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Original Article

Platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), and diastolic dysfunction as neonatal sepsis mortality predictors in preterm neonates

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Abstract

Background Neonatal sepsis is a significant challenge in neonatal care, particularly among preterm neonates who are highly vulnerable due to their underdeveloped immune systems. Traditional markers for predicting the outcomes of neonatal sepsis, such as procalcitonin and C-reactive protein, are not always available all across places.

Objective To evaluate the predictive value of platelet lymphocyte ratio (PLR), neutrophil lymphocyte ratio (NLR), and diastolic dysfunction for neonatal sepsis mortality in preterm neonates.

Methods A prospective cohort study was conducted in 42 preterm neonates with neonatal sepsis admitted to Dr. Moewardi Hospital. The PLR and NLR were collected at two time points: the first blood specimen was drawn within the first 24 hours of life and the second was collected 72 hours later. Diastolic function was assessed by echocardiography performed within 48-72 hours after the diagnosis of sepsis. Mortality during treatment was recorded as the dependent variable. The relationships among these variables were analyzed with bivariate and multivariate analyses, and the significance level was set at $P<0.05$.

Results Of 42 subjects, 57.1% died. Increased NLR and diastolic dysfunction were significantly associated with an increased risk of mortality (OR 3.64; $P=0.049$ and OR 25.0; $P<0.001$, respectively), while PLR was not. Multivariate analysis revealed that diastolic dysfunction remain a significant independent predictor of mortality (adjusted OR 28.9;$P=0.001$), whereas NLR did not maintain statistical significance ($P=0.093$).

Conclusion Diastolic dysfunction was an independent predictor of mortality in preterm neonatal sepsis. The NLR and PLR did not associate with mortality in preterm neonatal sepsis. Rigorous monitoring of cardiovascular function is crucial in the management of neonatal sepsis. **[Paediatr Indones. 2025;65:216-23; DOI: https://doi.org/10.14238/pi65.3.2025.216-23**].

Keywords: *neonatal sepsis; preterm; PLR (platelet lymphocyte ratio); NLR (neutrophil lymphocyte ratio); diastolic dysfunction; mortality*

Neonatal sepsis remains a major problem as the third highest cause of death globally. The high infant mortality rate is partly due to neonatal infections and prematurity. A systematic analysis involving 103 countries reported that the incidence of premature birth in the last decade was 13.4 million annually worldwide.[1] The Indonesian Ministry of Health reported in 2018 that the prevalence of prematurity was 29.5 per 1,000 live births, with a mortality rate of 45%.[2]

Neonatal sepsis is a manifestation of systemic infection causing hemodynamic disturbances occurring within the first 28 days of life. Sepsis can be caused by bacteria, fungi, or viruses.[3,4] Preterm neonates have immature immune systems, characterized by lower complement levels, reduced opsonization capability, and diminished quantity and quality of polymorphonuclear cells, resulting in more severe sepsis than that of full term neonates.[5] Innate and adaptive immune functions of preterm neonates are not fully developed. The skin and

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mucous membrane integrity are not fully formed.[6] Regarding the adaptive immune system of preterm neonates, there are three mechanisms of neonatal sepsis, namely the overexpression of genes leading to increased production of pro-inflammatory cytokines such as IFNα/β, IFNγ, IL-1, and IL-6, an increase in pathogen recognition receptors, notably toll-like receptors (TLR), and a deficiency in maternally derived transplacental immunoglobulin G.[5]

Neutrophils, a component of the innate immune system, possess pattern recognition receptors (PRR) that detect pathogen-associated microbial components (PAMPs) and damage-associated molecular patterns (DAMPs) in microbes and damaged tissue, to combat pathogens.[7] A compensatory increase in neutrophils triggers a process known as emergency granulopoiesis. Granulocyte-colony stimulating factor (G-CSF) increases granulopoiesis, thereby boosting neutrophil levels while suppressing lymphopoiesis.[8]

Platelets play a role in both innate and adaptive immune systems. Through TLR-4, -6, and -9, platelets are activated by lipopolysaccharides from gram-negative bacteria, enhancing the processes of adhesion and aggregation.[9] The increase of inflammatory mediators in sepsis such as TNF-α, IL-1β, and IL-6 stimulates platelet production in bone marrow, increasing the number of circulating platelets during the early phase of inflammation.[10] Thus, PLR can potentially serve as an acute hematological marker suggesting the severity of inflammation.

