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Short Communication

Role of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio in diagnosing neonatal sepsis

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Abstract

Clinical manifestations of neonatal sepsis are often unspecified. Therefore, sepsis biomarkers could be used to support diagnosis while waiting for blood culture results, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). The aim of this study was to evaluate the role of NLR and PLR as diagnostic markers in neonatal sepsis. A cross-sectional study was conducted at Haji Adam Malik General Hospital, Medan, Indonesia, from April to October 2019. This study included neonates aged less than 28 days, diagnosed with suspected sepsis, and had no previous history of antibiotics administration. Patients underwent clinical assessment, laboratory examination, and blood culture. Patients were grouped into sepsis and non-sepsis based on the blood culture results. The median hematological examination and the range of NLR and PLR in both the sepsis and non-sepsis groups were subjected to analysis using the Mann-Whitney U test to assess differences. NLR and PLR optimal cut-off values were determined using a receiver operator curve (ROC) with a confidence interval of 95%. A total of 137 neonates were enrolled, of which 49 were classified as sepsis and 89 as non-sepsis based on blood culture results. The optimal cutoff values for NLR and PLR were 2.75 and 11.73. Using those cutoff values, NLR and PLR could predict neonatal sepsis with sensitivities of 52.1% and 47.9%, specificities of 50.6% and 47.2%, area under the curve (AUC) of 0.46 and 0.47, with p=0.525 and p=0.662, respectively. Further investigation is warranted to refine the NLR and PLR utility and enhance diagnostic accuracy in clinical practices.

Keywords: Neonatal sepsis, diagnosis, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, blood culture

Introduction

Neonatal sepsis is a clinical syndrome from a variety of systemic diseases associated with bacteremia in the neonatal period. Neonatal sepsis occurs in 1–5 out of every 1000 live births, particularly affecting very low birth weight (VLBW) infants, who face mortality rates ranging from 13% to 25% [1]. The risk of neonatal sepsis increases in early gestational age, prematurity, chorioamnionitis and premature rupture of membranes, and history of central venous catheter use [2,3]. Neonatal sepsis is divided into early-onset sepsis (EOS) and late-onset sepsis (LOS), with early onset typically occurring within the first three days of life, often transmitted from mothers, while LOS is defined as sepsis occurring after three days of life, via vertical transmission or postnatal environment [1,4]. According to the World Health Organization (WHO), EOS is 2.6 times more common than LOS [5]. Etiologic microorganisms are typically encountered during

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intrapartum or through the maternal genital tract [1,4]. Microorganisms associated with EOS are *group B streptococcus, Escherichia coli, Staphylococcus aureus, pseudomonas sp*., and other Gram-negative enteric bacillus [4,6]. Several etiologic microorganisms associated with LOS are coagulase-negative *Staphylococcus, Staphylococcus aureus, Candida albicans, Escherichia coli, Klebsiella pseudomonas,* group B *Streptococcus*, and fungi [4].

Signs and symptoms of neonatal sepsis are frequently nonspecific and include temperature instability, lethargy, skin changes, feeding problems, and many others [1]. Isolation of bacteria from the culture is the gold standard for diagnosing sepsis [7]. Nonetheless, this approach is frequently time-consuming. However, even in cases of negative blood cultures, sepsis cannot be conclusively ruled out, as two-thirds of neonatal sepsis may exhibit low levels of bacteremia [8]. Infection markers such as complete blood count, immature-to-total neutrophil ratio, C-reactive protein (CRP), procalcitonin (PCT), cytokines (IL-6, IL-8, SIL2R, TNF-α) could help determine in diagnosing sepsis and initiating treatment while awaiting for culture results [9,10].

