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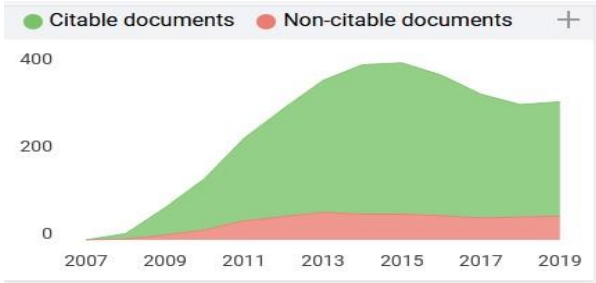

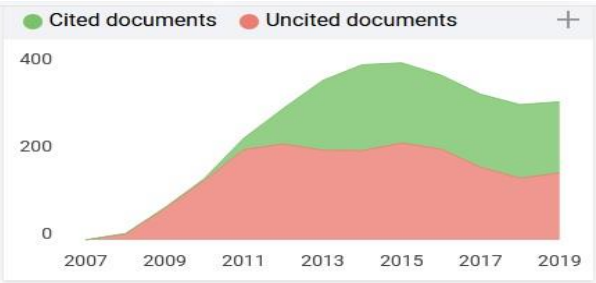

ORIGINAL ARTICLE

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Neutrophil-to-Lymphocyte Ratio as an Alternative Marker of Neonatal Sepsis in Developing Countries

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ABSTRACT

Objectives: We sought to analyze the neutrophil-to-lymphocyte ratio (NLR) as an alternative marker of neonatal sepsis. ***Methods:*** In this cross-sectional study, we undertook consecutive sampling in all inborn neonates admitted to the Neonatal Intensive Care Unit with clinical manifestations of neonatal sepsis. Neonates with congenital anomalies and referred neonates were excluded. Complete blood count, C-reactive protein (CRP), and blood culture were carried out as the septic workup examinations based on the local Clinical Practical Guidelines. NLR is obtained by dividing the absolute count of neutrophils from lymphocytes manually. A cut-off value of NLR is obtained using a receiver operating characteristic curve. ***Results:*** The median NLR value of the 104 neonates who met the inclusion and exclusion criteria was 3.63 (2.39–6.12). Neonates with NLR of 2.12 have the area under the curve of 0.630 (95% confidence interval (CI): 0.528–0.741) and 0.725 (95% CI: 0.636–0.814) when combined with CRP = 2.70 mg/dL. Neonates with NLR ≥ 2.12 in clinical neotnatal sepsis had almost double the risk of providing positive blood culture results (relative risk = 1.867, 95% CI: 1.077–3.235; p = 0.011). ***Conclusions:*** NLR, calculated from complete blood count, can be used as an alternative marker of easy and relatively inexpensive neonatal sepsis, especially in developing countries, and detection of proven neonatal sepsis to be better when combined with CRP.

Neonatal sepsis is a major problem for neonates worldwide and contributes to significant morbidity and mortality (term and preterm), especially in developing countries.[1,2] It is a clinical syndrome characterized by systemic infections and the isolation of pathogens in the blood (bacteremia) and occurs in infants in the first month of life.[3–6] As many as 1.6 million neonates die each year due to infection with 60% of deaths occurring in developing countries.[7] Neonatal sepsis is reported as 1–5 per 1000 live births in developed countries, and a higher incidence is reported in developing countries (10–50 per 1000 live births).[5,8,9]

Routine parameters used for neonatal sepsis have varying diagnostic values such as total leukocyte count, absolute neutrophil count (ANC), immature/total neutrophil (I/T) ratio, and C-reactive protein (CRP). Procalcitonin, a specific bacterial infection marker, has a high price and not always available in various health service facilities, especially in rural areas.[10] Blood culture as a gold standard marker, takes a long time, and often gave negative results.[1] The neutrophil-lymphocyte ratio (NLR) is inexpensive and included as part of complete blood counts and does not require additional examination.[10] Research on NLR in bacterial infections in children, especially neonates, was still limited. Normal NLR values in healthy neonatal or pediatric populations have only been reported once with an average NLR value of 0.52–0.91.[11] To date, no studies in neonates have been conducted in our hospital previously, so the purpose of this study was to analyze the NLR as an initial marker of neonatal sepsis that can be used in limited-resource areas.

