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Correlation of systemic immune-inflammation index with immature to total neutrophil ratio (IT Ratio) in septic neonates admitted to Wangaya Regional General Hospital Denpasar

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ABSTRACT

Introduction: Early diagnosis and management of neonatal sepsis plays an important role in determining patient outcomes. The Immature to Total Neutrophil Ratio (IT ratio) is one of the diagnostic criteria for neonatal sepsis. However, the IT ratio examination is separate from the complete blood examination, and must be carried out manually or with an automatic microscope. The systemic immune-inflammation index (SII) is calculated by multiplying the number of platelets by the number of neutrophils and dividing by the number of lymphocytes derived from the complete blood count (CBC) examination. Recent studies have shown that SII values increase significantly at the time of diagnosis of neonatal sepsis. This study aims to find the correlation between the IT ratio and SII in septic neonates.

Methods: This cross-sectional analytical observational study was conducted at the Wangaya Regional General Hospital, Denpasar. Data was taken from medical records of patients admitted from June 2022 to September 2023. Neonates with major congenital abnormalities, autoimmune diseases, immunodeficiency conditions and incomplete medical record data were excluded from the study. The correlation between the SII value and the IT ratio was analyzed using the Pearson correlation test. Data analysis was carried out using the SPSS version 25 software.

Results: This study consisted of 31 septic neonates who met the inclusion and exclusion criteria. Most of the subjects in this study were male and preterm neonates. The median IT ratio and SII were 0.20 and 875.92 x10^3/ul respectively. The correlation value or r value between SII and the IT ratio was 0.386 with a P value of 0.060.

Conclusion: Increased SII in septic neonates occurs due to thrombocytosis and neutrophilia as a response to systemic inflammation. Meanwhile, lymphocyte activation is inhibited which causes a decrease in immune function. Although no correlation between the IT ratio and SII was observed, further diagnostic research needs to be carried out to analyze the ability of SII to diagnose neonatal sepsis.

Keywords: neonatal sepsis, systemic immune-inflammation index, SII, IT ratio.

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INTRODUCTION

Neonatal sepsis is a syndrome comprising non-specific symptoms and signs resulting from bacteremia and systemic infection within the first 28 days of extrauterine life. It is a life-threatening condition that contributes to the highest morbidity and mortality in neonatal intensive care units of either low or high-income countries. According to the meta-analysis of epidemiological studies done by Fleischmann et al. in 2021, neonatal sepsis is projected to have engendered 2,824 instances in 100,000 live births, constituting 17.6% of total fatalities.[1] Global Burden of Disease in 2016/2017 also reported 1.3 million cases of neonatal sepsis with over 203,000 mortalities every year.[2] Patients with neonatal sepsis are also at increased risk of having neurodevelopmental problems, including cerebral palsy, visual impairment, impaired hearing and delayed cognitive development.[3]

Early identification and treatment of neonatal sepsis play significant roles in determining patient outcomes. To date, blood culture is still considered the gold standard to confirm the diagnosis of neonatal sepsis. However, factors such as low blood volume in neonates, intermittent bacteremia and exposure to intranatal maternal antibiotics could intervene in the result, thus delaying the diagnosis confirmation. In low-resource settings, diagnosis of neonatal sepsis is

often considered using diagnostic criteria based on clinical signs, two positive laboratory parameters and the presence of risk factors.[3]

Immature to Total Neutrophil Ratio (IT ratio) is defined as the proportion of immature cells, including blast cells, promyelocytes, myelocytes and band forms in comparison to total neutrophil count. The cut-off value to diagnose neonatal sepsis is 0.2. However, the IT ratio can not be obtained from routine blood count examination, it is done separately through manual count or automatic microscope. Increase of IT ratio is also observed in several non-infectious conditions, including perinatal hypoxia, maternal hypertension, stress during labor and prolonged induction of oxytocin.[4]

The systemic immune inflammation index (SII) was initially introduced by Hu et al. in 2014 as an inflammatory marker that reflects on platelet, lymphocyte, and neutrophil counts. SII is the ratio of neutrophils and platelet count to lymphocyte count, in which high neutrophils and platelet count indicate inflammation, while low lymphocytes indicate uncontrolled inflammatory processes.[5] Its performance has been validated in several studies and used to predict various conditions, such as necrotizing enterocolitis (NEC), urinary tract infection and hypoxic-ischemic encephalopathy.[6–8] Study by Aydogan et al. suggested that SII increased significantly at the time of neonatal sepsis diagnosis with sensitivity and specificity of 70% and 70.5% respectively, with the cut-off value of 517.19/mm^3.[9] Therefore, this study aims to further analyze the role of SII in septic neonates and its correlation to IT ratio; a parameter routinely used as neonatal sepsis diagnostic criteria in our centre.

