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The relationship between platelet to lymphocyte ratio with neonatal sepsis at Wangaya General Hospital

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ABSTRACT

Background: Neonatal sepsis is still a major health problem throughout the world and one of the leading causes of morbidity and mortality in neonates. This disease often goes undetected and causes death. The diagnosis and treatment of neonatal sepsis is still a problem today. According to current research, the platelet-to-lymphocyte ratio (PLR) plays a significant role in the inflammatory process. This study aims to contribute to the research on whether PLR is connected with the incidence of neonatal sepsis and can be used as a biomarker of neonatal sepsis.

Methods: This cross-sectional observational analytic study examines the link between platelet-to-lymphocyte ratio and neonatal sepsis. Based on medical records, this investigation's total number of

samples was 36 newborns.

Results: From June 2022 to June 2023, there were 539 newborns in the hospital. The prevalence of neonatal sepsis was 23 neonates (4,2%) and there were 14 neonates (2,6%) that fulfilled the criteria in this study. Based on the characteristics of PLR, the mean value in neonatal sepsis was found to be 125.71. Bivariate analysis using statistical Chi-square revealed that PLR had a p-value of 0.009, odds ratio of 6.7, and 95% CI of 1.5 - 29.6.

Conclusion: There was a correlation between PLR and neonatal sepsis in Wangaya Hospital. Patients with increased PLR were six times the odds of having neonatal sepsis compared to patients with non-increased PLR.

Keywords: Platelet lymphocyte ratio, Biomarker, Neonatal sepsis.

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INTRODUCTION

Neonatal sepsis makes a high contribution to morbidity and mortality in neonates and is a major global public health challenge.¹ Sepsis is a common condition in infants, affecting 1-5 per 1000 neonates in industrialized nations and 10-50 per 1000 neonates in impoverished areas.² Indonesia has a high neonatal mortality rate, estimated to be 15 deaths per 1000 live births with sepsis being the fourth leading cause of mortality (13%), this is higher than many neighboring countries.³ That figure is still far from the SDGs, which seek to cut newborn mortality rates to at least 12 deaths per 1000 live births by 2030.⁴ The age of newborns and the age at which symptoms are diagnosed are used to classify sepsis. Early-onset sepsis (EOS) is defined as symptoms appearing before the first week of birth. However, some experts

limit the term to illnesses discovered within the first three days of life.⁵ The start of symptoms after the first week of life is referred to as late-onset sepsis (LOS). Several definitions are available, ranging from the first three days of life to more than a week.⁶

Neonatal sepsis is classified into three types: suspected sepsis, clinical sepsis, and proven sepsis. Suspected sepsis, whether or not there is a clinical symptom, the existence of sepsis risk markers in the infant, or results indicative of sepsis in follow-up. Clinical sepsis is characterized by the presence of clinical and laboratory symptoms despite the absence of the causal pathogen. There are clinical and analytical signs in confirmed sepsis and pathogenic bacteria in sterile field cultures.⁷ In neonatal sepsis, signs and symptoms are often non-specific.⁸ The primary

point in treatment is early diagnosis and proper antibiotic treatment with blood culture results, and the usefulness of a suspicion index based on clinic and laboratory indicators should be stressed.⁹ Blood culture is the gold standard for detecting neonatal sepsis. However, it is time-consuming and frequently yields negative results.⁹ An inadequate sample may cause false negative blood culture results, the mother's antibiotic use, the antibiotic dose used before sampling, a low number of bacteria in the blood, or short-term bacteremia.⁷ Even today, diagnosing and treating neonatal sepsis remains difficult. In diagnosing neonatal sepsis, biomarkers that react quickly after initiating the inflammatory process are critical.¹⁰ Early and effective treatment is critical for outcome and prognosis in neonatal sepsis cases. In high-risk

infants, the administration of empirically selected broad-spectrum antibiotics is required. However, empirical treatment raises the risk of severe medication effects, nosocomial problems, and the emergence of resistant strains.¹³

According to current research, platelets and lymphocytes play an important part in the inflammatory process. PLR is a marker of the balance of inflammation and thrombosis. As a result, the inflammatory state causes increased megakaryocyte growth and thrombocytosis.^{14,15,16} Furthermore, increased platelet counts and decreased lymphocyte numbers have been linked to aggregation and inflammation and serve as risk markers. Blood culture examination as the gold standard of diagnosis has several weaknesses, so it encourages clinicians to find new markers with shorter examination times and more affordable costs.¹⁷ Research on PLR as a biomarker of neonatal sepsis diagnosis is still rare. Therefore, this study aims to determine the correlation of PLR with neonatal sepsis to be used as a biomarker of neonatal sepsis and reduce mortality and the inappropriate use of antibiotics in neonatal sepsis.

