Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.61, No.4(2021). p.186-91; DOI: 10.14238/pi61.4.2021.186-91

Original Article

Platelet-to-lymphocyte ratio, PELOD-2 score, and mortality rate in pediatric sepsis

Novie Homenta Rampengan, Gregory Joey, Ferry Kurniawan, Jeanette I. Ch. Manoppo, Ari Lukas Runtunuwu

Abstract

Background Sepsis is life-threatening organ dysfunction caused by a regulated immune response to infection. Sepsis remains the most common cause of death in infants and children worldwide. The *Pediatric Logistic Organ Dysfunction* (PELOD-2) score, one of the most widely used scoring systems in pediatric sepsis patients, has been shown to be accurate in predicting mortality. The platelet-to-lymphocyte ratio (PLR) is a new clinical indicator of inflammation in a variety of diseases including sepsis.

Objective To investigate the relationship between PLR, PELOD-2 score, and clinical outcomes in pediatric patients with sepsis.

Methods This retrospective cohort study was conducted in the Pediatric Intensive Care Unit (PICU), Prof R.D. Kandou Hospital, Manado, North Sulawesi, from February to August 2020. Subjects' PELOD-2 score and PLR were recorded once within the first 24 hours of PICU admission. We analyzed patients' PELOD-2 score, PLR, and mortality rate, with 95% confidence interval (CI) for each value.

Results Of 96 children with sepsis admitted to the PICU during the study period, 87 patients (46 boys; 52.9%) met the inclusion criteria. In total, 50 (57.47%) patients were non-survivors. Mean PLR values among survivors [77.54 (SD 50.08)] was significantly lower compared to the values among non-survivors [157.13 (SD 67.38)]; as well as the PELOD-2 score in the survivors group [12 (SD 1.32)] was significantly lower than its value in the non-survivors [14.65 (SD 2.09)]. Spearman's analysis showed a moderately positive correlation between PLR and PELOD-2 score ($r=0.444$; 95%CI 0.44 to 1; $P<0.01$). Biserial point correlation analysis revealed a significant association between PLR and mortality rate ($rpb=0.566$; $P<0.0001$),with elevated PLR related to an increased risk of mortality.

Conclusion There are positive correlations between PLR, PELOD-2 score, and mortality rate in pediatric patients with sepsis. Higher PLR and PELOD-2 score are associated with higher mortality. **[Paediatr Indones. 2021;61:186-91 ; DOI: 10.14238/pi61.4.2021.186-91**].

Keywords: *platelet to lymphocyte ratio; pediatric sepsis; organ dyscfunction; PELOD2; PLR; mortality*

Sepsis is a life-threatening organ dysfunction caused by a regulated immune response to infection. Sepsis is the most common cause of death in infants and children worldwide.[1-3] Identification of patients at high risk of death and anticipation of poor outcomes in the earlier phase of disease are essential to provide adequate intervention to patients.[4]

The incidence of sepsis has increased in the last 30-40 years in both developed and developing countries. More than 4,300 deaths per year or about 7% of total deaths in children are caused by severe sepsis. In the United States, the incidence of severe sepsis was 0.56 cases per 1,000 population per year, with the highest incidence in the infant age group.[5] At the Cipto Mangunkusumo Hospital PICU, Jakarta, Indonesia, of a total 502 admitted pediatric patients, 19.3% were diagnosed with sepsis, with a mortality rate of 54%.[6] Sepsis is not only a health problem, but also a socioeconomic challenge worldwide. The impact of sepsis on survivors can persist even after the critical

From the Child Health Department, Universitas Sam Ratulangi/Prof. Dr. Kandou Hospital, Manado, North Sulawesi, Indonesia.

Corresponding author: Novie Homenta Rampengan, Departmen of Child Health, Universitas Sam Ratulangi/Prof Dr. Kandou Hospital Manado. . Jalan Raya Tanwangko, No.56 Manado 95115, North Sulawesi, Indonesia. Phone/fax: (0431) 821652/(0431)859091. Email: novierampengan@yahoo.com.