METHODS

We conducted a-six-month (April to September 2019) observational analytical study using a cross-sectional design with consecutive sampling in all inborn neonates treated in Neonatal Intensive

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Care Unit (NICU) with clinically neonatal sepsis. Complete blood count, CRP, and blood culture were carried out before giving antibiotics according to the local Clinical Practice Guidelines. As mentioned by Haque, suspected neonatal sepsis was characterized by the presence of one or more fetal inflammatory response syndrome (FIRS) criteria in conjunction with signs and symptoms of infection. FIRS manifested by at least two of the following criteria, tachypnea (respiratory rate/ > 60 bpm) plus either grunting/retraction or desaturation, body temperature abnormalities (> 37.9 °C or < 36 °C), capillary refill time (CRT) > 3 seconds, abnormal leukocyte count (< 4000 or > 34 000/mm^3), CRP > 10 mg/dL, IL-6 or IL-8 > 70 pg/mL, and positive 16S rRNA genes PCR. Sign and symptoms of infection can be grouped into clinical variables (temperature instability, heart rate (HR) ≥ 180 or ≤ 100, respiratory rate > 60 bpm plus grunting/retraction or desaturation, lethargy/altered mental status, glucose intolerance, plasma glucose > 10 mmol/L, and drinking intolerance), perfusion variable (CRT > 3 seconds, plasma lactic acid > 3 mmol/L), hemodynamic variables (blood pressure < 2 SD below normal age, systolic blood pressure < 50 mmHg for one day old, and < 65 mmHg for ≤ 1 month old), and inflammatory variables (leukocytosis > 34 000/mm^3; leukopenia < 4000/mm^3; immature neutrophils > 10%; I/T ratio > 0.2; thrombocytopenia < 100 000/mm^3; CRP > 10 mg/dL or > 2 standard deviation (SD) above normal value; procalcitonin > 8.1 mg/dL or > 2 SD above normal value; IL-6 or IL-8 >70 pg/mL; and positive 16S rRNA genes PCR.[7] Basic characteristics such as sex, gestational age, birth weight, Lubschenco score, mode of delivery, history of premature rupture of membranes, history of mother with preeclampsia/eclampsia, history of prenatal steroid use, and neonatal sepsis onset were evaluated in this study.

Ethical clearance in this study was approved by the Ethical Committee in Health Research of Dr. Soetomo General Academic Surabaya (ref. no. 1047/KEPK/III/2019).

Complete blood count performed by automated hematology analyzer and include white blood count (WBC) differential to evaluate the WBC based on light scattering characteristics. The ANC and absolute lymphocyte count were identified and counted in the WBC differential. The NLR is obtained by dividing the ANC by the absolute lymphocytes count recorded in the medical record manually. The diagnosis of neonatal sepsis is categorized into two groups based on blood culture results; proven neonatal sepsis if the blood culture results are positive and suspected neonatal sepsis if negative.

Data were analyzed using SPSS and presented as median and interquartile range. Sex, gestational age, birth weight, Lubchenco score, mode of delivery, history of premature rupture of membranes, history of mothers with preeclampsia/eclampsia, history of prenatal steroids, and neonatal sepsis onset were analyzed using the chi-square test. Total leukocyte count, ANC, absolute lymphocytes count, NLR, and CRP were analyzed using Mann-Whitney U test with significance defined as a p-value < 0.050. The NLR cut-off value was established using a receiver operating characteristic curve.

