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Neutrophil-to-Lymphocyte Ratio as a Risk Factor for Mortality and Length of Stay in Neonatal Sepsis

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Abstract

The neutrophil-to-lymphocyte ratio (NLR) is inexpensive and included as part of complete blood counts studied in various clinical conditions and sepsis. Alterations in NLR have been associated with disease severity and outcomes. The study aimed to determine whether NRL can be a prognostic marker for mortality/length of stay in neonatal sepsis. This retrospective cohort study examined the relationship between high NLR and mortality/length of stay in neonatal sepsis in neonates treated at RSUP Dr Wahidin Sudirohusodo Makassar from January 2018 to December 2020. Data from 138 neonates with complete medical records were analyzed. The NLR value increased more with mortality outcomes and length of stay less than seven days. No significant association was found between NLR and patient outcomes or length of stay. The study has found no association between NLR and outcomes or length of hospital stay in neonatal sepsis.

Keywords: Neutrophil-to-Lymphocyte Ratio, Neonates, Sepsis

Abstrak

Rasio neutrofil terhadap limfosit (NLR) merupakan penanda biologis yang mudah diakses dan telah dipelajari dalam berbagai kondisi klinis dan pada keadaan sepsis. Perubahan NLR dikaitkan dengan tingkat beratnya penyakit dan luarannya. Penelitian ini bertujuan untuk mengetahui apakah NRL dapat berfungsi sebagai penanda prognostik terhadap mortalitas/lama rawat inap pada sepsis neonatal. Penelitian kohort retrospektif ini meneliti hubungan antara NLR yang tinggi dengan mortalitas/lama rawat inap pada sepsis neonatorum pada neonatus yang dirawat di RSUP Dr. Wahidin Sudirohusodo Makassar dari Januari 2018 hingga Desember 2020. Pada penelitian ini didapatkan data dari 138 neonatus dengan rekam medis lengkap. Nilai NLR meningkat lebih besar seiring dengan angka mortalitas dan lama rawat inap kurang dari 7 hari. Tidak ada hubungan signifikan yang ditemukan antara NLR dan outcome pasien atau lama rawat inap. Penelitian ini tidak menemukan hubungan antara NLR dengan kematian atau lama rawat inap pada sepsis neonatal.

Kata kunci: Rasio Neutrofil terhadap Limfosit, Neonatus, Sepsis

Introduction

Neonatal sepsis is a clinical syndrome characterized by systemic infection and isolation of pathogens in the bloodstream (bacteremia), occurring in infants during the first month of life.[1] Recently, the Global Burden of Disease (GBD) Study 2016/2017 estimated 1.3 (95% CI 0.8 to 2.3) million annual incident cases of neonatal sepsis worldwide, resulting in 203,000 (95% CI 178,700 to 267,100) sepsis-attributable deaths.[2] Neonatal sepsis is the second most common cause of death in neonates, and approximately 1.6 million neonates die each year due to infections.[3]

The gold standard for diagnosing neonatal sepsis is blood culture. However, it can be challenging due to various factors, including small blood volume obtained from neonates and low or intermittent bacteremia.[4] Many sepsis biomarkers have been studied to determine their utility in the diagnosis of neonatal sepsis. An ideal biomarker should have high sensitivity, specificity, positive predictive value, and negative predictive value (NPV).[5]

The neutrophil-to-lymphocyte ratio (NLR) is an easily accessible biological marker studied in various clinical conditions, including sepsis. NLR represents the ratio of absolute neutrophil count to absolute lymphocyte count obtained from a complete blood count (CBC).[6] Many studies have shown that the NLR is more reliable for diagnosing neonatal sepsis than neutrophil or lymphocyte counts alone.[7,8]

However, the clinical utility of NLR in neonatal sepsis remains controversial and requires further investigation. Limited studies have examined the association between NLR and mortality rates or length of hospital stay in neonatal sepsis.[9] In addition, there are only a few studies of NLR related to neonatal outcomes in the NICU conducted in Indonesia,[10] but no study have assessed the relationship between NLR and length of hospital stay in neonatal sepsis conducted in Indonesia.

