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Relationship Between PLR Value and Severity of Dengue Infection Pediatric Patients in RSUD dr. Soebandi Jember

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Abstract

Dengue infection is a disease caused by dengue virus infection and transmitted by the Aedes mosquito, and is a major health problem in children, especially in developing countries. The Platelet-to-Lymphocyte Ratio (PLR) is a novel inflammatory biomarker that has recently been frequently studied and play a role in the assessment of dengue severity viral infection, and Research has indicated that the PLR (Platelet-to-Lymphocyte Ratio) may offer a more effective comparison for assessing the severity of viral infectious diseases when contrasted with the Neutrophil-to-Lymphocyte Ratio (NLR). Research suggests that the Platelet-to-Lymphocyte Ratio (PLR) could serve as a promising biomarker for assessing the severity of dengue infections. This is particularly advantageous for developing countries, as PLR is an inexpensive and readily available measure in various clinical settings. This research is a correlative analytical observational study using a cross-sectional approach. This research design was carried out by collecting data from children diagnosed with dengue infection as well as data on platelets and lymphocytes on the first day of admission to the hospital. This research uses stratified random sampling. Data were analyzed using Spearman correlation with a confidence level of 99%. The results of Spearman's correlation analysis showed a strong significant relationship with $p<0.01$ ($p=0.000$) and a correlation coefficient of - 0.753. In conclusion, there is a significant relationship between the Platelet-to-Lymphocyte Ratio (PLR) value with the severity of dengue infection in pediatric patients RSUD Dr. Soebandi Jember.

Keywords: PLR; dengue infection; children; platelets; lymphocytes

Introduction

Dengue infection is a disease caused by dengue virus infection and transmitted by the Aedes mosquito, and it is a major health problem in children, especially in developing countries. The World Health Organization has reported a substantial rise in dengue cases over the past 19 years, with nearly 5 million cases recorded, 90% of which involve children, and approximately 2.5% resulting in fatalities (Fadilla et al., 2020). According to data from the Ministry of Health, by the end of 2022, Indonesia reported a total of 143,000 dengue infection cases, with East Java being the second highest province, accounting for 13,189 cases. In 2022, the Ministry of Health reported that the Case Fatality Rate (CFR) for dengue infections in Indonesia is projected to be 0.93%. In 2020, data from the Jember District Health Service reported 945 instances of dengue infection, with a mortality rate of 0.3%. The classifications of dengue infection include Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS) (Yulianto et al., 2017). DSS is also referred to as DHF degrees III and IV (Widodo, 2017).

Dengue infection presents with symptoms including pain, erythema, and loss of appetite. Dengue Hemorrhagic Fever (DHF) exhibits more severe symptoms such as bleeding and plasma leakage in the lungs (pleural effusion) and abdomen (ascites). Severe Dengue (DSS) represents a more critical condition than DHF, characterized by shock (Widodo, 2017). It is crucial to assess the severity of dengue infections in patients and initiate treatment promptly to prevent progression to a more severe state. Laboratory results serve as a vital parameter

for monitoring dengue infections, allowing for a better understanding of any rapid deterioration in symptoms. Timely diagnosis and vigilant oversight by healthcare professionals are essential for the effective management of dengue infections (Made et al., 2022).

The Platelet-to-Lymphocyte Ratio (PLR) is an emerging inflammatory biomarker that has garnered significant attention in recent studies. It is instrumental in evaluating viral infectious diseases, and its application as a biomarker for various viral infections shows greater promise and efficacy compared to the Neutrophil-to-Lymphocyte Ratio (NLR) (Tasya et al., 2022). The PLR serves as an economical biomarker that is accessible across various clinical conditions, and it can function as a preliminary screening test conducted by general practitioners prior to any additional examinations (Simadibrata et al., 2022). The PLR can be derived from the comparison of absolute platelet counts and absolute lymphocyte counts (Ravindra et al., 2022). A study conducted in 2021 established a correlation between the Platelet-to-Lymphocyte Ratio (PLR) and the severity of dengue infection. It was determined that PLR serves as an effective predictor of dengue severity during days 4 to 6. Assessing the PLR value can assist healthcare professionals in the early diagnosis of more severe cases of dengue (Cai et al., 2021). Research in 2022 found that there was no relationship between the degree of dengue infection and PLR due to different times when laboratory results data were collected (Tasya et al., 2022). The most recent research in 2023 indicates a statistically significant relationship that predicts the severity of dengue infections with hemorrhagic symptoms (Jelia et al., 2023). The PLR demonstrates a notable distinction between patients who succumb to grade IV dengue fever and those who recover, and it can be conducted periodically to monitor the patient's clinical status (Verliyanti et al., 2023).

