Male	46	60,5
	Female	30	39,5
Age	Babies	11	14,5
	Children	8	10,5
	Teenagers	17	22,4
	Adults	38	50,0
	Elderly	2	2,6
Day of Fever	4	32	42,1
	5	30	39,5
	6	6	7,9
	7	8	10,5
Length of Stay	3 days	21	27,6
	4 days	27	35,5
	5 days	17	22,4
	6 days	11	14,5
Degree of Illness	DF	21	27,6
	DHF	55	72,4
<b>Total</b>		<b>76</b>	<b>100,0</b>

Source: Primary data, 2022-2024

### Analysis of sample distribution based on neutrophil, lymphocyte and platelet levels

Table 2 shows the distribution of neutrophil, lymphocyte, and platelet levels. A majority of patients had high neutrophil counts (53,9%) and normal platelet counts (84,2%). Lymphocyte levels were more varied, with 48,7% of patients having normal levels.

**Table 2. Neutrophil, lymphocyte, and platelet levels in dengue infection**

	Level	Frequency (n)	Percentage (%)
Neutrofil	High	41	53,9
	Normal	29	38,2

	Level	Frequency (n)	Percentage (%)
Limfosit	Low	6	7,9
	High	10	13,2
	Normal	37	48,7
Trombosit	Low	29	38,2
	High	12	15,8
	Normal	64	84,2
<b>Total</b>		<b>76</b>	<b>100,0</b>

Source: Primary data, 2022-202

### Analysis of the relationship of Neutrophil-lymphocyte Ratio (NLR) with the severity of dengue infection

Table 3 illustrates the relationship between NLR and the severity of dengue infection across different age groups. The average NLR for patients with Dengue Fever (DF) was 4,7 (SD = 5,2), and for those with Dengue Hemorrhagic Fever (DHF), it was 5,0 (SD = 5,6). The p-value of 0,986 suggests no significant relationship between NLR and the severity of dengue infection.

**Table 3. Relationship between NLR and the degree of dengue infection**

Age Group	Diagnose	NLR			p-value
		Average	Standard Deviation	Min-max	
Children	DF	2,9	1,9	1,4-7,6	0,607
	DHF	3,5	3,7	0,7-17,4	
Adults	DF	5,7	6,3	0,7-24,3	0,675
	DHF	6,5	6,8	1,4-25,3	
All groups	DF	4,7	5,2	0,7-24,3	0,986
	DHF	5	5,6	0,7-25,3	

Note: Spearman test, significant if p-value <0,05

### Analysis of the Relationship of Platelet-lymphocyte Ratio (PLR) with the Severity of Dengue Infection

Table 4 presents the relationship between PLR and the severity of dengue infection. The average PLR for DF patients was 162,5 (SD= 155,1), while for DHF patients, it was 156,7 (SD= 159,7). The p-value of 0,926 indicates no significant relationship between PLR and dengue severity.

**Table 4. Relationship of PLR with the degree of dengue infection**

Age Group	Diagnose	PLR			p-value
		Average	Standard Deviation	Min-max	
Children	DF	207,0	154,7	13,7-478,6	0,254
	DHF	163,2	184,1	20,0-904,7	
Adults	DF	135,1	155,0	21,9-615,8	0,333
	DHF	150,1	133,2	3,9-676,7	
All groups	DF	162,5	155,1	13,7-615,8	0,926
	DHF	156,7	159,7	3,9-904,7	

Note: Spearman test, significant if p-value <0,05

**Analysis of the relationship between Neutrophil-lymphocyte Ratio (NLR) and Platelet-lymphocyte Ratio (PLR) with length of hospitalization in patients with dengue infection**

Table 5 explores the correlation between NLR, PLR, and length of hospitalization. Across all groups, the NLR showed no significant correlation ( $R= 0,143, p= 0,271$ ), and PLR showed no significant relationship either ( $R= 0,002, p= 0,987$ ).

**Table 5. Relationship between NLR and PLR with length of hospitalization of dengue infection patients**

Age Group			NLR	PLR
Children	Length of Stay	<i>R-Value</i>	-0,052	-0,096
		<i>P-Value</i>	0,764	0,576
Adults	Length of Stay	<i>R-Value</i>	0,241	0,104
		<i>P-Value</i>	0,134	0,524
All groups	Length of Stay	<i>R-Value</i>	0,143	0,002
		<i>P-Value</i>	0,271	0,987

Note: Spearman test, significant if p-value <0,05

**Analysis of the relationship between Neutrophil-lymphocyte Ratio (NLR) and Platelet-lymphocyte Ratio (PLR) in patients with dengue infection**

Table 6 presents the significant positive correlation between NLR and PLR across all age groups ( $R= 0,478, p\text{-value} <0,001$ ), with a similar trend observed in both children ( $R= 0,555, p\text{-value} <0,001$ ) and adults ( $R= 0,496, p= 0,001$ ).

**Table 6. Relationship between NLR and PLR in dengue infection patients**

Age Group			PLR
Children	NLR	<i>R-Value</i>	0,555
		<i>P-Value</i>	<0,001
Adults	NLR	<i>R-Value</i>	0,496
		<i>P-Value</i>	0,001
All groups	NLR	<i>R-Value</i>	0,478
		<i>P-Value</i>	<0,001

Note: Spearman test, significant if p-value <0,05

**Analysis of the relationship between Neutrophil-lymphocyte Ratio (NLR) and platelet levels in patients with dengue infection**

Table 7 shows the relationship between NLR and platelet levels. There was no significant correlation between NLR and platelet levels in any age group, with the combined data yielding an R-value of 0,123 ( $p\text{-value}= 0,290$ ).

