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Original Article

Platelet-lymphocyte ratio and sepsis outcomes in children

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Abstract

Background Sepsis is the most common cause of death in infants and children worldwide. Identification of patients with a high risk of death and accurately anticipating outcomes in the early phase is very important in order to provide adequate intervention to the patient. Predictors and scoring systems have been used to determine the prognosis of sepsis n children. The platelet-lymphocyte ratio (PLR), a newly-used marker for inflammation, has received recent attention, as it can act as an indicator in a variety of diseases, including sepsis.

Objective To investigate the relationship between PLR and clinical outcomes in pediatric patients with sepsis.

Methods This study was conducted using an analytic, observational method with a prospective cohort approach in children with sepsis in the Pediatric Intensive Care Unit (PICU) of Prof. Dr. R. D. Kandou Central General Hospital, Manado, North Sulawesi, from February to August 2020. We analyzed patients' platelet-lymphocyte ratio (PLR), mortality rate, and length of stay using *SPSS software*. The PLR were recorded once within the first 24 hours of PICU admission.

Results Of 96 PICU patients, 87 patients were eligible for this study. In total, 50 patients (57.47%) died. Mean PLR was 77.53 among sepsis survivors and 157.2 among non-survivors (rpb=0.566, P<0.0001) indicating a strong relationship between PLR and mortality. We also found a strong positive linear relationship between PLR and PICU length of stay.

Conclusion Platelet-lymphocyte ratio is a predictor of sepsis outcomes that can be easily and inexpensively checked. Thus, it can be used in regions with limited health facilities. **[Paediatr Indones. 2021;61:322-7 ; DOI: 10.14238/pi61.6.2021.322-7**].

Keywords: *sepsis; platelet-lymphocyte ratio; PLR; clinical outcomes*

Sepsis is an organ dysfunction that threatens a person's life and caused by immune dysregulation against an infection. It is the most common cause of death in infants and children, worldwide.[1-3] In the early phase, identification of patients with a high risk for death and accuracy in anticipating outcomes is very important to provide adequate, life-saving intervention to the patient.[4]

The incidence of sepsis has increased in the last 30-40 years, both in developed and developing countries. More than 4,300 deaths per year or around 7% of the total deaths in children are caused by severe sepsis. The incidence of severe sepsis in the United States is 0.56 cases per 1,000 population per year. The highest incidence occurs in infants (5.16 cases per 1,000 population per year) and sharply declines in children age 10-14 years old (0.2 cases per 1,000 population per year).[3] In the PICU at Cipto Mangunkusumo Hospital, Jakarta, 19.3% of 502 patients experienced sepsis, with a mortality rate of 54%.[5] Sepsis is not just a health problem, but a worldwide socio-economic challenge, as sepsis significantly decreases quality of life and increases mortality. The impact is clear in terms of short term morbidity and mortality. The impact of sepsis on the individual still remains after the crisis period of the disease, and increases in mortality after

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ICU discharge are frequently reported. Furthermore, inflammation that occurs while receiving ICU care may cause further damage. Thus, an accurate prognosis of sepsis is important. Nevertheless, to date, no definitive laboratory test can accurately predict the relationship between sepsis severity and mortality.

Several predictors and scoring systems have been used to determine the prognosis of sepsis in children. One of the most frequently used in pediatric patients is the *Pediatric Logistic Organ Dysfunction* (PELOD)-2 score, which has proven to be accurate in predicting mortality in sepsis patients. However, many PELOD-2 criteria require specific examinations that facilities with limited equipment cannot perform.[1-3] In the last few years, platelets and lymphocytes counts have been found to play important roles in the inflammatory process.[6] Thus, the platelet-to-lymphocyte ratio (PLR) has received attention as a potential indicator of inflammation in a variety of diseases, including sepsis.[7] Studies have shown that PLR can be used for early diagnosis and detection of sepsis in neonates; high PLR was associated with high mortality in sepsis.[8] The PLR parameter can be easily and inexpensively obtained from routine blood examinations and is equally meaningful compared to other expensive inflammatory indicators such as interleukin (IL)-6, IL-8, IL-1 β, and TNF-α.

Although PLR has been frequently used in diagnosis and prognosis of sepsis in neonates and adults,6-8 It has not been studied much in the pediatric population. Some studies have shown non-significant results when using PLR as a predictor for sepsis outcomes.[8]

We aimed to more clearly determine the relationship between PLR and sepsis outcomes in children, with the hope of improving our understanding and potentially guiding treatment protocols. Our findings may serve as a foundation for future studies, in order to decrease mortality and morbidity of sepsis in children.