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) can be easily calculated from the white cell differential count, and they are considered parameters for predicting neonatal sepsis [11,12]. Neutrophils act as the first line of defense against microbial invasion through phagocytosis. The increased NLR is associated with disease severity, making it more sensitive to microbial infection [13]. PLR increases during the inflammatory response due to alterations in the body's microcirculation, increased blood vessel permeability, platelet activation, and platelet aggregation [14]. This cascade further exacerbates the body's inflammatory response [15,16]. Some previous studies have investigated the role of NLR and PLR as diagnostic markers in neonatal sepsis [16]. However, their value in predicting remains unclear. The aim of this study was to evaluate the role of NLR and PLR as diagnostic markers in neonatal sepsis.

Methods

Study design, setting and sampling

A cross-sectional study was conducted at the neonatology unit of Haji Adam Malik Hospital, Medan, Indonesia, from April to October 2019. This study employed consecutive sampling from neonates with suspected sepsis during the study period that met the inclusion and exclusion criteria. A minimum sample size of 93 was achieved based on the calculation using the formula for diagnostic test study.

Patients and criteria

This study included neonates aged less than 28 days, diagnosed with suspected sepsis, and had no previous history of antibiotics administration. Suspected sepsis was diagnosed by pediatrician by judging the clinical signs. Neonates with congenital or acquired immunodeficiency problems, such as primary immunodeficiency disease, any hematological disorders that interfere with the production of leucocytes and platelets, and incomplete data were excluded from the study.

Data collection

Demographic data and clinical data were collected, including gestation, birth weight, birth length, appearance, pulse, grimace, activity, and respiration (APGAR) score, mode of delivery, maternal risk factors for neonatal sepsis, and outcomes. Other clinical data was also gathered based on the patient's symptoms related to the sepsis. Laboratory tests and blood culture were performed using an automated BACT/ALERT microbial detection system (bioMérieux, Marcy l'Étoile, France) by collecting 5 mL of blood from the patients on hospital admission. To determine bacteria, the blood plasma was inoculated and cultivated in blood, chocolate, MacConkey agar and Saboraud dextrose agar. The following laboratory parameters were measured from each patient: hemoglobin, white blood cell count (WBC), platelet count, neutrophil count, and lymphocyte count. In addition, NLR and PLR were calculated. Based on the blood culture results, patients were grouped into sepsis and non-sepsis.

Statistical analysis

The demographic characteristics and clinical signs of each study group were presented descriptively. The median hematological parameters and the range of NLR and PLR in both groups (sepsis and non-sepsis) were compared using the Mann-Whitney U test to see any differences. NLR and PLR optimal cut-off values were measured using receiver operator curve (ROC) analysis with a confidence interval of 95%. Statistical significance was defined as a *p*-value <0.05. All statistical analysis was performed using SPSS Statistics version 22 (SPSS Inc., Chicago, USA).

Results

Characteristics of the patients

A total of 137 neonates with suspected sepsis were recruited in this study, as presented in **Table 1**. There were 48 neonates with sepsis and 89 without sepsis. Most of the neonates with sepsis were male (68.8%) and aterm (62.5%). The mean birth weights were heavier in the sepsis group. The median APGAR score in one minute and five minutes was 7 and 8.5, respectively, in the sepsis group, and 7 and 8, respectively, for the non-sepsis group. Most of the neonates were born via cesarean section, with fetal distress (41.6%) being the most prevalent maternal risk factor for neonates with sepsis. Among the neonates with sepsis, the mortality rate was 41.7%, which was higher compared to the non-sepsis group (22.5%).