**Table 7. Relationship between NLR and Platelet level in Dengue Infection Patients**

Age Group			Platelet
Children	NLR	<i>R-Value</i>	0,062
		<i>p-Value</i>	0,704
Adults	NLR	<i>R-Value</i>	0,242
		<i>p-Value</i>	0,151
All groups	NLR	<i>R-Value</i>	0,123
		<i>p-Value</i>	0,290

Note: Spearman test, significant if p-value <0,05

This study found a predominance of male (60,5%) and adult (50,0%) patients, which aligns with previous research suggesting higher dengue incidence among males due to greater outdoor activity and subsequent exposure to *Aedes aegypti* mosquitoes (Asishe *et al.*, 2024). The majority of patients were examined on the 4th day of fever (42,1%), a critical phase when laboratory results typically show significant changes, including reduced platelet counts and increased hematocrit, which could indicate potential complications like plasma leakage (Recker *et al.*, 2024). Hospitalization length (3-4 days) is consistent with the fact that most patients enter the recovery phase around day 7 (Putri *et al.*, 2024). A higher incidence of Dengue Hemorrhagic Fever (DHF) (72,4%) was observed, supporting the finding that DHF requires more intensive medical attention and leads to longer hospital stays (Syuhada *et al.*, 2022).

In terms of hematological parameters, the study revealed high neutrophil counts in 53,9% of patients, which is consistent with the innate immune response observed in the acute phase of dengue infection (Wahid, 2016). Most patients (48,7%) had normal lymphocyte levels, suggesting a typical adaptive immune response activation. A majority (84,2%) exhibited low platelet counts, which is a hallmark of DHF, linked to platelet destruction, bone marrow suppression, and increased consumption during the infection (Opasawatchai *et al.*, 2019; Sihombing and Salim, 2023).

Regarding the Neutrophil-Lymphocyte Ratio (NLR), patients with DHF showed higher NLR values compared to those with Dengue Fever (DF), which can be explained by the more severe inflammatory response in DHF, leading to higher neutrophil counts (WHO, 2011). This finding was in line with previous studies suggesting that NLR increases with the severity of dengue infection. However, statistical analysis ( $p = 0,986$ ) indicated no significant relationship between NLR and disease severity across all age groups, including children and adults. This lack of significance could be due to the timing of data collection (days 4-7 of fever), a period that might not capture the peak of immune responses, particularly the more dramatic fluctuations in neutrophil and lymphocyte levels seen in later phases (Priyanto *et al.*, 2023). Additionally, the sample size might have limited the ability to detect significant correlations, as dengue's immune response varies significantly between individuals.

Similarly, Platelet-Lymphocyte Ratio (PLR) showed no significant correlation with disease severity ( $p = 0,926$ ), even though lower PLR values were observed in DHF cases. The lower PLR in DHF likely reflects a more pronounced decrease in platelet levels due to plasma leakage and platelet consumption during bleeding (Tasya *et al.*, 2022). This result suggests that while platelet and lymphocyte changes are correlated with disease progression, PLR may not be as sensitive to subtle differences in disease severity. The insignificant relationship between PLR and severity could also be attributed to the timing of measurement and the biological variability in platelet counts across individuals.

Furthermore, no significant relationship was found between NLR and PLR with the length of hospitalization ( $p = 0,271$  and  $p = 0,987$ , respectively). While NLR and PLR provide insights into the inflammatory status of patients, hospitalization duration is influenced by a broader range of factors, including clinical complications such as plasma leakage, bleeding, and shock, as well as the patient's response to supportive care (WHO, 2011; Cahyani *et al.*, 2020). Comorbid conditions, such as diabetes or hypertension, might also contribute to prolonged hospitalization, further complicating the relationship between inflammatory markers and clinical outcomes.

Interestingly, a significant positive correlation was found between NLR and PLR ( $R = 0,478$ ,  $p < 0,001$ ), suggesting that both ratios are influenced by similar immune

responses. This is expected, given that both NLR and PLR involve neutrophils, platelets, and lymphocytes, which are central to the immune response in dengue (Rotty et al., 2023). The relationship between NLR and PLR could be valuable in distinguishing between acute and chronic phases of dengue infection, or identifying non-infectious conditions involving platelet abnormalities (WHO, 2011).

Finally, the lack of a significant relationship between NLR and platelet levels ( $p=0,290$ ) across all age groups is consistent with findings that platelet changes in dengue are primarily caused by factors such as direct platelet destruction by the virus and bone marrow suppression (Sihombing and Salim, 2023). Neutrophils may not be as directly involved in regulating platelet counts, making the relationship between NLR and platelet levels less pronounced. In summary, while NLR and PLR provide insights into the inflammatory and immune responses in dengue patients, the study did not find significant associations with disease severity or length of hospitalization, possibly due to the timing of measurements, biological variability, or sample size limitations. The relationship between NLR and PLR, however, offers potential for further investigation, particularly in distinguishing between acute and chronic disease phases. Further studies with larger sample sizes and data collected at different stages of the disease are needed to better understand the prognostic value of these markers in dengue infection.

## CONCLUSIONS

This study found no significant correlation between the Neutrophil-Lymphocyte Ratio (NLR) and Platelet-Lymphocyte Ratio (PLR) with the severity of dengue infection, suggesting that while these markers reflect immune responses, they may not serve as reliable clinical biomarkers for assessing disease severity. Despite a significant positive correlation between NLR and PLR, these ratios did not predict hospitalization duration. The findings highlight the need for further research into the immunological parameters of dengue to identify more effective biomarkers. Limitations of this study include the timing of measurements and sample size, which may have influenced the results. Future studies should explore additional biomarkers and examine different stages of infection to better understand their role in managing dengue.

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