The myocardium of preterm neonates is physiologically more susceptible to damage from sepsis due to less contractility than term neonate.[11] Inflammatory mediators of sepsis, such as TNF-α, IL-1β, IL-6, calcium balance disruptions, and decreased NO, cause myocardial dysfunction and diastolic relaxation, increase systemic vascular resistance, and disrupt the diastolic filling phase.[11] Diastolic dysfunction, indicated by a decreased E/A ratio on echocardiographic examination, has been shown to significantly correlate with mortality in neonates with sepsis.[12] Accordingly, diastolic dysfunction in neonates can indicate the severity of the inflammatory process.

In contrast to hematologic markers such as PLR and NLR that primarily reflect systemic inflammation, the assessment of diastolic function offers a more direct insight into cardiovascular compromise, a critical yet often underappreciated component of neonatal sepsis. Echocardiographic evaluation of diastolic function, especially through the E/A ratio, is a non-invasive, bedside-accessible, and relatively cost-effective method. It does not rely on consumable reagents or laboratory turnaround time, making it highly applicable in resource-limited settings. Importantly, diastolic dysfunction may precede overt hemodynamic collapse, thus providing unique prognostic value beyond what is offered by PLR and NLR. In this regard, incorporating cardiac function assessment could enhance early risk stratification and guide more intensive monitoring or intervention strategies in critically ill preterm neonates with sepsis.

Most existing studies on neonatal sepsis prognosis focus solely on hematologic markers such as PLR and NLR, without considering cardiovascular involvement, which is a critical aspect of systemic inflammation and organ dysfunction. The novelty of this study lies in the integration of diastolic dysfunction assessment with PLR and NLR, offering a multidimensional prognostic approach. To our knowledge, this is among the first studies to evaluate diastolic function specifically in preterm neonates with sepsis in conjunction with these hematologic ratios. .

Studies investigating the role of diastolic function in neonatal sepsis particularly in preterm neonates are limited. Most published studies reported on hematological parameters such as PLR and NLR as prognostic indicators of mortality in neonatal sepsis. Therefore, we analyzed the capacities of PLR, NLR, and diastolic dysfunction to predict mortality of preterm neonates with sepsis. While echocardiography may not be universally available at all primary care centers, it is increasingly accessible at tertiary or referral hospitals - often more so than advanced laboratory tests such as procalcitonin. Moreover, echocardiography provides immediate bedside information without the need for reagents or laboratory processing, making it a valuable tool.

Methods

We conducted a prospective cohort study in preterm neonates with gestational age ranging from 28 to 36 6/7 +6 weeks, defined as the duration of gestational age calculated from the first day of the last menstrual

period (LMP) or based on early ultrasound findings. All subjects included in this study were diagnosed with early-onset sepsis (EOS), defined as sepsis occurring within the first 72 hours of life. Neonates with late-onset sepsis (LOS) were not included in the cohort to ensure homogeneity of disease onset and to minimize confounding. These neonates were admitted to the Perinatology Unit of Dr. Moewardi Hospital between April and October 2023 and diagnosed with neonatal sepsis based on the high probable sepsis (HPS) and probable sepsis (PS) criteria by Gitto *et a*l.[13] We excluded neonates with major surgical interventions, congenital anomalies, septic shock, hypoxic-ischemic encephalopathy (HIE), and those born to mothers with immunodeficiency diseases. Informed consent was obtained from subjects' parents. The study subjects were followed-up throughout their hospital stay until discharge or death. Initial laboratory data were taken at the time of neonatal sepsis diagnosis, followed by the second data collection 72 hours later. Echocardiographic examination was done once during the hospital stay. This study was approved by the Ethics Committee of Dr. Moewardi Hospital in Surakarta. The primary outcome of this study was in-hospital mortality among preterm neonates diagnosed with early-onset sepsis. Secondary outcomes included the associations of PLR, NLR, and diastolic dysfunction with mortality.

A diagnosis of neonatal sepsis was established if the sepsis criteria set by Gitto *et al.*[13] were met, including clinical manifestations associated with sepsis, C reactive protein (CRP) level ≥ 0.5 mg/dL, at least two elevated serum sepsis markers other than CRP, and blood culture. The characteristic data collected were sex, gestational age, chronological age (recorded at the time of discharge or death), mode of delivery, birth weight, length of hospital stay, heart rate, and supportive parameters including laboratory and echocardiography findings. Laboratory parameters included platelet, lymphocyte, and neutrophil counts, and CRP. Blood laboratory examinations were performed at the Clinical Pathology Laboratory of Dr. Moewardi Hospital. Changes in PLR, NLR, and CRP levels were calculated from the two measurements. Diastolic dysfunction was determined based on E/A ratio by echocardiography during hospitalization.

