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Original Article

Neutrophil-lymphocyte count ratio correlation to procalcitonin and PELOD-2 score in pediatric sepsis

Desak Gede Arie Yudhantari, Dadang Hudaya Somasetia, Eddy Fadlyana, Djatnika Setiabudi

Abstract

Background Sepsis is a leading cause of children's mortality worldwide. Procalcitonin (PCT) is a widely used infection marker, but has limitations in terms of cost and availability. The neutrophil-lymphocyte count ratio (NLCR) is easy to perform, low-cost, and widely used as a diagnostic and prognostic marker of various inflammatory processes.

Objective To investigate possible correlations of NLCR to PCT and pediatric logistic organ dysfunction-2 (PELOD-2) score among pediatric sepsis patients.

Method A retrospective study was conducted by reviewing the Pediatric Sepsis Registry at Dr. Hasan Sadikin General Hospital, Bandung, West Java, from January 2019–June 2020. We recorded patients' characteristics, PELOD-2 score, NLCR, and PCT results. Correlation analysis was conducted using Spearman's Rank test with significance value of $P<0.05$.

Results Ninety patients were included in the study. Most patients were male (56.7%), under 2 years of age (57.8%), and had lower respiratory tract infection (67.8%) as the most common source of infection. The NLCR value had significant, positive correlations to PCT ($r=0.642$; $P<0.001$) and PELOD-2 score ($r=0.233$; $P=0.027$) in pediatric sepsis patients.

Conclusion The NLCR is directly proportional to PCT in pediatric sepsis patients. This result suggents that NLCR may have a potential role as an alternative marker for sepsis in emergency setting. **[Paediatr Indones. 2021;61:211-6 ; DOI: 10.14238/pi61.4.2021.211-6**].

Keywords: *neutrophil-lymphocyte count ratio; procalcitonin; pediatric; PELOD-2 score; sepsis*

Sepsis is one of the leading causes of mortality in children. In 2017, an estimated 48.9 million cases of sepsis were recorded worldwide, of which 25.2 million were children.[1] The mortality rate due to sepsis was high, both in developed and developing countries, at 5% and 35% respectively.[2]

In the early phase of sepsis, proinflammatory mediators induce the liver to express acute phase proteins, stimulate leukocyte production in the bone marrow, and accelerate the release of leukocytes into peripheral blood, as indicated by an increase in the number of neutrophil bands.[3] Persistent sepsis leads to apoptosis of lymphocytes, which increases the neutrophil-lymphocyte ratio.[4] The elevated levels of neutrophils encourage cytokine release and reactive oxygen species to locations far from the focus of infection, resulting in dysregulation of the immune system and failure of various organ systems.[5] The PELOD-2 score is a descriptive scoring system to assess the severity of organ system dysfunction, as well as predict prognosis in critically ill pediatric patients.[6]

From: Department of Child Health, Universitas Padjadjaran Medical School/ Dr. Hasan Sadikin General Hospital, Bandung, West Java, Indonesia.

Corresponding author: Desak Gede Arie Yudhantari, Department of Child Health, Universitas Padjadjaran Medical School/Dr. Hasan Sadikin General Hospital, Jalan Pasteur No. 38, Bandung, West Java, Indonesia. Phone +62-8111000156; Email: desak.arie@gmail.com.

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PELOD-2 score ≥8 is a good predictor for mortality, with a 22.2% risk of death.[7]

Sepsis is not easy to diagnose because in developing countries, the sepsis criteria are impractical in application.[8] The use of laboratory parameters to diagnose sepsis in such nations is constrained by funding and facility limitations, which further delays early detection of sepsis.[9] Procalcitonin (PCT) is a commonly used and specific marker of bacterial infection.[10] However, PCT has the disadvantage of being expensive. Hematological changes in sepsis patients, such as white blood cells count and its separated components; neutrophils count and lymphocytes count, are widely used to assess the inflammatory response in sepsis.[11] Neutrophil-lymphocyte count ratio (NLCR) is a parameter that can be used as a measure of systemic inflammation.[12] The NLCR is easy to calculate and available from routine blood examination panels. It has been widely studied as a predictive and prognostic parameter for various types of diseases such as malignancy,[13] as well as autoimmune[14] and trauma/postoperative conditions.[15]