METHODS

This was an observational analytic study with a cross-sectional design. The samples in this study were neonates treated in the rooms of Perina and Neonatology Intensive Care Unit (NICU) at Wangaya Hospital from June 2022 until June 2023. The total samples in this study were 36 neonates based on medical records. This study sample was selected by consecutive sampling. Subjects were neonates aged 0 to 28 days old who were diagnosed with suspected sepsis, clinical sepsis and proven sepsis. Exclusion criteria were subjects with autoimmune diseases, congenital abnormalities, incomplete data of medical records, and premature birth (<37 weeks gestation). This study's dependent variable was neonatal sepsis, and the independent variable was the platelet-to-lymphocyte ratio. Neonatal sepsis in this study included patients with suspected sepsis, clinical sepsis, and proven sepsis. Suspected, clinical, and proven sepsis are assumed to be neonatal sepsis. PLR is platelet divided by absolute lymphocyte value using a cut-

off of 90.846.¹⁸ PLR is normal/decreased if ≤ 90.846 and PLR is increased if >90.846 . In this research, univariate analysis was used to describe the characteristics of respondents, followed by bivariate analysis to find the relationship between dependent and independent variables by using the Chi-Square test. The relationship will be significant if the p-value is <0.05 with a 95% confidence interval. The analysis was made using the Statistical Product and Service Solution (SPSS) version 26 program.

RESULT

This study examined the relationship between platelet-lymphocyte ratio and the occurrence of neonatal sepsis at Wangaya General Hospital from June to September 2023. The population of this study was neonate patients who fulfilled the inclusion and exclusion criteria from June 2022 to June 2023 and had platelet levels and lymphocyte levels recorded. During the study period there were 539 newborns in the hospital. Then, 147 infants were excluded because they were born prematurely and had congenital abnormalities. Then the samples were categorized into two groups: healthy babies and babies with suspected sepsis, clinical sepsis or proven sepsis. From a total of 392

samples, 23 samples with clinical sepsis/proven sepsis were excluded because they did not have complete data, resulting in a total of 14 samples with suspected sepsis, clinical sepsis or proven sepsis. Then the remaining 16 samples were taken from healthy born babies who had complete data.

Table 1 shows the characteristics of the subjects. In total, 19 subjects (52.8%) were male, while the remaining 17 subjects (47.2%) were female. The study's findings revealed that there was no significant association between gender and the occurrence of neonatal sepsis. Furthermore, based on Table 1, those who had severe asphyxia were 3 subjects (8.3%), those who experienced moderate asphyxia were 14 subjects (38.9%), and those who did not experience asphyxia were 19 subjects (52.8%). According to the study's findings, there was no significant association between the incidence of asphyxia and neonatal sepsis ($p=0.161$).

Table 2 shows the platelet-to-lymphocyte ratio features in neonatal sepsis patients. There is a minimal value of 21, which means that there is just one sepsis sample with a platelet-to-lymphocyte ratio of 21. When calculating the mean PLR in sepsis without 1 sample with a value of 21, the result is 133.7.

Table 1. Subject characteristics

Variable	Frequency	Percent (%)	p
Gender			
Male	19	52.8	0,765
Female	17	47.2	
Asphyxia			
No	19	52.8	0,161
Moderate	14	38.9	
Severe	3	8.3	

Table 2. Characteristics of platelet to lymphocyte ratio

Condition	Mean	Minimum-Maximum	Median	SD
Neonatal sepsis	125.71	21-254	146.00	62.832
None neonatal sepsis	73.91	16-167	71.00	33.147

Table 3. The relationship of platelet to lymphocyte ratio with neonatal sepsis

Increased PLR	Neonatal Sepsis		P value	OR	95% CI
	Yes	No			
Yes	10	6	0,009	6.67	1.5-29.6
No	4	16			
Total	14	22			

Description : Yes = Increased PLR $> 90,846^{18}$
No = Non-increased PLR $\leq 90,846^{18}$

Table 3 shows the research findings about the relationship between platelet lymphocyte ratio and the incidence of neonatal sepsis. The statistical analysis revealed a significant ($p=0.009$) connection between PLR and the incidence of neonatal sepsis. According to the risk estimate calculation results in Table 3, the odds ratio value was 6.67 with a 95% confidence interval of 1.5-29.6. This means that patients with an increased platelet-lymphocyte ratio have an odds of 6.67 times experiencing neonatal sepsis compared to patients who have a non-increased platelet-lymphocyte ratio.

