

Procalcitonin level, neutrophil to lymphocyte count ratio, and mean platelet volume as predictors of organ dysfunction and mortality in children with sepsis

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Abstract

Background Procalcitonin (PCT) level is one of known biomarker in septic diagnosis, but limited studies report its benefit in predicting the outcomes of children with sepsis. Neutrophil to lymphocyte (NLR) and mean platelet volume (MPV) are simple biomarkers of inflammation that can be measured in routine hematological examination which role in predicting organ dysfunction remain unclear.

Objective To understand the correlations between PCT level, NLR, and MPV, tested in the first day of admission with outcomes of septic children in intensive care unit.

Methods This retrospective cohort study obtained the data from medical record of pediatric patients admitted in PICU and HCU. The PCT, NLR, and MPV levels were assessed in the first day of admission. Organ dysfunction was identified using qSOFA score more than 2 points, assessed at the third day of admission.

Results Sixty-nine septic children were reviewed. PCT level correlated significantly with qSOFA score ($R=0.639$; $P=0.000$); as well as with mortality ($R=0.747$; $P=0.000$). Receiver operating characteristic (ROC) curve of PCT level had area under curve (AUC) of 0.922 to predict organ dysfunction (cut-off 3.425; sensitivity 95.8%; specificity 52.4%) and AUC of 0.952 to predict mortality (cut-off 21.165; sensitivity 96.4%; specificity 78%).

Moreover, NLR correlated significantly with qSOFA ($R=0.407$; $P=0.001$), but did not correlate with mortality. The ROC of NLR to predict organ dysfunction was 0.829 (cut-off 3.52; sensitivity 87.5%; specificity 66.7%). There was no correlation between MPV with qSOFA score neither with mortality. Linear regression test showed that PCT level and NLR simultaneously had correlated with qSOFA score ($R=0.696$; $P=0.000$) and mortality ($R=0.748$; $P=0.000$). Meanwhile, PCT and MPV simultaneously had correlation with qSOFA score ($R=0.688$; $P=0.000$) and mortality ($R=0.733$; $P=0.000$). Moreover, NLR and MPV simultaneously had correlation with qSOFA score ($R=0.453$; $P=0.002$). All three independent variables (PCT level, NLR, and MPV) simultaneously correlated with qSOFA score ($R=0.744$; $P=0.000$) and mortality ($R=0.739$; $P=0.000$).

Conclusion There are significant correlations between each, PCT level and NLR with qSOFA score as well as with mortality. There is no correlation between MPV with qSOFA score, nei-

ther with mortality. There are significant correlations between PCV level and NLR with or without MPV with qSOFA score as well as with mortality. [Paediatr Indones. 2023;63:14-20; DOI: <https://doi.org/10.14238/pi63.1sup.2023.14-20>].

Keywords: sepsis; procalcitonin; qSOFA; neutrophil to lymphocyte count ratio; mean platelet volume; mortality

Sepsis, a dysregulated immune response against infection, is one of major children health problem, both in developed and developing countries. A study in 2015, involving 128 PICUs in 26 countries noted severe septic prevalence as high as 8.2%. Another multicenter cohort involving 7 Europe countries reported 59% of septic patients had septic shock with mortality rate reached 10%.^{1,2} Mortality and morbidity of sepsis in children can be caused by multi-factors. Organ dysfunction related to sepsis is the main cause of morbidity and mortality

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in children with sepsis. A previous study showed that 49% of death in children with sepsis occurred in the first 7 days; and refractory shock that occurred in the first three days of admission was the main cause of death among patients.¹ Seventy percent of death related to sepsis occurred in the first 72 hours of PICU admission.³

Quick Sequential Organ Failure Assessment (qSOFA) is considered as one of easy tool that can be used widely in intensive care unit to early identified septic patient that had bad poor prognosis. Compared with other prognostic scores, qSOFA has better mortality predictor (AUC 0.72) than SIRS and qPELOD, with AUC 0.64 and 0.60, respectively.^{4,5} Procalcitonin level is a well-known biomarker in sepsis diagnosis, but only a few studies reported its performance in predicting outcomes in children with sepsis. Neutrophil to lymphocyte (NLR) and mean platelet volume (MPV) can be obtained easily in complete blood count. Several studies reported their usefulness in sepsis diagnosis, but lack of studies reported their performances in predicting organ dysfunction and mortality, especially in children with sepsis. We aimed to find out the correlation between PCT level, NLR, and MPV, tested in first day of admission with outcomes of septic children in intensive care unit.