Therefore, this study aims to assess the association of NLR with the risk of mortality and length of hospital stay in neonatal sepsis. By examining NLR as a potential prognostic marker, this research will provide insights into the clinical implications of NLR in assessing the severity and prognosis of neonatal sepsis. The findings may contribute to early identification and management of neonates at risk of adverse outcomes, potentially improving patient outcomes and reducing mortality rates.

Methods

This retrospective cohort study examined the relationship between high NLR and mortality/length of stay in neonatal sepsis in neonates. The research was conducted at Dr. Wahidin Sudirohusodo Teaching Hospital in Makassar. The data collection period spanned from January 2018 to December 2020. The study population included all neonates aged 0-28 days who were admitted to the Neonatal Intensive Care Unit (NICU) at Dr. Wahidin Sudirohusodo Teaching Hospital during the specified time period. Inclusion Criteria: Neonates diagnosed with neonatal sepsis confirmed by positive blood culture for bacteria, and complete medical record data. Exclusion Criteria: Growth of fungi in blood culture, newborn

infants with congenital abnormalities, infants discharged at their request, blood culture containing contaminating bacteria.

Consecutive sampling of NICU patients' medical records was performed. Relevant data related to the study, including demographic information, clinical characteristics, and laboratory results, were recorded from the medical records. The NLR value was stated directly in the laboratory examination results. The NLR value is high if >3.63 and normal if ≤3.63.[11] The data were compiled and organized for analysis.

The research obtained ethics approval from the Health Research Ethics Commission of the Faculty of Medicine, Hasanuddin University no 381/UN4.6.4.5.31/pp36/2023. Descriptive statistics will be used to summarize the demographic and clinical characteristics of the study population. The association between high NLR and mortality as well as length of hospital stay will be assessed. The level of significance will be set at $p < 0.05$.

Results

A hundred and thirty-two subjects were eligible for the study. The characteristics of the subjects can be seen in table 1.

Table 1. Characteristics of the Subjects

	Characteristics of the Subjects	NLR >3,63 (n = 61)	NLR ≤ 3,63 (n = 71)	p-value
1	Gender			
	Male	34 (49,3%)	35 (50,7%)	0,460*
	emale	27 (42,9%)	36 (57,1%)	
2	Birthweight			
	< 2500 gram	34 (47,9%)	37 (52,1%)	0,677*
	2500-<4000 gram	27 (44,3%)	34 (55,7%)	
3	Gestational age			
	< 37 weeks	25 (45,5%)	30 (54,5%)	0,883*
	37-42 weeks	36 (46,8%)	41 (53,2%)	

* *Chi-Square test*

The study was conducted from March 2022 to June 2023 using data from the medical records of neonates with neonatal sepsis registered at RSUP Dr. Wahidin Sudirohusodo Makassar from January 2018 to December 2020. Within this timeframe, a total of 138 infants were initially sampled, but only 132 infants met the inclusion and exclusion criteria due to incomplete medical records. Subsequently, an analysis was performed to assess the relationship between high NLR and increased mortality and length of hospital stay in neonatal sepsis. Based on sample characteristics, there was no relationship between NLR and gender, birthweight or gestational age ($p>0.05$).

Table 2. Relationship between Sample Characteristics and Patient Outcomes

	Sample characteristics	Died (n = 68)	Survive (n = 64)	p-value
1	Gender			
	Male	36 (52,2%)	33 (47,8%)	0,874*
	Female	32 (50,8%)	31 (49,2%)	
2	Birthweight			
	<1000 gram	7 (70%)	3 (30%)	
	1000-<1500 gram	10 (62,5%)	6 (37,5%)	0,070*
	1500-<2500 gram	27 (60%)	18 (40%)	
	2500-<4000 gram	24 (39,3%)	57 (60,7%)	
3	Gestational age			
	<28 weeks	3 (60%)	2 (40%)	
	28-<32 weeks	19 (73,1%)	7 (26,9%)	0,037*
	28-<37 weeks	14 (58,3%)	10 (41,7%)	
	37-<42 weeks	32 (41,6%)	45 (58,4%)	

**Chi-Square test*

Table 2 displays the analysis of the relationship between sample characteristics and patient outcomes. Regarding gender, the analysis did not reveal a significant association between gender and outcomes ($p>0.05$). Based on birth weight, the analysis did not reveal a significant association was found between birth weight and outcomes ($p>0.05$). Regarding gestational age, the analysis revealed a significant association between gestational age and outcomes ($p<0.05$).