DISCUSSION

Neonatal sepsis is a systemic response to infection in newborns, which is one of the major causes of mortality and morbidity in neonates worldwide.¹ In this study, there was no significant difference regarding gender. This is in agreement with Parajuli et al.¹⁹ and Xiao et al.²⁰, who found the same result. However, Soliman et al.²¹ found that 60% of the babies in the sick group were males, which is consistent with numerous earlier investigations.^{22,23} This could be related to mutations in X-linked immunoregulatory genes involved in thymus function or immunoglobulin production.²⁴ Trotman and Bell²⁵, on the other hand, discovered that the female gender was related to worse outcomes in patients with bacterial sepsis. As a result, the influence of gender on sepsis was inconclusive.

According to the findings of this study, there is no substantial link between the occurrence of asphyxia and neonatal sepsis. This study is in accordance with the study by Widayati²⁶ that found no relationship between asphyxia and the incidence of neonatal sepsis. Another study by Getabelew²⁷ and Adatara²⁸ found that infants with asphyxia have a risk of 3.5 and 2.6 times experiencing sepsis when compared to infants without asphyxia. Infants who experience asphyxia usually require respiratory support, which increases the risk of exposure to pathogens. Besides that, infants are more likely to have poor adaptation to extra-uterine life caused by stress that occurs during labor, so they are more susceptible to infection.^{26,28}

Previous research has revealed that a high platelet-lymphocyte ratio (PLR) is associated with an increased mortality risk in sepsis patients with an increase in platelet count and a reduction in lymphocyte count. However, some pathogenic microorganisms, particularly in bloodstream infections, can cause thrombocytopenia by inducing death in platelets. Thrombocytopenia occurs in 20-30% of people infected with *S.aureus*, *E.coli*, or *S.pneumonia*, showing that platelet activity from pathogens leads to thrombocytopenia. In 1 sample, it may be caused by a specific pathogen so that platelet values do not increase and lymphocytes do not decrease. In general, up to 20% of sepsis patients develop thrombocytopenia, and 10% of them have severe thrombocytopenia.²⁹

The findings of this study, which revealed a significant relationship between PLR and the incidence of neonatal sepsis, are consistent with the findings of Arcagok et al.¹⁷, who discovered that the platelet lymphocyte ratio was significantly ($p<0.001$) higher in the neonatal sepsis group than in the control group, with a positive predictive value of 94.3% to 97.4% and a negative predictive value of 88.6% to 91.8% in the diagnosis. As a result, it is possible to conclude that PLR can be used to predict neonatal sepsis.¹⁷ The findings of this study are also consistent with the findings of Zhang et al.¹⁸, who discovered that the platelet-lymphocyte ratio has a high predictive value of early-onset neonatal sepsis ($p=0.012$), with the odds of neonates with PLR increasing 11.54 times more than those with PLR not increasing.¹⁸ Similarly, the results of a study conducted by Mahmoud *et al.*³⁰ showed that the lymphocyte platelet ratio was significantly ($p=0.0001$) higher in the neonatal sepsis group than the control group, with a positive predictive value of 72% and a negative predictive value of 73% in cases diagnosed with sepsis. In conclusion, One of the markers for predicting early-onset neonatal sepsis is the platelet-lymphocyte ratio.³⁰⁻³³ But there is 1 study with different results, which is the results of research by Mira et al., where there is no association between PLR and early onset sepsis.³⁴ This can be caused because preterm neonates

were not excluded. This may be because preterm infants have a lower mean platelet count than term infants, with similar normal values in healthy elderly, children and adults ($150-450 \times 10^3$).³⁵

Blood analysis is a simple and straightforward procedure in which platelet and lymphocyte counts are routinely utilized as clinical markers.³¹ When there is inflammation, many cytokines and chemokines suppress lymphocyte growth and activation, reducing the number of lymphocytes throughout the body. Furthermore, during systemic inflammation, megakaryocytes increase their rate of proliferation, resulting in thrombocytosis.³² However, the prognostic usefulness of platelets in sepsis is still unknown. Several studies have found a link between platelet count and illness severity. Platelets were not related to early onset neonatal sepsis, according to Can et al.³³ Platelet to lymphocyte ratio (PLR) is a new and simple metric that has been shown to have a strong predictive value in the diagnosis of inflammatory disorders in adults.¹⁷

CONCLUSION

In this study, from the statistical analysis of the relationship between platelet to lymphocyte ratio in neonatal sepsis patients, it was found that there was a significant relationship between PLR and the incidence of neonatal sepsis, where an increased PLR had a six times higher probability of experiencing neonatal sepsis compared to a PLR that did not increase.

ETHICAL CLEARANCE

This study was reviewed and approved by the Ethical Committee of Wangaya General Hospital with the following number: 070/3798/RSUDW before the study was conducted.

CONFLICTS OF INTEREST

There are no conflicts of interest in this study.

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None.

AUTHOR'S CONTRIBUTION

All authors contributed to the manuscript writing and agreed to the final version of the manuscript for publication.

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