RESULTS

The number of inborn neonates admitted to the NICU during the six-month study period was 492, and 260 of them were suspected neonatal sepsis. A total 156 neonates were excluded from the study due to congenital abnormalities (n = 36) and were referred from other hospitals (outborn neonates, n = 120), so the total subjects who met the inclusion criteria were 104 neonates [Figure 1]. Neonatal sepsis in this study had an incidence of 10.6% with 52 (50.0%) neonates categorized as proven neonatal sepsis. Gram-negative bacteria dominated as the cause of neonatal sepsis (75.0%), with extended-spectrum β-lactamase producing *Klebsiella pneumoniae* (+) isolates making up 61.5%. Table 1 informs the subjects and laboratory characteristics of the subjects in this study. The median NLR (p = 0.018) and CRP (p = 0.001) in the proven neonatal sepsis neonates

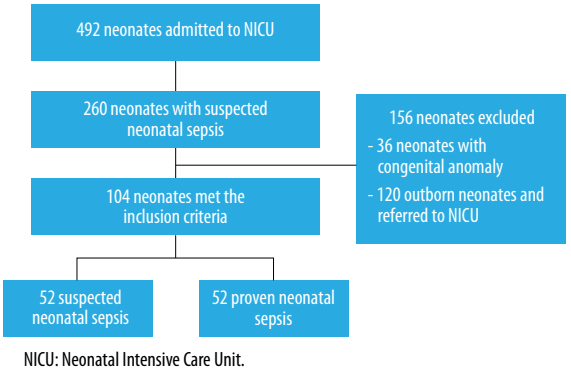

Figure 1: Flow diagram the research design.

Table 1: Subjects characteristics.

Variables	Proven neonatal sepsis n (%)	Suspected neonatal sepsis n (%)	Total n (%)	*p*-value
Sex				0.239*
Male	30 (57.7)	24 (46.2)	54 (51.9)	
Female	22 (42.3)	28 (53.8)	50 (48.1)	
Gestational age				0.184*
Extremely preterm (< 28 weeks)	5 (9.6)	3 (5.8)	8 (7.7)	
Very preterm (≥ 28–32 weeks)	8 (15.4)	18 (34.6)	26 (25.0)	
Moderate late preterm (≥ 32–37 weeks)	33 (63.5)	24 (46.2)	57 (54.8)	
Term (≥ 37 weeks)	6 (11.5)	7 (13.5)	13 (12.5)	
Birth weight				0.008*
Normal	3 (5.8)	7 (13.5)	10 (9.6)	
Low birth weight (< 2500 g)	27 (51.9)	16 (30.8)	43 (41.3)	
Very low birth weight (< 1500 g)	20 (38.5)	17 (32.7)	37 (35.6)	
Extremely low birth weight (< 1000 g)	2 (3.8)	12 (23.1)	14 (13.5)	
Lubschenco score				0.512*
Appropriate for gestational age	39 (75.0)	36 (69.2)	75 (72.1)	
Small for gestational age	13 (25.0)	16 (30.8)	29 (27.9)	
Mode of delivery				0.222*
Spontaneous	16 (30.8)	22 (42.3)	38 (36.5)	
Sectio caesaria	35 (67.3)	28 (53.8)	63 (60.6)	
Others	1 (1.9)	2 (3.8)	3 (2.9)	
History of premature rupture of membrane				1.000*
Yes	15 (28.8)	15 (28.8)	30 (28.8)	
No	37 (71.2)	37 (71.2)	74 (71.2)	
History of preeclampsia/eclampsia				0.543*
Yes	21 (40.4)	18 (34.6)	39 (37.5)	
No	31 (59.6)	34 (65.4)	65 (62.5)	
History of prenatal steroid				0.464*
Yes	12 (23.1)	9 (17.3)	21 (20.2)	
No	40 (76.9)	43 (82.7)	83 (79.8)	
Onset neonatal sepsis				0.003*
Early-onset neonatal sepsis	13 (25.0)	28 (53.8)	41 (39.4)	
Late-onset neonatal sepsis	39 (75.0)	24 (46.2)	63 (60.6)	
Total leucocyte count, /mm^3, median (IQR)	11 700 (6405–17 590)	10 215 (4920–16 010)	11 265 (5745–17 265)	0.465**
Absolute neutrophil count, /mm^3, median (IQR)	7310 (4920–11 580)	5390 (2995–10 495)	6375 (3260–11 205)	0.155**
Absolute lymphocyte count, /mm^3, median (IQR)	1840 (1120–3145)	2155 (1270–3540)	2010 (1160–3245)	0.359**