Table 1. Characteristics of the neonates included in the study (n=137)

Characteristics	Frequency (percentage)	
	Sepsis (n=48)	Non-sepsis (n=89)
Sex		
Male	33 (68.8)	50 (56.2)
Female	15 (31.3)	39 (43.8)
Gestation		
Preterm (24–36 weeks)	17 (35.4)	40 (44.9)
Aterm (37–40 weeks)	30 (62.5)	45 (50.6)
Post-term (≥41 weeks)	1 (2.1)	4 (4.5)
Birth weight, grams		
Mean±standard deviation (SD)	2693.1±717.30	2551.7±82.09
Median (range)	48.4 (38.0–54.0)	47.0 (34.0–54.0)
APGAR score, median (range)		
One minute	7.0 (1.0–8.0)	7.0 (2.0–8.0)
Five minute	8.5 (5.0–10.0)	8.0 (5.0–9.0)
Mode of delivery		
Normal spontaneous delivery	14 (29.2)	25 (28.1)
Cesarian section	34 (70.8)	64 (71.9)
Maternal risk factors for neonatal sepsis		
Chorioamnionitis	0 (0.0)	10 (11.2)
Vaginal discharges	5 (10.4)	12 (13.5)
Urinary tract infection	2 (4.2)	4 (4.5)
Premature rupture of membrane	6 (12.5)	4 (4.5)
Low birth weight	4 (8.3)	18 (20.2)
Fever, unspecified	7 (14.6)	19 (21.3)
Fetal distress	20 (41.6)	18 (20.2)
Unknown	4 (8.3)	4 (4.5)
Outcome		
Discharged	28 (58.3)	62 (69.7)
Death	20 (41.7)	20 (22.5)
Leave against medical advice	0 (0.0)	7 (7.9)

APGAR: appearance, pulse, grimace, activity, and respiration score

Clinical signs of neonatal sepsis

From 137 neonates, the clinical signs of neonatal sepsis present in the patients are presented in **Table 2**. Respiratory distress was the most frequently observed (35.7%), followed by poor feeding (18.8%), jaundice (9.8%) and anemia (9.8%).

Table 2. Clinical signs of neonatal sepsis

Clinical sign	Frequency (percentage)*
Respiratory distress	40 (35.7)
Apnea	7 (6.3)
Poor feeding	21 (18.8)
Jaundice	11 (9.8)
Hypotension	6 (5.4)
Temperature instability	5 (4.5)
Cyanosis	4 (3.6)
Anemia	11 (9.8)
Lethargy	7 (6.3)

*One patient may have more than one manifestation

Hematologic examination

Median hemoglobin level was significantly lower in the sepsis group compared to the non-sepsis group (12.6 g/dL vs 14.6 g/dL, respectively; p=0.012). Similarly, the median platelet and neutrophil counts were significantly higher in the non-sepsis group compared to the sepsis group (220.5×10^3 vs 269.0×10^3/L and 62.7/µL vs 44.4/µL, respectively; with p=0.032 and p=0.003, respectively). The NLR and PLR values between the sepsis and non-sepsis groups were not significantly different (**Table 3**).

Table 3. Laboratory characteristics of the study groups (n=137)

Parameters	Median (min-max)		p-value
	Sepsis (n=48)	Non-sepsis (n=89)	
Hemoglobin, g/dL	12.6 (6.6–20.2)	14.6 (4.6–22.3)	0.012*
WBC, $\times10^9$/L	13.4 (1.0–59.7)	12.5 (1.9–39.1)	0.534
Platelet, $\times10^3$/L	220.5 (3.0–581.0)	269.0 (10.0–846.0)	0.032*
Neutrophils, /µL	44.4 (3.3–86.3)	62.7 (22.0–94.6)	0.003*
Lymphocyte, /µL	20.3 (1.4–72.9)	23.7 (3.1–57.0)	0.377
Neutrophil-to-lymphocyte ratio (NLR)	2.8 (0.1–12.5)	2.7 (0.3–29.5)	0.525
Platelet-to-lymphocyte ratio (PLR)	11.4 (0.1–161.5)	12.0 (0.4–130.3)	0.662

* Statistically significant at $p<0.05$

Blood culture assessment

Most pathogens found in the sepsis group were Gram-negative bacteria, including *Escherichia sp., Pseudomonas sp., Serratia sp., Acinetobacter sp., Elizabethkingia sp.,* and *Enterobacter sp. Klebsiella sp.* (10.9%) was the most prevalent identified pathogen. Additionally, Gram-positive bacteria were also identified, such as *Bacillus sp., Corynebacterium sp., Enterococcus sp., Staphylococcus sp., and Cryptococcus sp. Klebsiella sp.* and *Staphylococcus sp* (**Table 4**).