MATERIAL AND METHODS

Study design and setting

This was a single-institution, cross sectional, retrospective analytic observational study conducted at Wangaya Regional General Hospital. Secondary data between June 2022 and September 2023 were obtained in several units (Perinatology and Neonatal Intensive Care/NICU) where septic neonates were admitted. Recorded data were anonymized. The study was performed after the Institutional Research Ethics Board of Wangaya Regional General Hospital approved the protocol.

Study population

Neonates aged 0 – 28 days diagnosed with neonatal sepsis admitted to Perinatology and NICU in Wangaya General Hospital from June 2022 until September 2023 were enrolled in this study. Those patients with complete medical records were eligible for this study. Estimation of sample size was calculated and the final sample size was 31. Samples were collected constitutively. Neonates with major congenital anomalies (as stated from the medical records), autoimmune disease, immunodeficiency and incomplete medical records were excluded.

Neonatal sepsis was defined as a clinical syndrome of systemic disease accompanied by bacteremia in neonates within the first month of life. Diagnosis of neonatal sepsis in our centre was confirmed if the patient fulfilled clinical symptoms and signs suggestive of sepsis, at least 2 positive laboratory parameters, presence of risk factors (1 major risk factor or 2 minor risk factors) :

a. Symptoms and signs (change in skin color, temperature irregularity, abnormal behaviors, tone, feeding intolerance, gastrointestinal, cardiopulmonary problems and metabolic derangement).
b. Laboratory parameters (WBC count < 5,000 or > 35,000/mL; neutropenia < 1,500/µL or neutrophilia, thrombocyte < 150,000/mL; CRP > 5 mg/dL; procalcitonin > 5 ng/ml; IT ratio of > 0.2; vacuolization or positive toxic granule found in peripheral blood smear; positive 2 sites blood culture).
c. At least 1 major risk factor or 2 minor risk factors for infection.

Data collection and analysis

We collected (1) patient demographics data: gender, gestational age, birth weight, (2) neonatal sepsis onset: early onset neonatal sepsis, late-onset neonatal sepsis, (3) diagnosis, (4) CBC result, (5) IT ratio, (6) blood culture result, (7) duration of hospitalization, (8) antibiotics given and (9) outcome. SII was calculated retrospectively based on data obtained at the time of neonatal sepsis diagnosis. Categoric data were presented as frequency (n) and percentage (%). Numeric data were presented as means and standard deviations for normally distributed data, while medians with interquartile ranges were used if data were not normally distributed. The correlation between the SII and IT ratio was analyzed using the Pearson correlation test. A *P* value less than 0.05 was considered statistically significant. Correlation or r-value of at least 0.6 was considered strongly correlated. Statistical analysis was performed with SPSS ver 25.

RESULTS

A total of 44 septic neonates were admitted to Wangaya Regional General Hospital from June 2022 until September 2023. Eight patients were excluded due to major congenital abnormalities and 5 patients were also excluded due to incomplete medical records data. Thirty-one subjects fulfilled the inclusion criteria and were analyzed. Demographic characteristics of the research subjects are shown in Table 1. The study population consisted of 19 males (61.3%) and 12 females (38.7%), with a median birthweight of 2.05 kilograms (IQR 1.55 kilograms) and mostly preterm (61.3%). Among them 41.9% had early onset neonatal sepsis. As many as 41.9% of patients were also diagnosed with neonatal pneumonia. The culture was not done in 67.7% of subjects, 19.4% showed no growth and *Klebsiella pneumoniae* was found in 6.5% of patients. Antibiotics of Ampicillin and amikacin were used in 48.4% of cases. The median duration of hospitalization was 15 days (IQR 21 days) and 83.9% of neonates survived at the end of care.

As shown in Table 1, median neutrophils and platelets were 10.89 x10^3/uL and 259 x10^3/uL, respectively. In comparison, the mean lymphocyte level was 4.69 x10^3/uL. Each patient's SII was calculated with a median [IQR] of 875.92 [1,190.91]. The mean [SD] IT ratio at the time of neonatal sepsis diagnosis was 0.20 [0.08]. The Pearson correlation test is shown in Table 2. Results showed that the correlation or r value of the SII to IT ratio was 0.386 with a P value of 0.060. This meant that there was a weak correlation