The chronological age data were analyzed by calculating median and range values. Bivariate analysis was performed using Mann-Whitney U test for non-normally distributed numeric data and Chi-square test for dichotomous variables. Logistic regression was applied to the multivariate analysis. Analyses were performed with *SPSS® 26* statistical software. The significance level was set at $P<0.05$.

Results

A total of 42 neonates met the inclusion criteria, of whom 24 (57.1%) did not survive. Subjects were predominantly male (57.1%). More than 50% of subjects were categorized as moderate to late preterm. Cesarean section was more common than vaginal delivery (71.4% vs. 28.6%, respectively). The mean gestational age was significantly lower in the deceased group compared to the survived group [31.03 (SD 2.62) weeks *vs.* 32.76 (SD 1.80) weeks; $P=0.021$], and the mean birth weight was also significantly lower [1,463.96 (SD 413.32) g *vs.* 1,807.78 (SD 406.86) g; $P=0.010$), both based on independent T-test analyses (**Table 1**). All neonates in this study were diagnosed with EOS, reflecting a uniform point of disease onset across the cohort. This inclusion criterion strengthens the comparability of inflammatory and cardiac response patterns observed. However, due to the clinical protocol in our setting, echocardiography and laboratory evaluations were performed once sepsis was clinically evident, meaning that many subjects were already in a severe stage of the disease at the time of assessment. This may explain the high mortality rate observed (57.1%) and the strong association between diastolic dysfunction and mortality. The predominance of severe cases may also contribute to the limited prognostic value of PLR and NLR observed in this study, as these parameters may be more dynamic in the earlier inflammatory phase.

Bivariate analysis revealed that increased PLR had no association with mortality (OR 1.85; $P=0.353$). However, increased NLR (OR 3.64; $P=0.049$) and diastolic dysfunction (OR 25.0; $P<0.001$), and birth weight under 1500 grams (OR 8.00; $P=0.010$) were significantly associated with mortality (**Table 2**).

Multivariate logistic regression analysis showed that diastolic dysfunction remained a significant independent predictor of mortality in preterm

neonates with sepsis (adjusted OR 33.903; 95%CI 4.443 to 258.681; P=0.001). In contrast, increased NLR (adjusted OR 3.968; 95%CI 0.549 to 28.697; P=0.172) and birth weight under 1500 grams (adjusted OR 8.840; 95%CI 0.907 to 86.168; P=0.061) were not significantly associated with mortality after adjustment (**Table 3**).

Table 1. Baseline characteristics of subjects

Variables	Outcomes		P value
	Deceased (n=24)	Survived (n=18)	
Sex, n			0.553
Male	14	10	
Female	10	8	
Mean chronological age (SD), days	11.29 (8.15)	10.27 (6.21)	0.662
Mean gestational age (SD), weeks	31.03 (2.62)	32.76 (1.80)	0.021
Mean birth weight (SD), grams	1,463.96 (413.32)	1,807.78 (406.86)	0.010
Delivery type, n			0.200
Cesarean section	19	11	
Vaginal	5	7	
Mean PLR (SD)			
1st	82.36 (86.73)	104.42 (102.04)	0.454
2nd	58.35 (87.43)	71.91 (65.47)	0.584
Mean NLR (SD)			
1st	4.66 (4.54)	3.00 (2.27)	0.164
2nd	4.52 (3.80)	1.68 (1.05)	0.004
Mean E/A ratio (SD)	0.84 (0.19)	1.47 (0.30)	0.000

Table 2. Analysis of PLR, NLR, and diastolic dysfunction with mortality

Variables	Outcomes		OR (95%CI)	P value
	Deceased (n=24)	Survived (n=18)		
ΔPLR, n			1.85 (0.50 to 6.89)	0.353
Increased	10	5		
Decreased	14	13		
ΔNLR, n			3.64 (0.98 to 13.52)	0.049
Increased	14	5		
Decreased	10	13		
Diastolic dysfunction, n			25.00 (4.85 to 128.86)	<0.001
Yes	20	3		
No	4	15		
Birth weight, n			8.00 (1.50 to 42.65)	0.010
<1500 grams	12	2		
≥1500 grams	12	16		

Table 3. Multivariate analysis mortality predictor for neonatal sepsis in preterm neonates

Variables	B	S.E.	Adjusted OR	95%CI	P value
Increased NLR	1.378	1.010	3.968	0.549 to 28.697	0.172
Diastolic dysfunction	3.523	1.037	33.903	4.443 to 258.681	0.001
Birth weight <1500 grams	2.179	1.162	8.840	0.907 to 86.168	0.061

Discussion

Neonatal sepsis affected 3,930 neonates out of 100,000 live births worldwide, with a mortality rate of 17.6%.[14] In 2023, a study on early-onset neonatal sepsis revealing a mortality rate of 56%, with the largest gestational age group being 28-33 weeks (52.9%).[15] In our study, the mortality rate of neonatal sepsis was 57.1%., which is higher than the global average reported in previous studies. This may be attributed to the study population being composed exclusively of preterm neonates with early-onset sepsis, a group known to have more severe clinical courses due to immature immune and cardiovascular systems. Additionally, most subjects were already in a clinically severe condition at the time of diagnosis and echocardiographic assessment, which may have contributed to the high mortality rate observed.