Table 4. Etiologies of neonatal sepsis (n=48)

Pathogen	Frequency (percentage)
Gram-negative bacteria	
Escherichia sp.	1 (7.0)
Pseudomonas sp.	2 (1.5)
Serratia sp.	1 (0.7)
Acinetobacter sp.	4 (2.9)
Elizabethkingia sp.	1 (0.7)
Enterobacter sp.	2 (1.5)
Klebsiella sp.	15 (10.9)
Mycoides sp.	1 (0.7)
Stenotropomonas sp.	2 (1.5)
Gram-positive bacteria	
Bacillus sp.	5 (3.6)
Corynebacterium sp.	2 (1.5)
Enterococcus sp.	3 (2.2)
Staphylococcus sp.	8 (5.8)
Cryptococcus sp.	1 (0.7)

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) sensitivity and specificity in diagnosing neonatal sepsis

The study established an NLR cut-off value of 2.75 (based on ROC analysis) for predicting neonatal sepsis, demonstrating a sensitivity of 52.1% and a specificity of 50.6%. The area under

the curve (AUC) of ROC was 0.46. The positive predictive value (PPV) and negative predictive value (NPV) were 36.2% and 66.1%, respectively, with p=0.525. The PLR cut-off value of 11.73 was identified for predicting neonatal sepsis, with a sensitivity of 47.9% and a specificity of 47.2%. The AUC was 0.47, with a PPV of 32.8%, an NPV of 62.6%, and a p=0.662 (**Table 5** and **Figure 1**).

Table 5. Diagnostic values of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as predictors for neonatal sepsis

Marker	Area under the curve	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	*p*-value
NLR (2.75)	0.46	52.1	50.6	36.2	66.1	0.525
PLR (11.73)	0.47	47.9	47.2	32.8	62.6	0.662

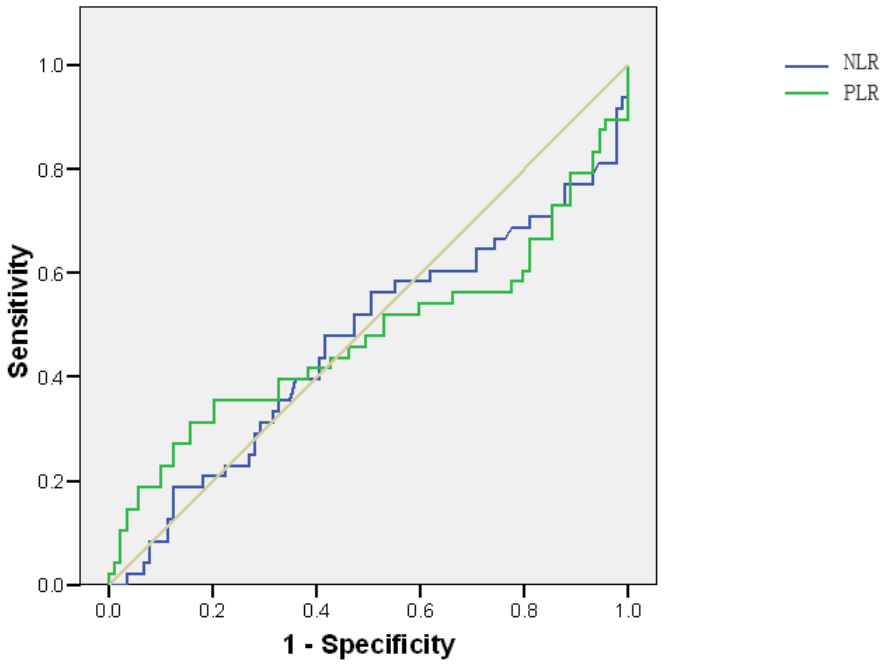

Figure 1. Receiver operating characteristic curve of neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) as predictors for neonatal sepsis.