Methods

This prospective cohort study was conducted at Prof. R.D. Kandou Hospital, Manado, North Sulawesi, from February to August 2020 and approved by the local Ethics Committee. Children aged between 1 month and 18 years who were hospitalized in the PICU were included in the study. Subject's parent providing informed consent. Patient were excluded from the study if they had other pre-existing comorbid disease such as malignancy, autoimmune disease, chronic kidney disease, post surgery, obesity, malnutrition or any parental refusal of treatment. Subject's demographic data and laboratory results were collected. Mortality and lenght of stay of subjects in PICU were also recorded for the study outcome. Complete blood count measurements were retrieved for the calculation of PLR. The PELOD-2 score was used to evaluate organ dysfunction and diagnosed sepsis. The blood sample and scoring was recorded within the first 24 hours of PICU admission.

In our study, univariate analysis was used for the distribution of study variables and descriptive statistics (mean, standard deviation, and median). Bivariate analyses were logistic regression for analyzing the relationship between PLR and mortality, and Pearson's correlation/simple linear regression for analyzing PLR and PICU length of stay. Analyses were performed using *SPSS software version 25*.

Results

Of 96 children aged 1 month to <18 years diagnosed with sepsis, 87 children fulfilled the inclusion criteria. Nine children were excluded due to poor nutrition (2 patients), post-surgical condition (4 patients), acute leukemia (1 patient), or refusal of one or more therapy (2 patients). The study flow chart is shown in **Figure 1**.

The subjects' age range was 1 month to 211 months. The mean age of survivors was 50 months, while the mean age of those who died was 59.62 months. Of 46 (52.9%) males, 25 survived and 21 died. Of 41 (47.1%) females, 25 survived and 16 died. The characteristics of subjects are shown in **Table 1**.

The mean PLR was 111.39 of all subjects, 77.53 in survivors, and 157.12 in those who died (**Table 2**). Biserial point correlation analysis revealed a strong association between PLR and mortality. Mean PLR was significantly higher in those who died than in survivors ($r=0.566$; $P<0.0001$) (**Figure 2**).

Simple logistic regression analysis used to revealed the relationship between PLR and the chance of dying ($P<0.0001$). The graph in **Figure 3** shows that higher

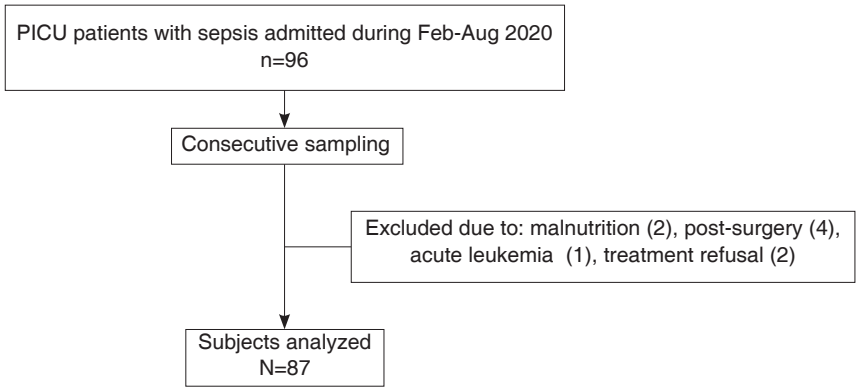

Figure 1. Study flow chart of subject inclusion

Table 1. Characteristics of subjects

Characteristics	(N=87)
Age, months	
Survived (n=50)	
Mean (SD)	50 (43.36)
Median (range)	39.50 (1-192)
Died (n=37)	
Mean (SD)	59.42 (76.24)
Median (range)	26 (1-211)
Sex, n (%)	
Male	46 (52.9)
Female	41 (47.1)
Hemoglobin, g/dL	
Mean (SD)	11.001 (2.37)
Median (range)	10.80 (6.7-19.2)
Leukocyte count, /mm^3	
Mean (SD)	20,254.02 (8810.43)
Median (range)	19,400 (3,100-43,200)
Platelet count, /mm^3	
Mean (SD)	398,724.14 (191,222.97)
Median (range)	356,000 (28,000-944,000)
Absolute lymphocyte count, /mm^3	
Mean (SD)	4,833.45 (3525.56)
Median (range)	4,112 (350-19,886)
PLR	
Mean (SD)	111.39 (69.97)
Median (range)	110.07 (11.01-368.57)
PELOD-2 score	
Mean (SD)	13.22 (2.083)
Median (range)	13 (11-20)
PICU length of stay, days	
Mean (SD)	6.7 (3.86)
Median (range)	6 (2-19)

PLR increased the risk of death.