Birth weight was associated with mortality in preterm infant neonatal sepsis. Systematic review and meta-analysis has reported that the case fatality rate reached 24% in infants with very low birth weight (<1,500 grams).[16] However, another study in Dr. Moewardi Hospital, Surakarta, Indonesia in 2023 found no correlation between neonates with birth weight under 2,500 grams and mortality.[15] Our findings aligned with previous reports that birth weight below 1,500 grams was significantly associated with mortality. Preterm neonates with lower birth weights exhibit an overexpression of genes affecting innate immunity responses and inflammatory processes, in which the inflammatory cytokines such as IFNα/β, IFNγ, IL-1, and IL-6, as well as receptors like TLR increase.[5]

The NLR and PLR are easily measurable markers of inflammation. Various studies have demonstrated that NLR and PLR can be used to predict prognoses of several diseases, including sepsis. A Swiss study in 2022 compared NLR with PLR as predictors of mortality in neonatal sepsis, and found that NLR was not superior to PLR for mortality prognosis.17 Nugroho et al. suggested that NLR can be a diagnostic marker for neonatal sepsis.[18] The increase in NLR was not independently associated with mortality after multivariate analysis. sis. We also did not find a significant relationship between PLR and mortality, in contrast to a previous study which showed that low PLR was associated with poor prognosis.[17] This discrepancy with other reports may reflect differences in population characteristics, inflammatory phase at the time of sampling, or cut-off values used. These findings suggest that while NLR and PLR may reflect inflammatory status, they may have limited predictive value for mortality in preterm neonates with early-onset sepsis.

Increased NLR and PLR reflect excessive inflammatory activity. Increased neutrophil results from local infection at the onset of sepsis, as the initial antimicrobial agents. Pathogen-associated microbial components comprise gram-negative bacteria containing lipopolysaccharides, gram-positive bacteria consisting of peptidoglycan, and viruses with their own unique markers. These components are recognized by PRRs in the infected tissue and in the bone marrow, in which hematopoietic progenitor cells express TLRs. This pathogen recognition process is followed by disruptions in transcription and translation mediated by C-EBPα and C-EBPβ genes. The C-EBPβ gene enhances the proliferation of myeloid progenitor cells, while the C-EBPα gene inhibits proliferation. Dominant expression of the C-EBPβ gene stimulates the proliferation and differentiation of granulocytes mediated by IL6, IFNα, IFNγ, granulocyte-colony stimulating factor (GCSF), and granulocyte macrophage colony-stimulating factor (GMCSF). This process results in an increase in neutrophils as a marker of the inflammatory process severity.[8] In premature neonates, this mechanism is accompanied by compensatory suppression of lymphopoiesis.[8]

In response to infection, a competent immune system stimulates the activation and proliferation of T and B lymphocytes. Naive T lymphocytes will differentiate into T helper cells 1, 2, 17, and cytotoxic cells, whereas B lymphocytes turn into plasma cells in order to neutralize pathogens. In premature neonates, these differentiations are limited. During gestation, lymphopoiesis occurs later than myelopoiesis. The maturation time of lymphocytes in premature infants is shorter than that of term neonates due to their immature thymus. In addition, premature neonates have immature PRRs.[19] This explains the suppression of lymphocyte counts in neonatal sepsis, especially in premature neonates.

Severe inflammatory responses to infection significantly impact the platelet count and function.

Sepsis commonly triggers thrombocytopenia. This is primarily driven by direct interaction with pathogens through PRRs such as TLR2 and TLR4. This interaction leads to platelet activation, consumption, and clearance, contributing to a decrease in platelet count. Inflammatory mediators, including TNF-α and IL-1β, can suppress platelet production in the bone marrow. Sepsis may also induce inappropriate platelet activation and aggregation, leading to the formation of microthrombi in the microvasculature.[9,20] This process consumes platelets, worsening thrombocytopenia, and causes organ dysfunction due to impaired blood flow. Sepsis alters platelet reactivity and adhesive properties, potentially disrupting normal coagulation processes and increasing the risk of bleeding complications.[20] All of these mechanisms explain the pathophysiology of thrombocytopenia in sepsis. Nonetheless, cytokine production can also result in thrombocytosis. Platelets are formed in the bone marrow from the mature megakaryocytes. The production of megakaryocytes is enhanced by cytokines such as thrombopoietin (TPO), IL-3, IL-6, IL-9, IL-11, and stem cell factor (SCF). In addition, IL-6 promotes neutrophil recruitment. These conditions trigger the release of inflammatory cytokines, causing platelet formation in the bone marrow, which results in an increased PLR.[21]