Submitted February 23, 2021. Accepted August 16, 2021.

period of illness, and an increased mortality after discharge from the intensive care facilities is frequently reported. Therefore, identification of septic patients who are at risk of worse prognosis and outcome is very important. Nevertheless, to date there are no laboratory markers that definitively correlate with the severity and mortality of patients with sepsis.[1-3]

Scoring systems to determine the prognosis and outcomes of sepsis in pediatric patients have been extensively studied. One of the most widely used is the PELOD-2 score, which has been shown to be accurate for predicting mortality in sepsis patients. However, some parameters of the score are cumbersome, and cannot not be conducted in resource-limited settings.[1-3] In recent years, some studies have reported that platelets and lymphocytes play important roles in the inflammatory process. Platelet-to-lymphocyte ratio (PLR) is a newly-proposed clinical indicator of inflammation in a variety of diseases including sepsis. It has received attention among clinicians in recent studies. Several studies have shown that PLR could be used to detect and diagnose neonatal sepsis and a high PLR value has also been associated with higher mortality rate in sepsis. The PLR is a simple and inexpensive parameter performed from routine hematological testing. This parameter is as significant as other advanced and expensive inflammatory markers, such as interleukin (IL)-6, IL-8, IL-1β, and TNFα.[7-9] Although PLR has often been used for sepsis diagnosis and prognosis in neonates and adults,[7-9] it has not been widely studied in the older pediatric population. Therefore, we aimed to investigate the relationship between PLR, PELOD-2 score, and clinical outcomes in pediatric patients with sepsis.

Methods

This retrospective 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. Subjects' parents provided informed consent. Patients were excluded from the study if they had other pre-existing comorbid diseases or conditions such as malignancy, autoimmune disease, chronic kidney disease, trauma, post-operative conditions, obesity, malnutrition, or any parental refusal of treatment. Subjects' demographic data and laboratory findings were collected. Mortality was also recorded as the study outcome. Complete blood count measurements were retrieved for the calculation of PLR. The PELOD-2 score was used to evaluate organ dysfunction, which included five main components: neurologic (*Glasgow Coma Scale* and papillary reaction), cardiovascular (serum lactate and mean arterial pressure), renal (serum creatinine), respiratory (PaO_2, $PaCO_2$ and need for invasive ventilation), and hematologic (leucocyte count and platelet count). The PELOD-2 score cut-off value used was 11. The score was recorded once within the first 24 hours of PICU admission.

Numerical data are presented in mean, standard deviation, and median, while categorical data are presented in numbers and percentages. Biserial point correlation was used to analyze for a possible association between PLR and mortality rate; simple logistic regression was used to analyze PLR and mortality risk. Spearman's rho analysis was used to analyze PELOD-2 score and PLR. Analyses were performed with *SPSS 25 (IBM)* software.

Results

There were 96 pediatric patients with a diagnosis of sepsis admitted to the PICU during the study period. The characteristics of subjects are shown in **Table 1**. The mean PELOD-2 score was 13.22 (SD 2.08) and the mean PLR value was 111.39 (SD 69.97). A total of 87 children met the inclusion criteria, of whom 46 were boys (52.9%). Nine patients were excluded because of malnutrition (2 patients), post-operative condition (4 patients), acute lymphoblastic leukemia (1 patient), and parental treatment refusal (2 patients) (**Figure 1**).

Fifty patients (57.47%) were non-survivors. Mean PLR in survivors group was significantly lower compared to the non-survivors [77.54 (SD50.08) *vs.* 157.13 (67.38), respectively; P=0,00). In addition, PELOD-2 scores among the survivors were significantly lower compared to non-survivors (12 *vs.* 14.15; P=0.00) (**Table 2**).

Spearman's analysis revealed a statistically significant moderate correlation between PLR and PELOD-2 score (r=0.444; 95%CI 0.44 to 1; P<0.01)