Despite the usefulness of NLCR, there have been limited studies on its use in pediatric sepsis patients. A previous study showed a correlation between NLCR and PCT, however, the study did not involve Asian subjects, therefore, the correlation of NLCR and PCT in a wider population remains to be seen. In addition, a correlation between NLCR and PELOD-2 score, to our knowledge, has not been shown. As such, we aimed to assess for potential correlations between NLCR and PCT and the pediatric sepsis severity, based on PELOD-2 score.

Methods

This retrospective study was done with secondary data from the Sepsis Registry of the Emergency and Pediatric Intensive Care Division, Department of Child Health, Universitas Padjadjaran Faculty of Medicine/Dr. Hasan Sadikin General Hospital, Bandung, West Java, from January 2019 to June 2020. The minimum required sample size was 89, calculated based on previous studies,[16-19] with 95% confidence interval and power of 80%.

Sepsis was defined as life-threatening organ dysfunction caused by dysregulation of the host immune response to infection. *The Sepsis Registry* at our institution is based on recommendations of the *Indonesian Emergency and Pediatric Intensive Care Working Group* and the *American Academy of Pediatrics* (AAP).[20] Patients with PELOD-2 score ≥ 2 were categorized as having sepsis. PELOD-2 score was assessed by calculating 10 variables which represent 5 organ system dysfunctions: cardiology, respiratory, renal, neurology, and hematology.[6,20]

The inclusion criteria were children aged 1 month-18 years who were diagnosed with sepsis; treated in the pediatric ward, pediatric intensive care unit, or pediatric emergency unit at Dr. Hasan Sadikin General Hospital, Bandung; and had complete *Sepsis Registry* data. Exclusion criteria were pediatric patients with blood malignancy, thyroid disease, liver disease, immunocompromized status, post-operative or post-trauma conditions, or had received antibiotics, steroids, or immunosuppressant drugs before establishing a diagnosis of sepsis. In addition, patients whose procalcitonin was not collected at the time of sepsis diagnosis were excluded. From 232 available case records, only 90 patients met the inclusion criteria.

Subjects' age, sex, source of infection, PELOD-2 score, NLCR, and PCT were recorded. The PELOD-2 score was taken at the time of sepsis diagnosis. The NLCR and PCT were obtained from laboratory data taken after sepsis diagnosis.

The *IBM SPSS Statistics software version 23.0* was used for analyses. Categorical data were presented in numbers and percentages while numeric data were presented in median and range. Numerical data distribution was determined using Kolmogorov-Smirnov normality test. Since NLCR and PCT levels were not normally distributed, non-parametric statistical analyses were used. Spearman's Rank was used to analyze for correlations between NLCR and PCT, as well as NLCR and PELOD-2 score. Results with P values <0.05 were considered to be statistically significant, with 95% confidence intervals. This study was approved by the Health Research Ethics Committee of the Universitas Padjadjaran Medical School/Dr. Hasan Sadikin General Hospital, Bandung.

Results

During the study period, 232 pediatric patients were

registered in the *Sepsis Registry.* Ninety subjects met the inclusion criteria. The characteristics of subjects are listed in **Table 1**.

Most subjects were male (56.7%) and the largest age group was 1-23 months (57.8%). The most common source of infection was lower respiratory tract infection (67.8%). An overview of the results of the NLCR, PCT, and PELOD-2 scores are presented in **Table 2**.

The NLCR and PCT levels had a significant positive correlation, with correlation coefficient r=0.642 (P<0.001), which indicated a strong correlation (0.6<r<0.8) (**Figure 1**). The NLCR and PELOD-2 score also had a significant positive correlation (r=0.233; P=0.027), but the correlation was weak (0.2<r<0.4) (**Figure 2**).