Pearson's correlation test revealed a strong positive linear relationship between PLR and PICU length of stay (r = 0.694b; P<0.0001). **Figure 4** shows that higher PLR was associated with longer PICU length of stay.

Discussion

Sepsis is a condition characterized by an uncontrolled systemic inflammatory response followed by increased vascular permeability and plasma protein leakage induced by inflammatory mediators, potentially leading to hypotension, shock, multiorgan dysfunction syndrome (MODS), and even death.[1,9,10]

In sepsis, platelets and leukocytes play an important role in inflammation. Platelets and neutrophils interact during inflammation, with reactions occurring on the endothelial surface.[10] Platelets directly activate neutrophils and monocytes to migrate to the site of tissue destruction (chemotaxis). Furthermore, platelets also indirectly activate the interaction between neutrophils and monocytes, through several mechanisms, including triggering of neutrophil TREM-1, which leads to various pro-inflammatory responses.[11] Lymphocytes can act as anti-inflammatory stimuli, through production of lymphocyte apoptotic products. An excess of apoptotic lymphocytes contributes to immunosuppression in sepsis, usually leading to septic shock, then progressing into a state of immune paralysis before death.[12,13]

There were more males (52.9%) than females (47.1%) in our study, similar to that reported by another study.[13] Male sex hormones suppress the immune response, while female sex hormones provide natural

Table 2. Characteristics of PLR and sepsis outcomes

Parameter	Outcomes	
	Survived (n=50)	Died (n=37)
Platelet count, /mm^3		
Mean (SD)	349,020 (187,116.63)	465,891.89 (177,844)
Median (range)	334,000 (28,000-944,000)	408,000 (129,00-774,000)
Lymphocyte count, /mm^3		
Mean (SD)	5,936.06 (4,148.546)	3,343.43 (1.515,624)
Median (range)	4,774.5 (1,271-19,886)	3,080 (350-6.348)
PLR		
Mean (SD)	77.54 (50.08)	157.13 (67.38)
Median (range)	66.24 (11.01-236.45)	152.29 (11.57-368.57)