** Chi-Square's test. ** Mann-Whitney U test.*
IQR: interquartile range.

was significantly higher than in the suspected group [Figure 2].

Neonates with NLR of 2.12 have an area under the curve (AUC) of 0.630 (95% confidence interval (CI): 0.528–0.741) with a cut-off 2.12. The AUC of NLR did not differ statistically when compared to CRP at a cut-off 2.70 mg/dL, which was 0.690 (95% CI: 0.592–0.793; p = 0.454) [Figure 3a]. A better AUC of 0.725 (95% CI: 0.636–0.814) can be achieved if NLR is combined with CRP [Figure 3b]. The NLR has high sensitivity of 80.8% but low specificity of 42.3%. The positive predictive value (PPV) and negative predictive value (NPV) were 58.3% and 68.8% with 62.5% accuracy. The combination of NLR and CRP have 75.0% sensitivity, 67.3% specificity, 69.6% PPV, 72.9%

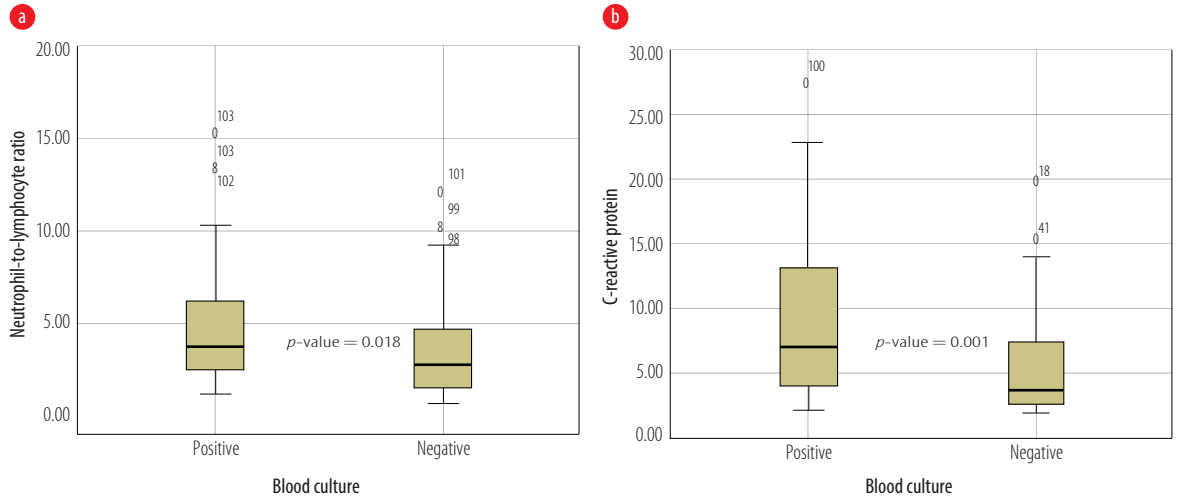

Figure 2: Box plot of **(a)** neutrophil-lymphocyte ratio and **(b)** C-reactive protein based on blood culture (Mann-Whitney U test).

NPV and 71.2% accuracy. Neonates with an NLR ≥ 2.12 have almost twice the risk of giving a positive blood culture result (relative risk (RR) = 1.867, 95% CI: 1.077–3.235; p = 0.011), whereas when combined with CRP > 2.70 mg/dL, the risk of giving positive blood culture results is more than doubled (RR = 2.106, 95% CI: 1.396–3.179; p < 0.001).