Although elevations in neutrophil and platelet counts alongside decreased lymphocyte levels may biologically reflect the inflammatory response in neonatal sepsis, our study did not find significant associations between both of PLR and NLR with mortality. , and the association between NLR and mortality was not maintained after multivariate adjustment. These findings suggest that while PLR and NLR may provide insight into immune dynamics, their utility as independent prognostic markers in preterm neonatal sepsis remains limited. Further studies with larger sample sizes and more refined stratification may help clarify their role in clinical decision-making.

Diastolic dysfunction, a disturbance of heart's relaxation and filling, has been associated with increased mortality in preterm neonatal sepsis. This may result from reduced cardiac output and tissue hypoxia.[22] Myocardial dysfunction mechanisms include decreased right ventricular preload due to secondary compensations of vasodilation and increased vascular permeability, increased myocardial microcirculation caused by endothelial dysfunction, impaired blood flow distribution, cytokine effects, complement cascade, and abnormalities in beta-adrenergic signal transduction. The primary cytokines affecting the heart muscle causing myocardial edema as well as disrupting myocardial function and compliance are IL-1β, IL-6, and TNFα. In septic conditions these cytokines are abundant, thus, diastolic dysfunction is common in sepsis.[11]

Preterm neonates have immature myocardium and underdeveloped cardiovascular systems.[23] Thus, their hearts contain more collagen and fewer myocytes than those of term neonates, causing more spastic and less compliant hearts. In such conditions, the heart works harder by increasing heart rate in order to maintain the stroke volume.[24] Increased heart rate also obstructs the ventricular filling process during the diastolic phase, leading to compromised diastolic filling time. Frank-Starling's law pronounced that reduced diastolic filling time can decrease cardiac output, resulting in shock conditions and increased mortality.[11] Diastolic dysfunction, indicated by a decreased E/A ratio correlates with mortality in neonates with sepsis as reported by previous studies revealing that low E/A ratios is common in septic neonates.[12,25]

The underlying mechanisms by which NLR, PLR, and diastolic dysfunction may influence clinical outcomes in neonatal sepsis involve systemic inflammatory, endothelial dysfunction, and myocardial depression. These processes are interrelated in pathophysiology of sepsis. However, in our study, only diastolic dysfunction showed a statistically and independent association with mortality. While NLR and PLR reflect components of the inflammatory response and are biologically plausible as prognostic markers. Excessive inflammatory response causes endothelial dysfunction and myocardial depression, which in turn results in diastolic dysfunction and ultimately increases the risk of death.[11] Nevertheless, in our study, multivariate analysis revealed that diastolic dysfunction was the only factor significantly associated with mortality. This finding may have been due to the therapy given, which was not analyzed. Furthermore, the immature immune system in preterm neonates makes the granulopoiesis process less reactive compared to that of full-term neonates.[5] This condition may explain why NLR and PLR were not the primary factors for mortality prognosis in

preterm neonatal sepsis.

A limitation of our study was that subjects' echocardiographic measurements were not performed at the same age, which may have affected the outcomes. The younger the chronological age, the lower the E/A ratio is. We diagnosed sepsis right after the first blood test, as indicated by high CRP levels. However, in premature neonates, sepsis diagnosis can be established earlier by clinical signs of sepsis. Therefore, most of our subjects had already in a severe stage of sepsis.

Another limitation of this study is the absence of a time-to-event (survival) analysis, which is generally recommended in prognostic studies to evaluate the dynamic risk of mortality over time. However, we did not perform survival analysis such as Kaplan-Meier or Cox regression due to the relatively small sample size and the lack of exact time-point documentation for mortality events. Additionally, the study was designed to identify predictors of in-hospital mortality as a dichotomous outcome, rather than time-dependent risk. Future studies with larger sample sizes and longitudinal data are warranted to apply time-to-event models and better capture the prognostic dynamics in neonatal sepsis.

In summary, diastolic dysfunction plays a significant role in predicting neonatal sepsis mortality in preterm neonates. Therefore, close monitoring of cardiovascular function is crucial in the management of neonatal sepsis.

Conflict of interest

None declared.

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