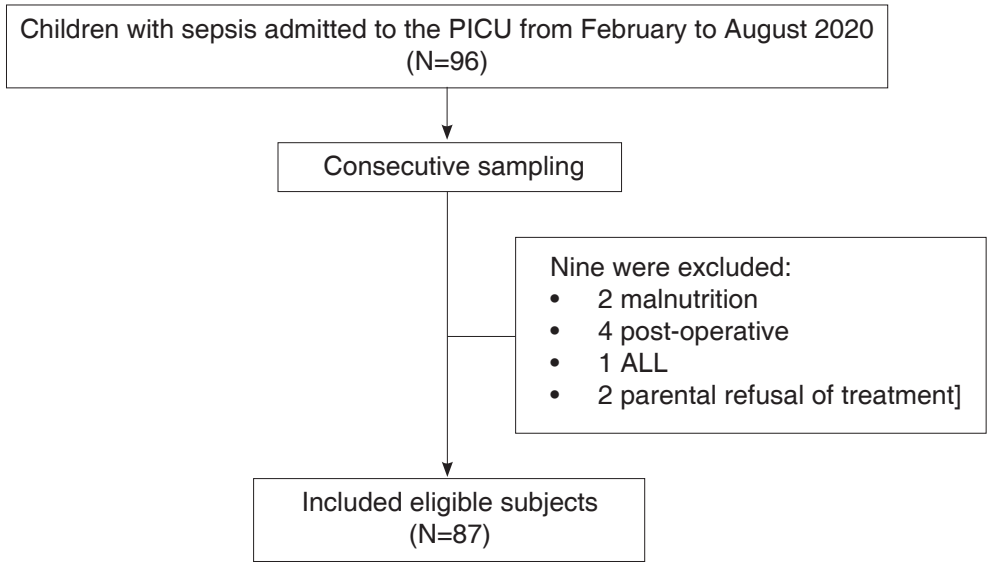

Figure 1. Study flow chart

Table 1. Characteristics of study subjects

Characteristics	(N=87)
Age, months	
Survivors	
Mean (SD)	50 (43.36)
Median (range)	39.50 (1-192)
Non-survivors	
Mean (SD)	59.42 (76.24)
Median (range)	26 (1-211)
Gender, n (%)	
Male	46 (52.9)
Female	41 (47.1)
Hemoglobin level , 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 (8,810)
Median (range)	19,400 (3,100 – 43,200)
Platelet count, /mm3	
Mean (SD)	398,724 (191,222)
Median (range)	356,000 (28,000-944,000)
Absolute lymphocyte count, /mm^3	
Mean (SD)	4,833.45 (3,525)
Median (range)	4,112 (350-19,886)
Platelet-to-lymphocyte ratio (PLR)	
Mean (SD)	111.39 (69.97)
Median (range)	110.07 (11.01-368.57)
PELOD-2 score	
Mean (SD)	13.22 (2.08)
Median (range)	13 (11-20)
Length of stay, days	
Mean (SD)	6.7 (3.86)
Median (range)	6 (2-19)

(**Table 3**). Furthermore, biserial point correlation analysis revealed a significant association between PLR and mortality rate (rpb=0.566; P<0.0001). Simple regression logistic showed an association between PLR and mortality risk in septic patients (P<0.0001). Elevated PLR was related to an increased risk of mortality.

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. Sepsis remains a major cause of morbidity and mortality in critically ill patients. Plasma leakage due to endothelial barrier dysfunction in sepsis creates severe microcirculation failure, resulting in tissue hypoperfusion. This condition leads to organ dysfunction and death.[1,11,12]

In sepsis, platelets and leukocytes play an important role in inflammation. Platelets and neutrophils interact during inflammation, with reactions occurring on the endothelial surface.[12] Platelets directly activate neutrophils and monocytes to migrate to the site of tissue destruction (chemotaxis). Furthermore,

Table 2. The PLR value and PELOD-2 score among subjects

Parameter	Outcomes		P value
	Survivors (n=37)	Non-survivors (n=50)	
Platelet count, /mm^3			
Mean (SD)	349,020 (187,116)	465,892 (177,844)	0.00
Median (range)	334,000 (28,000-944,000)	408,000 (129,000-774,000)	
Lymphocyte count, /mm^3			
Mean (SD)	5,936 (4,149)	3,343 (1,516)	0.00
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)	0.00
Median (range)	66.24 (11.01-236.45)	152.59 (11.57-368.57)	
PELOD-2 score			
Mean	12 (1.32)	14.65 (2.09)	0.00
Median (range)	12 (4.5-7.9)	15 (5.2-9.3)	

Table 3. Correlation between PLR value and PELOD-2 score

Spearman's rho	PLR	PELOD-2	P value
PLR	1	0.444*	<0.01
PELOD-2 score	0.444*	1	

*Correlation was significant at the 0.01 level (2-tailed)

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.[14] 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.[15,16]

Recent studies showed that platelets and lymphocytes have an important role in inflammation during sepsis. This study is the first conducted in children to determine the relationship between PLR, PELOD-2 score, and septic outcomes. We found more boys diagnosed with sepsis in the PICU than girls (52.9% *vs.* 47.1%, respectively), similar to a previous study (54.8% *vs.* 46.2, respectively).[17] Previous studies reported that this finding is related to sex hormones, as male sex hormone tends to suppress the immune response in sepsis, while the female sex hormone has a natural protective effect against inflammation.[18,19]

In our study, there was a moderate positive correlation between PLR and mortality rate (rpb=0.566; P<0.0001). Mean PLR was significantly higher in non-survivors than in survivors (157.12 *vs.* 77.53, respectively). Comparable findings were also reported by a study which found the usefulness of neutrophil-to-lymphocyte ratio (NLR) and PLR to predict early onset sepsis in neonates. There was a positive relationship between NLR and PLR for determining sepsis group, with NLR of 6.76 and PLR cut-off point of 94.05 for predicting neonatal sepsis (97.4% sensitivity and 100% specificity).[8]