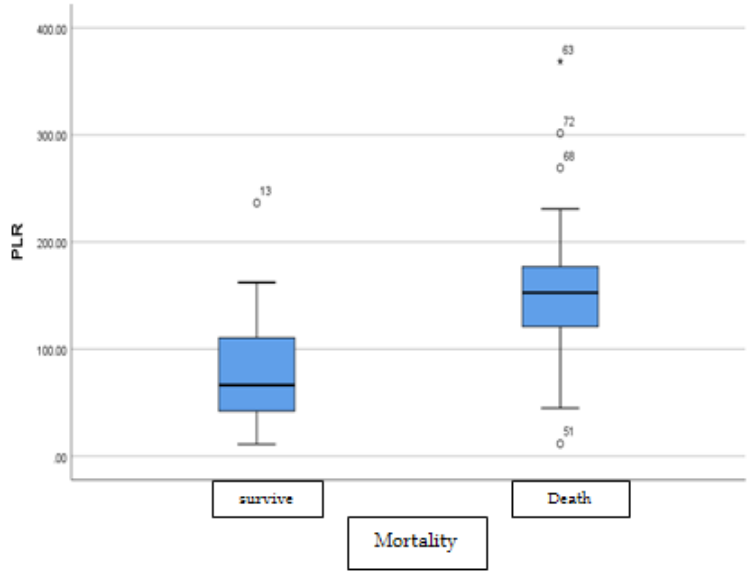

Figure 2. Distribution of PLR based on mortality

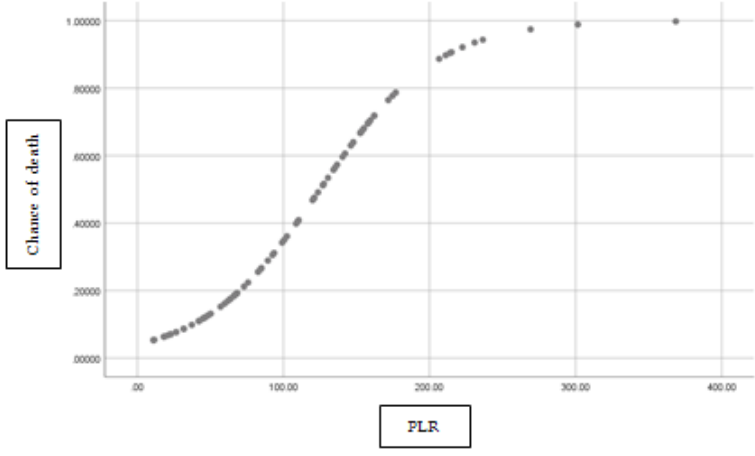

Figure 3. Relationship of PLR with risk of mortality

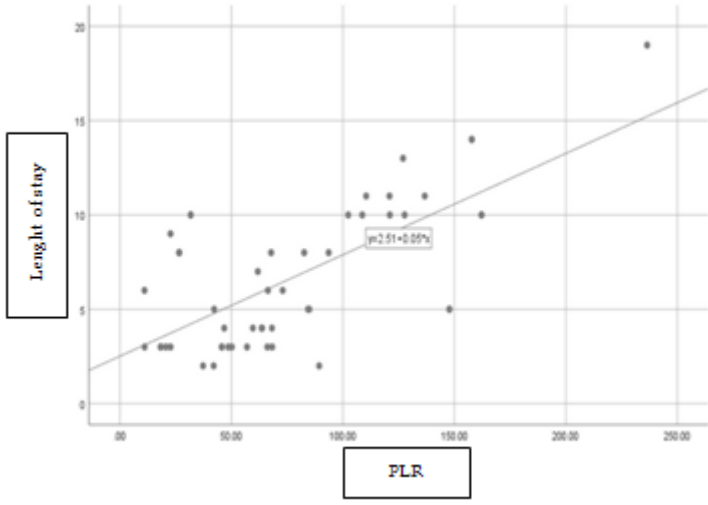

Figure 4. Analysis of PLR and PICU length of stay

protection against inflammation.[14]

We found a strong relationship between PLR and mortality (r=0.566; P<0.0001). The mean PLR after entering the intensive care unit was higher in patients that died (157.12) compared to those who survived (77.53). Similar results were obtained from a previous study concerning the use of neutrophil-lymphocyte ratio (NLR) and PLR to detect early onset of sepsis in neonates, which found a positive relationship between NLR and PLR in the sepsis group, with NLR 6.76 and PLR 94.05 as cut-offs for neonatal sepsis (sensitivity 97.4; specificity 100%).[7]

In adults, a study showed that the PLR in adult sepsis patients who survived [111 (16-537)] was significantly lower than in patients who died [209 (52-1143)] (P<0.001).[15] We also found higher PLR in those who died. A previous study also showed that PLR can be used as a predictor of mortality in pediatric PICU patients, with a higher PLR value correlating with a higher mortality rate and deterioration of clinical condition, PELOD-2 score >20 predicted 72.2% mortality while an increased PLR value predicted 77.8% mortality. Another study in adult patients using SOFA score calculated within 24 hours of ICU admission, showed that a high PLR value was significantly related to mortality. On the other hand, a low PLR value did not show the same result. The PLR value was considered to be significant if it was >200 with an OR of 1.0002 (95%CI 1.19 to 1.67). A high PLR value was associated with a high mortality in the following days.[6]

In our study, the mean PICU length of stay of survivors was 6.7 (range 2-19) days. There was a strong positive linear relationship between PLR and length of stay (r=0.694; P<0.0001). Severe inflammation can worsen the clinical condition or course of disease, as well as worsen the prognosis. Thus such patients require treatment for a longer period of time. To our knowledge, this study is the first to find a significant relationship between PICU length of stay of sepsis patients and the PLR as the predictor. Other studies have assessed for relationships between PLR value to predict the length and cost of hospital stay for a variety of diseases. A study in patients with diabetic foot ulcers (DFU), and found that a high PLR value was directly proportional to the length of hospital stay (PLR 140.8 in DFU grade 2 *vs.* 222.1 in DFU grade 4; LOS: 7.9 days *vs.* 12.5 days), in terms of cost, no significant difference was found.[17] A study compared PLR value with ICU length of stay in post-transhiatal surgical patients with cervical anastomosis. They showed an increased length of stay for patients with a higher pre-operation PLR value.[18] Even though previous studies did not concern sepsis patients,[17-18] PLR is a widely studied inflammation biomarker in a variety of diseases in which higher PLR value corresponds to a more severe inflammation process.

In children, PLR studies have been limited to an overall critical patient condition. Our study provides information for medical staff, especially intensive

care physicians, in that PLR can be used to predict mortality and PICU length of stay in children with sepsis. Furthermore, PLR is a predictor that can be easily and inexpensively checked and thus, can be used in regions with limited facilities.

Conflict of Interest

None declared.

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