Table 1. Demographic characteristics of study population

Variables	Frequency (n=31)
Gender	
Male	19 (61.3%)
Female	12 (38.7%)
Gestational Age	
Aterm neonates	12 (38.7%)
Preterm neonates	19 (61.3%)
Birth weight (kgs; Median [IQR])	2.05 [1.55]
Neonatal sepsis onset	
EONS	18 (58.1%)
LONS	13 (41.9%)
Secondary diagnosis	
Neonatal pneumonia	13 (41.9%)
HMD	6 (19.4%)
Anemia	4 (12.9%)
NEC	2 (6.5%)
Acute gastroenteritis	2 (6.5%)
Congenital syphilis	3 (9.7%)
Encephalopathy	1 (3.2%)
Neutrophils count (x10^3/uL; Median [IQR])	10.89 [8.63]
Platelets count (x10^3/uL; Median [IQR])	259 [114]
Lymphocytes count (x10^3/uL; Mean [SD])	4.69 [2.65]
SII (Median [IQR])	875.92 [1,190.91]
IT ratio (Mean [SD])	0.20 [0.08]
Blood culture results	
Klebsiella Pneumoniae	2 (6.5%)
Pseudomonas Aeruginosa	1 (3.2%)
Seratia Marcescen	1 (3.2%)
No growth	6 (19.4%)
Blood culture not performed	21 (67.7%)
Duration of hospitalization (days; Median [IQR])	15 [21]
Antibiotic	
Cefotaxime	12 (38.7%)
Ampicillin amikacin	15 (48.4%)
Meropenem	3 (9.7%)
Ceftazidime	1 (3.2%)
Outcome	
Alive	26 (83.9%)
Dead	4 (16.1%)

Notes:
Abbreviations: kgs, kilograms; EONS, Early Onset Neonatal Sepsis; LONS, Late Onset Neonatal Sepsis; HMD, Hyaline Membrane Disease; NEC, necrotizing enterocolitis; IQR, interquartile range; SD, standard deviation; SII, Systemic Immune-Inflammation Index; IT ratio, Immature to Total Neutrophil Ratio.

Table 2. Pearson Correlation Test of SII to IT ratio

		IT Ratio
SII (*Systemic Immune Inflammation Index*)	**r value**	0.341
	P value	0.060

*P-value < 0.05 is considered significant
Notes:
Abbreviations: IT ratio, Immature to Total Neutrophil Ratio; r value, correlation value.

between the two parameters, however it was not statistically significant.

DISCUSSION

Neonatal sepsis is still the leading cause of morbidity and mortality in neonates around the world. Demographic characteristics of patients in this study showed that most septic neonates were males, preterm and had lower birth weight. The association between gender and the incidence of neonatal sepsis remains unknown and is still controversial. Some studies postulate that the increased risk of neonatal sepsis in male patients is related to several factors that regulate the synthesis of globulin in the X chromosome. Males only have 1 X chromosome, which might explain lowered protective and immunity systems.[10,11] In preterm and low birth weight neonates, the cellular and humoral immunity are still immature, including the phagocytic function, thus putting them at risk of infection. Aterm neonates tend to have more mature innate immunity, especially T-helper 2 cells, that contribute to the production of anti-inflammatory cytokines.[10]

Early onset neonatal sepsis was more commonly observed in this study. This finding is similar to several other studies by Yu et al. and Nurrosyida et al., which also demonstrate a higher incidence of early-onset neonatal sepsis than late-onset neonatal sepsis. Early-onset neonatal sepsis is mostly caused by vertical infection through microbial transmission from the mother to the child during labor, while late-onset neonatal sepsis occurs due to horizontal transmission of pathogens from surrounding caregivers. Late-onset neonatal sepsis is more often observed in healthcare facilities.[12,13]

Blood cultures were not performed on the majority of study subjects. *Klebsiella pneumoniae* was the most common pathogen causing neonatal sepsis in our centre. It is also the pathogen that contributes to the majority of neonatal sepsis incidence in developing countries.[14] Although the growth of microorganisms from blood culture is diagnostic, the absence of growth does not exclude the diagnosis. Microorganisms may not grow through blood culture examination due to inadequate sampling, history of antibiotic

use in the mother, administration of antibiotics prior to sampling, low numbers of bacteria in the blood and short-term bacteremia.[12,14] Antibiotics of ampicillin and amikacin were most often used in this study. Current neonatal sepsis guidelines recommend beta-lactam antibiotics (most commonly ampicillin, flucloxacillin and penicillin) combined with an aminoglycoside (most commonly gentamicin) as first-line treatment for both early and late-onset neonatal sepsis.[15,16]

The median duration of hospitalization in this study was 15 days. Prolonged hospitalization may result in new-onset infection, higher costs and treatment difficulty. Several factors may influence the duration of hospitalization, including birth weight, presence of chorioamnionitis, neurological manifestation, comorbidity and gender.[17] Majority of septic neonates in our centre survived after several days of intensive care and monitoring. Maternal education, gestational age < 37 weeks, birth weight, onset to the need of intensive care, severe chest retraction, chorioamnionitis, history of rupture of membrane and high blood pressure also determine the outcome of septic neonates.[18]