DISCUSSION

Preterm and low birth weight (LBW) infants were the highest subjects to have neonatal sepsis in this study. This results were similar to the previous study reported in Denpasar in 2008 (50% preterm and 53.6% LBW neonates) and Surabaya in 2010 (77.78% preterm and 32% LBW neonates).[8,12] The incidence of neonatal sepsis is inversely related to birth weight and gestational age. It is mostly found in infants with very LBW < 1500 g and gestational age < 28 weeks.[5,13] Prematurity with sepsis as a complication was the leading cause of neonatal mortality. Higher neonatal death was also found at lower gestational age, with the majority born at < 26 weeks. The majority of neonatal death was noted in infants with a birth weight < 1000 g.[14] Our study included more males (51.9%). Similar results were reported by several previous studies ranging from 55.2 to 59.9% although there was no difference in the risk of neonatal sepsis by sex.[15–19]

As many as 75.0% of positive blood cultures were obtained in late-onset neonatal sepsis (LOS) and dominated by gram-negative bacteria. It is significantly 3.5-times more common than early-onset neonatal sepsis (EOS). LOS with positive

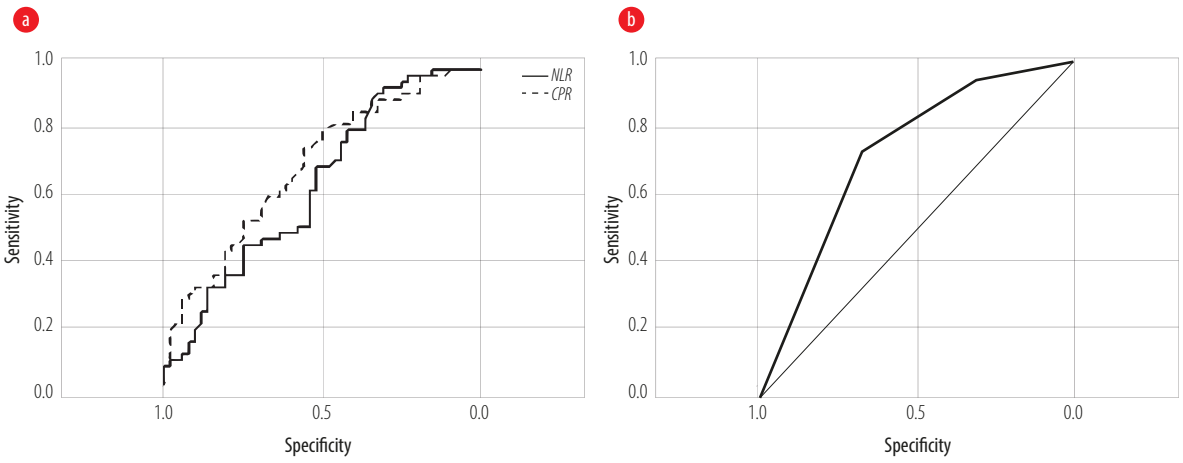

Figure 3: Area under curve **(a)** neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP) and **(b)** NLR combined with CRP as initial marker of neonatal sepsis.

blood cultures was also reported in previous studies by Shehab El-Din et al,[16] at 65% and Yusef et al,[20] at 72%. LOS was associated with nosocomial bacteria and more common in preterm neonates due to long term treatment in NICU.[1,21,22] Immature immune responses and high invasive life support such as central venous catheters (CVC) or endotracheal tubes and total parenteral nutrition (TPN) support make preterm neonates more susceptible to infection than term neonates.[1,5,21]The domination of gram-negative bacteria was also reported in a previous study, and it was found that intrapartum antibiotics, TPN duration, CVC duration, and mechanical ventilation duration were potential maternal and neonatal risk factors for late-onset gram-negative sepsis.[19] We did not evaluate the use of CVC, endotracheal tubes, and TPN in this study. Low humoral immune system in preterm neonates occurs because the transfer of transplacental immunoglobulin G from mother to fetus begins in the second trimester and peaks in the third trimester of pregnancy.[21,22]