The PLR was significantly lower in adult sepsis survivors than non-survivors (111 *vs.* 209, respectively; P< 0.001).[19] Another study also reported that PLR could be used as a predictor of mortality in PICU patients, with higher PLR related to increased risk of clinical deterioration and mortality. They also found PELOD-2 score >20 could predict 72.2% of mortality, and high PLR could predict 77.8% mortality cases.[20] In our study, mean PLR value [77.54 (SD 50.08) *vs.* 157.13 (67.38); P=0.00] and PELOD-2 score [12 (1.32) *vs.* 14.65 (SD 2.09); P=0.00 were significantly different between survivors and non-survivors. Another study reported that the percentage of patients with PELOD-2 score >7 was significantly higher in non-survivors compared to survivors (96% *vs.* 3.6%, respectively; OR=649).[21] We found a statistically significant moderate correlation between PLR and PELOD-2 score (r=0.444; 95%CI 0.44 to 1;P<0.01).

The PLR is an important marker of inflammation that has been widely studied in various diseases and settings. A high PLR value indicates a more severe inflammatory process. More severe inflammation could lead to clinical deterioration, worse prognosis, and death.[7-9,22-26] Various studies had assessed PLR

in septic patients, but the majority were conducted in adult populations. Very few studies were conducted in pediatric or neonatal populations, and many of them only assessed the usefulness of PLR in critically ill patients. Our findings may assist clinicians, particularly those who work in the PICU to predict prognosis and outcomes of critically ill patients with sepsis. The PLR is an easy and inexpensive clinical predictor, which can be used even in resource-limited settings.

The major limitations of our study were that it was retrospective and single-centered. The retrospective nature of this study also limited the temporal relationship between PLR and mortality, whereas the PLR value was only based on a single hematologic testing, and not a serial one. Further studies with larger and multi-center sampling are needed. In conclusion, there is a positive correlation between PLR value, PELOD-2 score, and mortality rate in pediatric patients with sepsis. Higher PLR and PELOD-2 score are associated with higher mortality.

Conflict of Interest

None declared.

Funding Acknowledgement

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

References

1. Somasetia DH. Pedoman nasional diagnosis dan tata laksana sepsis pada anak. In: Daud D, Rauf S, Salakede SB, Lawang SA. Kumpulan makalah pertemuan ilmiah tahunan VIII. Edisi 1. Makassar: Departemen Ilmu Kesehatan Anak FK UNHAS; 2016. p. 3-17.
2. Hadinegoro SR, Chairulfatah A, Latief A, Pudjiadi AH, Malisie RF, Alam A. Konsensus diagnosis dan tata laksana sepsis pada anak. Edisi 1. Jakarta: IDAI; 2016. p. 1-47.
3. Randolph AG, McCulloh RJ. Pediatric sepsis: important considerations for diagnosing and managing severe infections in infants, children and adolescents. Virulence. 2014;5:179-89. DOI: 10.4161/viru.27045.
4. Vincent JL, Pereira AJ, Gleeson J, De Backer D. Early management of sepsis. Clin Exp Emerg Med. 2014;1:3-7. DOI: 10.15441/ceem.14.005.
5. Watson RS, Carcillo JA, Linde-Zwirble WT, Clermont G, Lidicker J, Angus DC, *et al.* The epidemiology of severe sepsis in children in the United States. Am J Respir Crit Care Med 2003; 1:167(5):695-701. DOI: 10.1164/rccm.200207-682OC
6. Priyatiningsih DR. Karakteristik sepsis di pediatric intensive care unit RSUPN dr. Cipto Mangunkusumo. [dissertation]. [Jakarta]: Fakultas Kedokteran Universitas Indonesia; 2016.
7. Shen Y, Huang X, Zhang W. Platelet-to-lymphocyte ratio as a prognostic predictor of mortality for sepsis: interaction effect with disease severity-a retrospective study. BMJ Open. 2019;9:e022896.DOI: 10.1136/bmjopen-2018-022896.
8. Can E, Hamilcukan S, Can C. The value of neutrophil to lymphocyte ratio and platelet to lymphocyte ratio for detecting early-onset neonatal sepsis. J Pediatr Hematol Oncol. 2018;40:e229-32.DOI: 10.1097/MPH.0000000000001059.
9. Bharadwaj N, Singh HB, Anjum S, Tadury A. Does the platelet to neutrophil ratio and platelet to lymphocyte ratio predict newborn sepsis a case control study? Paripex Indian J Res. 2018;7:192-3.DOI:10.15296/ijwhr.2021.14.
10. Yildiz A, Yigit A, Benli AR. The prognostic role of platelet to lymphocyte ratio and mean platelet volume in critically ill patients. Eur Rev Med Pharmacol Sci. 2018;22:2246-52. DOI: 10.26355/eurrev_201804_14811.
11. Mayr FB, Yende S, Angus DC. Epidemiology of severe sepsis. Virulence. 2014;5:4-11. DOI: 10.4161/viru.27372.
12. Tayeh O, Tema KM, Eldesouky MI, Omara AA. Urinary albumin/creatinine ratio as an early predictor of outcome in critically-ill septic patients. Egyptian J Crit Care Med. 2016;4:47-55. DOI: 10.1016/j.ejccm.2016.03.002.
13. Ed Rainger G, Chimen M, Harrison MJ, Yates CM, Harrison P, Watson SP, et al. The role of platelets in the recruitment of leukocytes during vascular disease. Platelets. 2015;26:507-20. DOI: 10.3109/09537104.2015.1064881.
14. Page C, Pitchford S. Neutrophil and platelet complexes and their relevance to neutrophil recruitment and activation. Int Immunopharmacol. 2013;17:1176-84. DOI: 10.1016/j.intimp.2013.06.004.
15. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med. 2003;348:138. DOI: 10.1056/NEJMra021333.
16. Wesche DE, Lomas-Neira JL, Perl M, Chung CS, Ayala A. Leukocyte apoptosis and its significance in sepsis and shock. J Leukoc Biol. 2005;78:325-37. DOI: 10.1189/jlb.0105017.
17. Thapa S, Prasad PN, Shakya YM. Serum lactate-albumin ratio as predictor of mortality in severe sepsis and septic shock at Tribhuwan University Teaching Hospital, Kathmandu. Birat J Health Sci. 2017;2:191-5. DOI: 10.3126/bjhs.v2i2.18525.

18. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological differences. 2014;5:12-9. DOI: 10.4161/viru.26982.
19. Karagoz I, Yoldas H. Platelet to lymphocyte ratio and neutrophil to lymphocyte ratios as strong predictors of mortality in intensive care population. Rev Assoc Med Bras. 2019;65:633-6. DOI: 10.1590/1806-9282.65.5.633.
20. Mathews S, Rajan A, Soans ST. Prognostic value of rise in neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) in predicting the mortality in paediatric intensive care. Int J Contemp Pediatr. 2019;6:1052-8. DOI: 10.18203/2349-3291.ijcp20191044.
21. Misirlioglu M, Bekdas M, Kabakus N. Platelet to lymphocyte ratio in predicting mortality of patients in pediatric intensive care unit. J Clin Anal Med. 2018;9:488-92. DOI: 10.4328/JCAM.5809.
22. Uslu AU, Kucuk A, Sahin A, Ugan Y, Yilmaz R, Gungor T, *et al*. Two new inflammatory markers associated with disease activity score-28 in patients with rheumatoid arthritis: neutrophil-lymphocyte ratio and platelet-lymphocyte ratio. Int J Rheum Dis. 2015;18:731-5. DOI: 10.1111/1756-185X.12582.
23. Seo YJ, Joeng JH, Choi JY, Moon IS. Neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio: Novel markers for diagnosis and prognosis in patients with idiopathic sudden sensorineural hearing loss. Dis Markers. 2014;2014:702807. DOI: 10.1155/2014/702807.
24. Turkmen K, Erdur FM, Ozcicek F, Ozcicek A, Akbas EM, Ozbicer A, et al. Platelet-to-lymphocyte ratio better predicts inflammation than neutrophil-to-lymphocyte ratio in end-stage renal disease patients. Hemodial Int. 2013;17:391-6. DOI: 10.1111/hdi.12040.
25. Kim EY, Lee JW, Yoo HM, Park CH, Song KY. The platelet-to-lymphocyte ratio versus neutrophil-to-lymphocyte ratio: which is better as a prognostic factor in gastric cancer? Ann Surg Oncol. 2015;22:4363-70. DOI: 10.1245/s10434-015-4518-z.
26. Karagoz I, Yoldas H. Platelet to lymphocyte ratio and neutrophil to lymphocyte ratios as strong predictors of mortality in intensive care population. Rev Assoc Med Bras. 2019;65:633-6. DOI: 10.1590/1806-9282.65.5.633.