Table 3. Relationship between NLR and Patient Outcomes

Neutrophil-to-lymphocyte ratio	Died (n = 68)	Survive (n = 64)	p-value
High	35 (57,4%)	26 (42,6%)	0,212*
Normal	33 (46,5%)	38 (53,5%)	

**Chi-Square test*

Table 3 presents the relationship between NLR and patient outcomes. In the high NLR group, 57.4% (n=35) had a mortality outcome, while 42.6% (n=26) survived. In the normal NLR group, 46.5% (n=33) had a mortality outcome, and 53.5% (n=38) survived. The Chi-Square test indicated no significant association between NLR and outcomes ($p=0.212$, $p>0.05$).

Table 4. Relationship between NLR and Length of Hospital Stay

Neutrophil-to-lymphocyte ratio	Length of stay > 7 days (n =41)	Length of stay ≤ 7 days (n =4)	p-value
High	16 (88,9%)	2 (11,1%)	0,669*
Normal	25 (92,6%)	2 (7,4%)	

**Chi-Square test*

Table 4 shows the relationship between NLR and length of hospital stay in full-term infants. In the high NLR group, 88.9% (n=16) had a hospital stay longer than 7 days, while 11.1% (n=2) had a stay of 7 days or less. In the normal NLR group, 92.6% (n=25) had a hospital stay longer than 7 days, and 7.4% (n=2) had a stay of 7 days or less. The Chi-Square

test indicated no significant association between NLR and length of hospital stay in full-term infants (p=0.669, p>0.05).

Table 5. Relationship between NLR and Length of Hospital Stay in Preterm Infants

Neutrophil-to-lymphocyte ratio	Length of stay > 21 days (n =15)	Length of stay ≤ 21 days (n =4)	p-value
High	6 (75%)	2 (25%)	0,719*
Normal	9 (81,8%)	2 (18,2%)	

**Chi-Square* test

Table 5 presents the relationship between NLR and length of hospital stay in preterm infants. In the high NLR group, 75% (n=6) had a hospital stay longer than 21 days, while 25% (n=2) had a stay of 21 days or less. In the normal NLR group, 81.8% (n=9) had a hospital stay longer.

Discussion

Neonatal sepsis is a primary cause of neonatal mortality and is an urgent global health concern, especially within low-income and middle-income countries (LMICs), where 99% of global neonatal mortality occurs.[12] According to the Global Sepsis Alliance, infections leading to sepsis are responsible for about one-fifth of the world's annual 2.7 million neonatal deaths, it was about 25% of all neonatal deaths. The incidence of neonatal sepsis is around 40 times higher and mortality rates are two times higher in middle-income countries than in high-income countries.[13] Numerous clinical studies have shown that the neutrophil count, lymphocyte count, and NLR are predictors of sepsis.[6] NLR is inexpensive, included as part of complete blood counts, and does not require additional examination.[14] As the NLR value increases, the condition of neonatal sepsis becomes more severe, leading to longer hospital stays and increased vulnerability to death. Several studies have found that neonates with late-onset sepsis, particularly preterm infants, have higher average NLR values, longer hospital stays, and increased mortality rates.[15,16]

In this study, a total of 132 research samples were obtained from the medical records of neonatal sepsis patients registered at Dr. Wahidin Sudirohusodo Teaching Hospital in Makassar from January 2018 to December 2020. Out of the 132 children, 68 patients died, while 64 patients showed improvement. The analysis was conducted to determine the association between high NLR and increased mortality and length of hospital stay in neonatal sepsis.