Methods

This was a retrospective cohort study using medical record data of septic children admitted in PICU and HCU Saiful Anwar Hospital, Malang, East Java, since January 2019. The inclusion criteria were children aged 1 months to 18 years with sepsis diagnosed by 2005 *International Pediatric Sepsis Consensus Conference* (Table 1).⁶ Exclusion criteria were patients with congenital heart disease, hematologic disease, malignancy, and length of care in intensive care unit less than 3 days or more than 28 days.

Patient information regarding age, gender, and vital signs (body temperature, heart rate, respiratory rate, systolic and diastolic arterial pressures) were collected. Organ dysfunction was identified using qSOFA score (Table 2) more than 2 points.⁵ Kolmogorov-Smirnov normality test resulted all PCT level, NLR, and MPV values were in normal distribution and Pearson test was used to analyze correlations between those variables. The characteristics of subjects were presented in tables and narration. The optimal cut-off point analysis was presented in graphs and tables. The data obtained were analyzed by SPSS *Statistic 22*. This study was approved by the Research Ethics Committee of the Brawijaya University Medical School/Dr. Saiful Anwar Hospital, Malang.

Table 1. Sepsis definition based on 2005 *International Pediatric Sepsis Consensus Conference*⁶

<p>SIRS</p> <p>The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:</p> <ul style="list-style-type: none"> • Core temperature of >38.5°C or < 36°C. • Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise, unexplained persistent elevation over a 0.5- to 4-hr time period OR for children <1 year old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, β-blocker drugs, or congenital heart disease; or otherwise, unexplained persistent depression over a 0.5-hr time period. • Mean respiratory rate < 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia. • Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leukopenia) or < 10% immature neutrophils. <p>Infection</p> <p>A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen OR a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical exam, imaging, or laboratory tests (e.g., white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or purpuric rash, or purpura fulminans)</p> <p>Sepsis</p> <p>SIRS in the presence of or as a result of suspected or proven infection.</p> <p>Severe sepsis</p> <p>Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions.</p> <p>Septic shock</p> <p>Sepsis and cardiovascular organ dysfunction</p>

SIRS = systemic inflammatory response syndrome

Results

A total of 69 medical records were reviewed. Data of MPV in early admission was collected only from 57 samples. The basic characteristics of subjects are shown in **Table 3**.

Procalcitonin level in first day of admission had a significant correlation with qSOFA score in the third day of admission ($R=0.639$; $P=0.000$). Procalcitonin level in the first day of admission also had a significant correlation with mortality ($R=0.747$; $P=0.000$). Statistical analysis showed that NLR in the first day of admission had a significant correlation with qSOFA in the third day of admission ($R=0.407$; $P=0.001$). There was no correlation between NLR in the first day of admission with mortality. There was no correlation between MPV in the first day of admission with qSOFA score in the third day of admission, neither with mortality. Linear regression test showed that PCT level and NLR in the first day of admission simultaneously had correlations with qSOFA score in the third day of admission ($R=0.696$; $P=0.000$) and mortality ($R=0.748$; $P=0.000$). Procalcitonin level and MPV simultaneously had correlation with qSOFA score in the third day of admission ($R=0.688$; $P=0.000$) and mortality ($R=0.733$; $P=0.000$). The NLR and MPV simultaneously had correlation with qSOFA score in the third day of admission ($R=0.453$; $P=0.002$). While all three

independent variables (PCT level, NLR, and MPV) simultaneously had correlation with qSOFA score in the third day of admission ($R=0.744$; $P=0.000$) and mortality ($R=0.739$; $P=0.000$). All the correlation test performed to each and between variables can be seen in **Table 4**.

Receiver operating characteristic (ROC) curve of PCT level in the first day of admission had area under curve (AUC) 0.922 to predict organ dysfunction (cut off 3.425; sensitivity 95.8%; specificity 52.4%) and AUC 0.952 to predict mortality (cut off 21.165; sensitivity 96.4%; specificity 78%); meanwhile ROC of NLR to predict organ dysfunction had AUC 0.829 (cut off 3.52; sensitivity 87.5%; specificity 66.7%). These two ROCs can be seen in **Figure 1** and **2**.

Receiver operating characteristic curve of PCT in the first day of admission had AUC 0.952 to predict mortality (cut off 21.165; sensitivity 96.4%; specificity 78%).

After cut-off points for PCT level and NLR were determined, ROC curves were made to evaluate sensitivity and specificity of PCT dan NLR simultaneously as organ dysfunction and mortality predictors. Cut-off points used was 3.425 for PCT level and was 3.52 for NLR. These ROCs can be seen in **Figure 3** and **4**. The ROC curve showed that PCT and NLR simultaneously could be used as organ dysfunction predictors (AUC 0.948) and mortality predictor (AUC 0.690).