Discussion

Neonatal sepsis poses a life-threatening risk during the neonatal period and pathogens are typically acquired during the intrapartum period or from the mother's genital tract [1,4]. During the sepsis period, the number of leukocytes can vary according to the stage of sepsis, the host's immunologic status, and the etiology of infection. An increase in the neutrophil count and a decrease in the lymphocyte count are signs of infection [17]. The NLR and PLR have been the subject of considerable investigation due to their routine utilization, cost-effectiveness, and potential diagnostic value in neonatal sepsis [18] and other diseases [19,20].

A study demonstrated that the NLR was higher in the neonatal sepsis group compared to the control group, with an NLR cutoff value of 2.7 exhibiting a sensitivity of 80% and specificity of 57.1% [21]. Similarly, our study showed a cut-off value of NLR 2.75, an AUC of 0.46, with lower sensitivity and specificity, 52.1% and 50.6%, respectively. Another study analyzed NLR as a predictor of EOS in preterm infants [22]. Elevation of NLR represents a unique inflammatory marker that implicated the imbalance immune system in the pathogenesis of neonatal sepsis [23]. The NLR showed an AUC of 0.78 with a cut-off value of 1.77, sensitivity of 73%, and specificity of 78% [22]. In another study, neonates with a lower cut-off than this study, NLR≥2.12 had almost double the risk of positive blood culture in neonatal sepsis [24].

A previous study found that PLR is a valuable marker for predicting neonatal sepsis, with a sensitivity of 88.9% to 91.3% and a specificity of 94.7% to 97.6% [25]. A study reported that mean

platelet volume and NLR showed a significant difference between neonatal sepsis and control, while PLR was not significantly different [21]. A previous study revealed a cut-off value of PLR 94.05 as a predictive value for EOS with a sensitivity of 97.4%, specificity of 100%, and AUC 0.93 [17]. Our study showed a cut-off value of PLR 11.73 with AUC 0.47, lower than the previously mentioned study, with sensitivity and specificity only 47.9% and 47.9%, respectively. However, another study in 2022 found that NLR had high specificity in neonates with EOS and could be used to distinguish EOS from other diseases and guide the empirical use of antibiotics [26]. A combination of NLR and PLR could improve the accuracy about 72.2% in diagnosing neonatal sepsis [27].

Platelets are a key component of the hematologic system affected by neonatal sepsis. Parameters such as mean platelet volume, platelet distribution width, and plateletcrit reflect platelet morphology and kinetic proliferation, commonly used in clinical assessments during infection [28]. Thrombocytopenia in preterm newborns should not necessarily be linked to any specific infectious agent. While platelet counts are not specific for neonatal sepsis, they can serve as a preliminary diagnostic tool. Additionally, platelet counts would help in assessing treatment prognosis [29,30].

There were some limitations to this study. This study did not classify neonatal sepsis as early-onset or late-onset neonatal sepsis. Furthermore, our study population was limited and consisted of preterm and term infants, wherein the early period in the production and response of neutrophil and platelet in preterm infants remains poorly understood.

Conclusion

Our study suggested that the cut-off values of NLR and PLR (2.75 and 11.73, respectively) had low sensitivity and specificity for diagnosing neonatal sepsis. Further investigation is warranted to establish further data and evidence related to the diagnostic accuracy of NLR and PLR for neonatal sepsis in clinical practices.

Ethics approval

This study was approved by the Ethical Committee of Universitas Sumatera Utara, Medan, Indonesia (No. 311/TGL/KEPK DK USU-RSUP HAM/2019).

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

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