Regarding the characteristics of the research samples, based on gender, there was no association between gender and NLR in neonatal sepsis. Similar results were found in a study by Das et al., which analyzed the neutrophil values in 420 newborns admitted to a hospital in Kolkata, India, between May 2016 and June 2017. The statistical analysis did not find a significant difference between neutrophil levels and gender in neonates (p=0.936).[17] However, a

study by Christensen et al., which examined the blood neutrophil concentration in 30,354 neonates with gestational ages of 23-42 weeks, showed a significant difference between neutrophil levels and gender in infants ($p<0.001$).[18] The difference in findings may be attributed to different study populations, including healthy infants, and the lack of specific studies comparing NLR and gender in neonates.

Regarding birth weight, there was no association between birth weight and NLR in neonatal sepsis. Similarly, based on gestational age, there was no association between gestational age and NLR in neonatal sepsis. In 1994, Mouzinho et al. published information on neutrophil counts in healthy neonates with very low birth weight, which clearly demonstrated the different neutrophil dynamics between full-term infants and preterm infants. Most preterm infants were found to have neutropenia. Therefore, the reference range for newborns should be adjusted according to gestational age.[17]

This study shows that there was no relationship between NLR and outcomes in neonatal sepsis. In the study by Widjaja et al, a retrospective study used a cohort design among pediatric patients with sepsis and bacterial meningitis at Dr. Sardjito General Hospital Yogyakarta, Indonesia, during the period January 2016 to December 2020, showed that NLR was related to mortality in the study with a p value = 0,004.[19] In China, research by Yang et al. found that NLR was significantly higher in the death group than in the control group in 205 adult bloodstream infection patients.[20] The severity of disease in patients with bloodstream infection sepsis can be effectively reflected by NLR inflammatory factors. Patients with sepsis prognosis found that higher NLR tends to indicate higher sepsis mortality, and has predictive value for 28-day mortality in patients with sepsis.[21]

This study shows that there was no relationship between NLR and length of stay in neonatal sepsis. Ozdemir et al. studied and found that late-onset sepsis neonates in premature babies had a higher mean NLR for length of stay. Ozdemir et al. found premature late-onset sepsis neonates had a higher mean NLR (3,69 ± 3,0) compared with culture-negative infants (1,56 ± 1,83) and an NLR at a cutoff of 1.7 had a sensitivity of 73,1 % and specificity 78,7% for length of stay. The higher the NLR value, the more serious the condition of patients with neonatal sepsis will be, increasing the length of stay and making them more susceptible to death.[22] The research results of Zhong et al. with a retrospective study on a sample of critically ill children with severe sepsis who were treated in PICU, West China Hospital of Sichuan University, from January 2019 to January 2020, from statistical analysis tests found a significant difference between the severity of sepsis and NLR with a p value< 0,006.[23]

The immune system of premature infants tends to have lower levels of neutrophils and monocytes, leading to impaired pathogen destruction by these cells. Additionally, limited activation of T cells due to lower cytokine production further reduces their ability to fight bacteria and detect viruses within cells compared to term infants. While a series of prenatal and postnatal events accompanying preterm birth have the potential to modulate immunity, exposure to labor and vaginal delivery has been associated with increased neutrophil function, possibly due to the premature infant's immune system.[24] Studies on neutrophil levels in

neonates are limited. There is currently no direct comparison of NLR between preterm and term infants, particularly in the context of sepsis.

In conclusion, the study found no association between NLR and outcomes or length of hospital stay in neonatal sepsis. Further research is needed to explore these relationships in larger and more diverse populations.

Conclusion

The study found that there was no significant association between the Neutrophil-lymphocyte ratio (NLR) and outcomes or length of hospital stay in neonates with sepsis. This suggests that NLR may not be a reliable predictor of disease severity or prognosis in this population. However, the study did find a relationship between gestational age and outcomes in neonatal sepsis, indicating that prematurity may be a factor affecting the severity and prognosis of the condition. Further research is needed to explore other potential biomarkers or variables that may be more closely associated with outcomes in neonatal sepsis.

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