The World Health Organization states that the severity of dengue infection does not yield conclusive results when assessing platelet levels, hematocrit, and other comprehensive blood parameters (Made et al., 2022). Consequently, PLR is anticipated to serve as a novel biomarker for assessing the severity of dengue infection, particularly in developing nations. This study aimed to examine the correlation between PLR values and the severity of dengue infection among pediatric patients in RSUD dr. Soebandi Jember.

Methods

Research design

This study is a analytical observational investigation employing a cross-sectional methodology to examine the relationship between two symmetric variables over a specified timeframe within a population. The research design involved gathering Medical Records data room children ultimately diagnosed with dengue infection, specifically DF, DHF (DHF grades I and II), and DSS (DHF grades III and IV), along with information regarding platelet and lymphocyte counts on the first day of hospital admission. The Platelet to Lymphocyte Ratio (PLR) was calculated by dividing the absolute platelet count by the absolute lymphocyte count, followed by data analysis to elucidate the relationship between PLR values and the severity of dengue infection in children. This research was conducted at RSUD dr. Soebandi in Jember Regency, spanning from April 2024 to May 2024.

Study subjects

All medical records for pediatric patients between the ages of 0 and 18 who received treatment in RSUD dr. Soebandi Jember from January 2021 to April 2023 were ultimately diagnosed with dengue infection, specifically DF, DHF (DHF grades I and II), and DSS (DHF grades III and IV). These patients were confirmed to be free from other infectious diseases such as hepatitis, tuberculosis, pneumonia, and typhoid, as well as any hematological disorders or congenital diseases, based on the medical records reviewed.

Sample size determination

The sampling process employed a stratified random sampling technique. The overall population was categorized into three distinct subpopulations or strata: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS), adhering to specific inclusion and exclusion criteria. Subsequently, the necessary sample size was computed using the proportional allocation formula to ascertain the number of samples needed from each stratum. After determining the required sample size, the subjects within each stratum were assigned numerical identifiers, and a selection of samples was randomly drawn from each stratum utilizing the random module in the Python programming language. These randomly selected samples constituted the research samples for analysis in this study, with a total of 33 samples utilized.

Statistical analysis

Data analysis will be conducted using the Statistical Package for Social Science (SPSS) software. The analysis will encompass two methodologies: univariate and bivariate analysis. Univariate analysis will summarize the Platelet-to-Lymphocyte Ratio (PLR) and the severity of dengue infection in children, presented in a tabular format. Subsequently, bivariate analysis will employ Spearman correlation at a 99% confidence level to examine the relationship between the PLR and the severity of dengue infection in children.

Ethical clearance

This research was approved by the Ethics Committee of the Faculty of Medicine, University of Jember (Number: 1153 /UN25.1.10.2/KE/2024)

Results

This study was carried out in the Medical Records department at RSUD dr. Soebandi, analyzing medical record data of all pediatric patients aged 0-18 years who received treatment in the Aster room at RSUD dr. Soebandi Jember from January 2021 to April 2023, with a final diagnosis of dengue infection (DF, DHF, and DSS). A total of 33 samples were selected based on specific inclusion and exclusion criteria, resulting in 12 samples from the DF subpopulation, 12 from DHF, and 9 from DSS. Subsequently, all samples were coded using Microsoft Excel and randomized, with the actual names of the participants replaced by initials.

Discussion

Children aged over 5 years represented the group with the

highest number of cases across all degrees of severity of dengue infection. Research conducted at Abdul Wahab Sjahranie Hospital in Samarinda in 2021 supports this finding, revealing that the majority of patients diagnosed with dengue infection were older than 5 years. This trend may be attributed to the fact that children in this age group are more likely to engage in outdoor activities compared to younger children. The Aedes aegypti mosquito typically bites in the morning, particularly between 09:00 and 10:00 AM, increasing the likelihood of infection in children who are outside during these hours (Pratiwi et al., 2021). Similar findings were reported in a study conducted at Dr. Soetomo General Hospital in 2020, where children over the age of 5 years constituted the majority of dengue cases (Fadilla et al., 2020).