Nearly 90% of neonatal sepsis with positive blood cultures in this study had normal leukocyte counts (4000–34 000/mm^3). Abnormal total leukocyte counts were only found in eight neonates (four EOS and four LOS) with total leukocyte counts < 4000/mm^3 and no neonates with total leukocyte counts > 34 000/mm^3. Sucilathangam et al,[23] also reported that normal total leukocyte counts were obtained in 12/14 (85.72%) neonates with positive blood culture results. A normal total leukocyte count cannot rule out the presence of neonatal sepsis because 50.0% of neonatal sepsis with positive blood cultures have a normal total leukocyte count.[9]

Higher median NLR was found in proven neonatal sepsis or neonates with positive blood cultures, and higher mean NLR in positive blood cultures (3.69±3.0) compared to negative blood cultures (1.56±1.83, p < 0.001).[1] Significantly, higher NLR compared to healthy neonates were also reported in several studies. The term neonatal sepsis group had a significantly higher NLR than healthy term neonates reported by Can et al,[24] with 2.88±0.16 and 0.21±0.12, respectively (p = 0.02), and Omran et al,[25] with 2.9±1.7 and 1.6±0.4, respectively (p < 0.001). Overall studies in neonatal sepsis groups have higher NLR values compared to NLR values previously reported by Hamiel et al,[11] in healthy neonates or the pediatric population with an average NLR 0.52–0.91. The high NLR value in the sepsis group is due to an imbalance between the levels of neutrophils and lymphocytes. Increasing neutrophils is a first-line defense mechanism in the primary role of neutrophils as an innate immune system response to fight bacterial infections and stimulates the process of emergency granulopoiesis. An increase in neutrophil counts is accompanied by a decrease in lymphopoiesis and monocytopoiesis and also a decrease in neutrophil apoptosis but an increase in lymphocyte apoptosis resulting in neutrophilia and lymphocytopenia.[1,26–28]

The NLR cut-off in this study was higher than in previous studies. The NLR 1.81 cut-off value in neonates with risk factors for sepsis and neonatal sepsis in Dr. Moewardi Hospital, Surakarta, has 86.1% sensitivity, 85.1% specificity, 68.9% PPV, and 94.1% NPV.[29] The NLR cut-off in this study was lower than in some previous studies but with higher sensitivity. Omran et al,[25] obtained an average NLR value in 35 term neonates with positive and negative blood cultures compared to healthy term neonates of 2.9±1.7 with NLR 2.7 has 80% sensitivity and 57.1% specificity with AUC of 0.791±0.057. Ruslie et al,[30] obtained an NLR 9.4 cut-off value having a sensitivity of 61.5% and a specificity of 66.7% in 94 neonates with clinical manifestations of sepsis (positive blood culture versus negative blood culture), which was dominated by term neonates as the study population.

The AUC of NLR and CRP are not statistically significantly different, but the best AUC is obtained if both are combined. Only one previous study also reported the best AUC of 0.79 (95% CI: 0.70–0.88) was found when NLR and CRP were combined compared to NLR or CRP alone. The study was conducted in term neonates aged 7–28 days old until 90 days old who experience serious bacterial infection.[11]

This is the first study in Surabaya, Indonesia, that assesses NLR as a neonatal sepsis marker. The use of NLR is expected to reduce the use of antibiotics that are not appropriate, complications, and neonatal mortality due to infections, especially bacterial infections.

This study's limitation is that it was collected at only one research center and we excluded neonates transferred from other hospitals. This study also did not include healthy neonates as a control group so the normal range value of NLR could not be known.

CONCLUSION

The NLR, by dividing the absolute count of neutrophils from lymphocytes from complete blood count, can be used as an alternative marker of neonatal sepsis, especially in developing countries. It is an easy and relatively inexpensive examination. Better detection of proven neonatal sepsis can be achieved using NLR when combined with CRP.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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