Good outcomes in septic neonates are associated with early identification and antibiotic administration. Definitive diagnosis of neonatal sepsis is still relying on blood culture results. However, blood culture results take at least a few days, therefore resulting in delayed treatment. Several inflammatory parameters have been extensively studied in the past few years to find the ideal index required for early diagnosis of neonatal septicemia. Theoretically, the imbalance of inflammatory response and immune dysregulation are the basis of the pathogenesis of sepsis. This inflammatory activity can be detected through several markers from peripheral blood examinations, such as white blood cells, neutrophils, lymphocytes, platelet counts, and C-reactive protein. The systemic Immune Inflammation Index (SII) was initially introduced by Hu et al. to predict the outcome of hepatocellular carcinoma patients. It is the ratio of the multiplication of neutrophils and platelets count to lymphocyte count.[5]

Neutrophils, which have antimicrobial functions, will migrate to the site of infection. Neutrophils release into the peripheral circulation are controlled by the C-X-C chemokine receptor (CXCR)4, which interacts with CXCL12. As sepsis progresses, CXCL12 expression will be decreased and subsequently cause increased release of neutrophils into the peripheral blood.[19,20] Apart from neutrophils, in septicemia, increased platelet activation is also observed. Increased platelet activation in sepsis occurs due to increased expression of CD62P, CD63, CD31, increased fibrinogen binding and soluble GPVI. Platelets play an important role in regulating leukocyte function and inflammatory response. Platelet count reflects the excessive inflammatory response during sepsis.[21]

Lymphopenia in septicemia occurs due to several mechanisms, including decreased production of lymphocytes and their precursors in the bone marrow and thymus, increased release of lymphocytes into infected tissue and increased destruction through apoptosis. This process is mediated by proinflammatory mediators from the tumor necrosis factor (TNF) family. Apoptosis is more pronounced in patients with septic shock, causing persistent lymphocytopenia which is associated with poor outcomes. All of these processes underlie the increased SII level in sepsis.[22]

The results of this study showed that there was no significant correlation between SII and the IT ratio. The median SII level in this study was 875.92, which indicated that increased SII in septic neonates was observed. Prior studies conducted by Aydogan et al. showed that there was an increase in absolute neutrophils count, SII, and neutrophil-to-lymphocyte ratio at the time of diagnosis of neonatal sepsis. The Area Under the Curve (AUC) value for SII was 0.76 with a sensitivity and specificity of 70% and 70.5%, respectively. The cut-off to predict neonatal sepsis was 517.19.[9] Another study conducted by Liu et al. showed that adult septic patients with poor outcomes had higher SII (7,100 $\pm$ 13,200) than patients who survived. The combination of QSOFA and SII provided the best predictive value with an AUC of 0.852. In that study, the cut-off point for SII was found to be higher (1,766).[23]

Confounding factors that may interfere with the SII levels are congenital abnormalities, autoimmune diseases and immunodeficiency. All of these conditions had been previously excluded from this study. An insignificant correlation found in this study might be due to the number of preterm neonates (61.3%) involved in this study. The inflammatory response that occurs in the pathogenesis of sepsis is a complex process. Immature immune defenses in preterm babies may interfere with the results of this study. Additionally, the pathogen that caused neonatal sepsis in this study could also potentially affect the research results. Of the 31 patients studied, 67.7% did not undergo a blood culture examination. Jonathan et al. showed that there were significant differences in mean neutrophil, lymphocyte, and platelet counts between patients infected with gram-positive and negative bacteria.[24] Sumardi et al. showed that neutrophil values tend to be higher and lymphocyte values lower in gram-positive infections compared to gram-negative infections.[25] Another study by Guclu et al. showed that platelet count decreased within the first 3 days in septic patients infected with gram-positives, while it started decreasing within the first 4 days in septic patients infected with gram-negatives. To date, the dynamics of platelets count in various infections caused by different pathogens remain inconclusive.[26]

CONCLUSION

Systemic Immune Inflammation Index (SII) is a potential novel marker to diagnose neonatal sepsis. SII can be easily estimated through routine blood count examination, thus it is relatively quick to obtain, cost-effective and widely available. However, this study found no correlation between SII and IT ratio (a parameter mostly used in our centre to diagnose neonatal sepsis) at the time of neonatal sepsis diagnosis. Further diagnostic studies with a bigger sample size are needed. The weaknesses of this study, such as lower gestational age and varied pathogens included, should also be considered in future research.

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ETHICAL CLEARANCE

This study has been reviewed and approved by the Institutional Research Ethics Board of Wangaya Regional General Hospital with ethical clearance number 070/5380/RSUDW.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

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