Analysis of platelet data revealed that the percentage of thrombocytopenia was 100% in children with Dengue Shock Syndrome (DSS), 83.33% in those with Dengue Hemorrhagic Fever (DHF), and 50% in those with Dengue Fever (DF). These findings indicate that the severity of infection correlates with the degree of thrombocytopenia (Chatterjee et al., 2020).

Table 1. Age Characteristics of the Research Samples

Age	Frequency	
	n	%
DF		
<1	2	16.67
1-5	4	33.33
>5	6	50
DHF		
<1	3	25
1-5	1	8.33
>5	8	66.67
DSS		
<1	1	11.11
1-5	2	22.22
>5	6	66.67

Table 2. Gender Characteristics of Research Samples

Gender	Frequency	
	n	%
DF		
Boy	6	50
Girl	6	50
DHF		
Boy	4	33.33
Girl	8	66.67
DSS		
Boy	8	88.89
Girl	1	11.11

Table 3. Characteristics of Platelet Values of Research Samples

Platelet Value	Frequency	
	n	%
DF		
Low (<150)	6	50
Normal (150-450)	6	50
High (>450)	0	0
DHF		
Low (<150)	10	83.33
Normal (150-450)	2	16.67
High (>450)	0	0
DSS		
Low (<150)	9	100
Normal (150-450)	0	0
High (>450)	0	0

Table 4. Characteristics of Lymphocyte Values of Research Samples

Lymphocyte Value	Frequency	
	n	%
DF		
Low (<3000)	10	83.33
Normal (3000-9500)	2	16.67
High (>9500)	0	0
DHF		
Low (<3000)	6	50
Normal (3000-9500)	6	50
High (>9500)	0	0
DSS		
Low (<3000)	1	11.11
Normal (3000-9500)	5	55.55
High (>9500)	3	33.33

Table 5. Characteristics of PLR Values of Research Samples

PLR Value	Frequency	
	n	%
DF		
Low (<90)	3	25
Normal (90-210)	7	58.33
High (>210)	2	16.67
DHF		
Low (<90)	11	91.67
Normal (90-210)	1	8.33
High (>210)	0	0
DSS		
Low (<90)	9	100
Normal (90-210)	0	0
High (>210)	0	0

Table 6. Spearman Correlation Analysis Results

			Severity	PLR Value
Spearman's rho	Severity	Correlation Coefficient	1.000	-.753**
		Sig. (2-tailed)	.	.000
		N	33	33
	PLR Value	Correlation Coefficient	-.753**	1.000
		Sig. (2-tailed)	.000	.
		N	33	33

**. Correlation is significant at the 0.01 level (2-tailed).

Lymphocyte data also demonstrated that lymphocytosis occurred most frequently in the most severe cases, with a peak percentage of 33.33%. Regarding Platelet-to-Lymphocyte Ratio (PLR) values, all DSS cases showed low PLR levels, followed by 91.67% of DHF cases, indicating a possible association between lower PLR and increased severity of dengue infection.

Spearman correlation analysis yielded a correlation coefficient of -0.753 with a significance value of 0.000. A correlation coefficient in the range of 0.6 to 0.79 is considered strong, and the negative value indicates an inverse relationship: as PLR values increase, the severity of dengue infection decreases, and vice versa. The significance value of 0.000 indicates a statistically significant relationship between PLR and the severity of dengue infection in children, as it is lower than the threshold of 0.01. These findings are in line with previous research by (Cai et al., 2021), which also established a relationship between PLR and dengue severity. Furthermore, a

study conducted in 2023 demonstrated that PLR could be used as a predictive marker for dengue infection (Jelia et al., 2023). Another study by (Verliyanti et al., 2023) found significant differences in PLR between patients who survived and those who died from grade IV dengue, suggesting that PLR monitoring may be useful for tracking the clinical progression of dengue patients.

PLR (Platelet-to-Lymphocyte Ratio) is a comparative biomarker between platelets and lymphocytes. It serves as a cost-effective marker of inflammation and is readily available in most clinical settings (Simadibrata et al., 2022). In dengue infection, patients typically experience thrombocytopenia. The reduction in platelet count is caused by multiple mechanisms associated with dengue virus infection, primarily platelet destruction and platelet aggregation. This mechanism explains why the average platelet count in DHF (Dengue Hemorrhagic Fever) is lower than in DF (Dengue Fever) (Tasya et al., 2022). One key mechanism of platelet destruction involves binding to the C3b fragment of the complement system. Activation of the complement pathway leads to the production of C3 fragments, including C3b and its degradation products, such as iC3b and C3g (Koupenova et al., 2022). These fragments can bind to various cell surfaces, including platelets. The binding of C3b to platelets facilitates their opsonization by complement receptors on phagocytic cells, such as macrophages. As a result, C3b-tagged platelets become targets for enhanced phagocytosis, leading to accelerated platelet destruction and a consequent decrease in circulating platelet levels (Koupenova et al., 2022). Additionally, the C3a fragment acts as a potent anaphylatoxin that induces degranulation of mast cells and basophils, resulting in the release of histamine and other inflammatory mediators. This cascade promotes inflammation of the endothelial lining and increases capillary permeability, leading to plasma leakage from blood vessels into surrounding tissues (Propson et al., 2021).