Table 1. Characteristics of subjects (n = 90)

Characteristics	N=90
Gender, n (%)	
Male	51 (56.7)
Female	39 (43.3)
Age, n (%)	
1-23 mo	52 (57.8)
24-71 mo	17 (18.9)
72-155 mo	14 (15.6)
156-216 mo	7 (7.8)
Median (range)	16 (1-216)
Source of infection, n (%)	
Lower respiratory tract	61 (67.8)
Central nervous system	19 (21.2)
Gastrointestinal	6 (6.7)
Soft tissue	3 (3.3)
Burn injury	1 (1.1)

Table 2. Subjects' NLCR, procalcitonin, and PELOD-2 score results

Variables	N=90
Median NLCR (range)	3.21 (0.32–23.20)
Median PCT (range), ng/mL	6.89 (0.01–379.25)
Median PELOD-2 score (range)	3 (2–14)

Discussion

We evaluated NLCR as a potential biomarker for infection in sepsis patients, by analyzing for correlations with PCT and PELOD-2 score for sepsis severity. Most of our subjects were male, more than half were aged 1-23 months, and most had lower respiratory tract infections.

The NLCR and PCT in our pediatric sepsis patients had a significant, positive correlation (r=0.642; P<0.001). Similarly, an adult sepsis study in Turkey reported a significant correlation between NLCR and PCT, but with a weak level of correlation (r=0.308; P=0.01).[21] In addition, a Turkish study of pediatric sepsis patients showed a significant but weak correlation between PCT and NLCR (r=0.168; P= 0.02).[18]

During sepsis, the number of neutrophils initially increase, followed by an increase in lymphocytes. Persistent sepsis causes apoptosis of lymphocytes, increasing the neutrophil-lymphocyte ratio. Manifestations of neutrophilia and lymphocytopenia

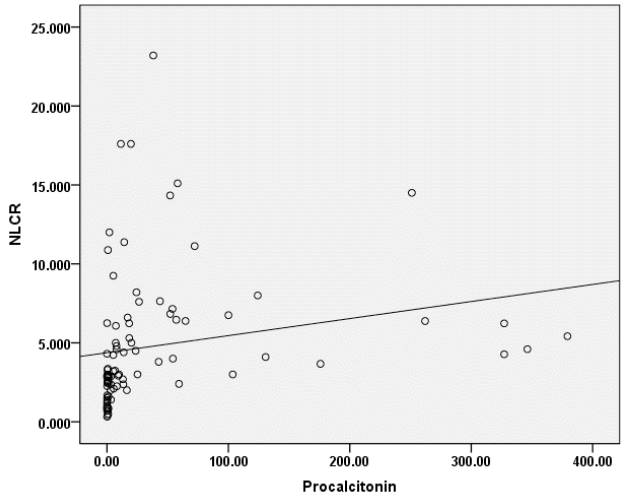

Figure 1. Correlation between NLCR and procalcitonin in pediatric sepsis

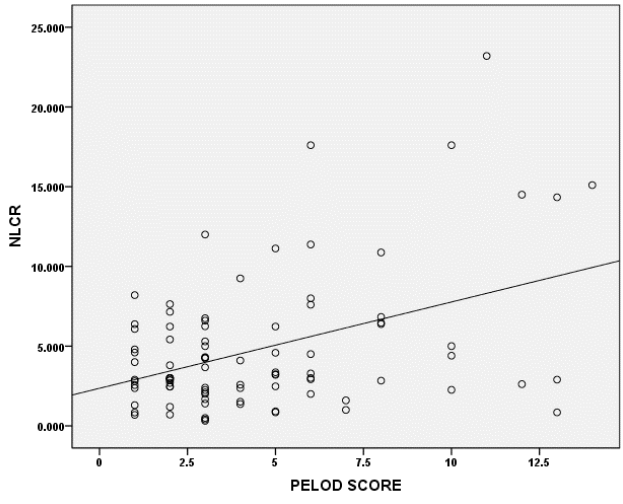

Figure 2. Correlation between NLCR and PELOD-2 score in pediatric sepsis

occur 4-8 hours after exposure to infection.[22] Another marker of infection, PCT, is fast and specific for detecting bacterial infection in critically ill patients. Procalcitonin increases within 3 to 4 hours, peaks within 6 hours, and remains in the blood for up to 24 hours after exposure to infection.[23] We noted an increase NLCR at the time of sepsis diagnosis, with a significant correlation between NLCR and PCT. This finding suggests that NLCR can be used as a marker for bacteremia and sepsis in an emergency setting.

There was also a significant, weak positive correlation between NLCR and sepsis severity based on PELOD-2 score (r=0.233; P=0.027). These results were consistent with a previous study in PICU patients that reported NLCR could predict the risk of death as well as the PELOD-2 score, as shown by an increase in NLCR, followed by worsening clinical conditions and increased mortality in subjects. An increase in NLCR value >0.2 was predictive of mortality, with 89.1% sensitivity and 61.1% specificity.[24]

The majority of our subjects comprised was the 1–23-month age group (57.8%). A systematic review of 23 studies in 16 developed and 7 developing countries also showed a higher incidence of sepsis in the infant group (516 cases per 100,000 population).[25] Compared to older children, infants tend to be more susceptible to severe infections because their innate and adaptive immune systems are not yet fully developed. The low production of IFN-γ and the lack of cytotoxic T cell response in children aged <2 years may result in uncontrolled viral/bacterial replication, making them prone to severe infections.[26]

The most common causes of sepsis in this study were lower respiratory tract infections (67.8%), followed by central nervous system infections (21.1%), gastrointestinal tract infections (6.7%), soft tissue infections (3.3%), and burns (1.1%). These results were consistent with the *2015 Sepsis Prevalence Outcomes and Therapies* (SPROUT) international prevalence study, which collected data on child sepsis from 128 PICUs in 26 countries spread across 6 continents. They reported the global prevalence of sepsis in PICUs to be 8.2%. The mean age of sepsis patients was three years, and most infections were found in the respiratory system (40%).[27]

The median NLCR was 3.21 (range 0.32-23.20) in our study. This NLCR was close to the result of a study of 68 pediatric patients with sepsis/bacteremia and viral infection in Lithuania, which showed a mean NLCR of 2.69 (SD 2) and an NLCR cut-off of 1.58 to predict sepsis/bacteremia, with 73.0% sensitivity and 57.7% specificity.[28] To date, there has been no consensus on a normal NLCR value that can be used universally.

The median PELOD-2 score in our study was 3 (range 2-14). A study of 2,594 PICU patients with infectious diseases showed that a PELOD-2 score ≥2 was associated with a significant increase in mortality by 7.3% compared to a PELOD-2 score <2 of 1.7%. A PELOD-2 score ≥2 reflects the presence of ≥1 organ dysfunction.[7] Another study in PICU patients with suspected infection reported that PELOD-2 score in the first 24 hours of treatment was a good predictor of mortality. The odds ratio of death for each point increases of PELOD-2 score on the first day was 1.5 (95%CI 1.39 to 1.63).[29]

To our knowledge, this study is the first to report a correlation between NLCR and PCT in Asian pediatric sepsis patients, as well as a correlation between NLCR and PELOD-2 score. However, as this study was retrospective, longitudinal studies are needed to monitor changes in NLCR values in pediatric sepsis patients as well as to determine the NLCR cut-off value.

In conclusion, NLCR is directly proportional to PCT levels in pediatric septic patients. As such, NLCR may be useful as a new infection marker, especially in health facilities with limited facilities and infrastructure.

Conflicts of Interest

None declared.

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