Thrombocytopenia is also driven by platelet aggregation triggered by antigen-antibody complexes. These complexes can bind to platelets via the Fcγ (Fragment crystallizable gamma) receptors on the platelet surface, which interact with the Fc portion of antibodies. Moreover, the dengue virus itself can directly bind to platelet surface molecules, further enhancing aggregation (Audia et al., 2021). This aggregation leads to the formation of microthrombi within blood vessels, which may impede blood flow and contribute to endothelial damage. Platelets aggregated due to antigen-antibody complexes are recognized as targets for destruction by the reticuloendothelial system (RES), primarily composed of macrophages in the spleen and liver. These macrophages express Fcγ receptors that detect the antibody-bound platelets. Upon recognition, the macrophages phagocytose and eliminate the platelets, causing a further decline in circulating platelet count (Audia et al., 2021). Dengue infection is also associated with impaired platelet function, particularly in the release of Adenosine Diphosphate (ADP), a crucial molecule in platelet aggregation (Widodo, 2017). Normally, ADP is released from platelet granules and strengthens aggregation by binding to specific ADP receptors on neighboring platelets. Impaired ADP release reduces the ability of platelets to aggregate and form an effective hemostatic plug, thereby increasing the risk of severe bleeding (Lunghi et al., 2020).

When a person is infected with the dengue virus through the bite of an infected Aedes mosquito, the virus initially targets dendritic cells. These infected dendritic cells then migrate to the lymph nodes, where the virus replicates and initiates an adaptive immune response. In the lymph nodes, activated dendritic cells present viral antigens to T cells, leading to the activation and proliferation of both CD8+ and CD4+ T cells (Khanam et al., 2022). CD8+ T cells function to recognize and destroy cells infected with the dengue virus, while CD4+ T cells regulate and amplify the immune response by releasing various cytokines. Cytokines such as IFN-γ, TNF-α, and IL-2 are released in large quantities, enhancing T cell proliferation and attracting more lymphocytes to the site of infection through chemotactic mechanisms. Additionally, increased cytokine production stimulates B cells components of the humoral immune response to produce specific antibodies against the dengue virus. At this stage, the lymphocyte count in the blood rises significantly (Setiawan et al., 2023). When thrombocytopenia (a decrease in platelet count) and lymphocytosis (an increase in lymphocyte count) occur simultaneously, the Platelet-to-Lymphocyte Ratio (PLR) becomes inversely proportional to the severity of infection. In other words, as dengue infection becomes more severe, platelet counts tend to decline while lymphocyte counts increase, resulting in a further decrease in PLR.

Although this study found a significant and strong correlation between PLR and the severity of dengue infection in children, several limitations should be considered. Notably, platelet and lymphocyte data were collected only on the first day of hospital admission, without follow-up measurements in subsequent days. Therefore, trends in platelet and lymphocyte levels over the course of the illness were not monitored, which may limit the interpretation of the dynamic relationship between PLR and disease progression.

Conclusion

The conclusion of this study is that there is a significant relationship between the Platelet-to-Lymphocyte Ratio (PLR) and the severity of dengue infection in pediatric patients in the Aster Room at RSUD dr. Soebandi Jember with a strong negative correlation level ($p = 0.000$ and correlation coefficient $= -0.753$).

Conflict of Interest

No potential competing interest was reported by the authors

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Author contribution

NJG : conceptualizer (main), methodology (main), journal submission (main), editing (main), writing (main), writing review (assistant); RR: drafting concept (main), writing review (main), correspondence writing (main), editing (main), methodology (assistant); MAS: methodology (assistant), writing review (main); RD: writing review (main), methodology (assistant); SR: writing review (main), methodology (assistant), editing (assistant), concept organizer (main), writing (assistant).

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