Table 2. Quick sequential organ failure assessment (qSOFA)⁵

Variables	Age	Score	
		0	1
Respiratory rate	0 days-1 week	≤ 50	>50
	1 week-1 month	≤ 40	>40
	1 month-1 year	≤ 34	>34
	2 -5 years	≤ 22	>22
	6 -12 years	≤ 18	>18
	13 -17 years	≤ 14	>14
Altered mentation (AVPU or pediatric GCS)	0 days-18 years	A	V, P, U
	0 days-18 years	15	<15
Systolic blood pressure	0 days-1 week	≥ 59	<59
	1 week-1 month	≥ 79	<79
	1 month-1 year	≥ 75	<75
	2 -5 years	≥ 74	<74
	6-12 years	≥ 83	<83
	13-17 years	≥ 90	<90

AVPU = alert, verbal, pain, unresponsive; GCS=Glasgow Coma Scale; quick sequential organ failure assessment (qSOFA) consists of total amount scores for respiratory rate according to children's age, pediatric GCS, and also systolic blood pressure.

The ROC curve showed that PCT and NLR simultaneously could be used as organ dysfunction predictor (AUC 0.948) and mortality predictor (AUC 0.690). Cut-off point used for ROC curve analysis to predict mortality was 21.165 for PCT. The same cut-off points for NLR were used to predict organ dysfunction because in previous analysis showed no significant use of NLR to predict mortality. The usefulness of PCT,

NLR, and MPV, simultaneously as organ dysfunction and mortality predictors can be seen in **Figure 5** and **6**.

Discussion

In this study, PCT level showed a good performance as organ dysfunction and mortality predictors, both, used alone or combined with NLR and or MPV. Procalcitonin serum concentration elevates 1000 to 10,000 times in 4 to 12 hours after appropriate stimulus, and reaches its maximum level in 24 hours.⁷ Measurement of PCT serum level in the first 24 hours of admission considered as reflection of inflammatory process severity in sepsis that eventually can lead to organ dysfunction.

A study in year 2017 on pediatric patient with burn injury shows that PCT level has 100% of sensitivity (95%CI 67.6 to 100%); 15% of sensitivity (95%CI: 7.1 to 29.1%), positive predictive value (PPV) 19% (95%CI 10 to 33.3%), and negative predictive value (NPV) 100% (95%CI 61 to 100%) in predicting 30 days mortality.⁸ Another study in year 2014 shows a significant difference (P=0.0016) of PCT level of patient with organ dysfunction (PELOD ≥ 12) compared to non-organ dysfunction (AUC 0.675; P=0.035). Cut-off point of PCT level used in this study was 4.05 ng/mL.⁹

The ROC curve analysis showed that NLR can be considered as a good predictor of organ dysfunction but not for mortality. A previous study in year 2017 shows a positive correlation between NLR score

Table 3. Subjects' characteristic

Characteristics	N=69
Gender, n(%)	
Male	44 (63.8)
Female	25 (36.2)
Age, n (%)	
1 month – 1 years	32 (46.4)
>1 years – 5 years	24 (34.5)
>5 years – 18 years	13 (18.8)
Mean age (SD), years	2.8 (4.60)
Mean length of stay (SD), days	10.49 (5.03)
Mortality, n(%)	28 (40.6)
Organ dysfunction, n	
Day 1 (qSOFA ≥ 2)	62 (89.9)
Day 3 (qSOFA ≥ 2)	48 (69.6)
End of ICU care (qSOFA ≥ 2)	28 (40.6)
Mean PCT level (SD), ng/mL	
Day 1	34.24 (33.47)
Day 3	18.73 (26.57)
Mean NLR (SD)	
Day 1	8.31 (8.75)
Day 3	6.83 (7.91)
Mean MPV (SD), fl	
Day 1	10.46 (1.05)
Day 3	9.92 (1.10)

Table 4. Correlation test results between PCT level, NLR, and MPV, with qSOFA on third day of admission and with mortality

Independent variables	Dependent variables	R	P value
1 st day PCT	3 rd day qSOFA	0.639	0.000
1 st day NLR		0.407	0.001
1 st day MPV		- 0.125	0.356
1 st day PCT	Mortality	0.747	0.000
1 st day NLR		0.201	0.098
1 st day MPV		0.071	0.601
PCT + NLR	3 rd day qSOFA	0.696	0.000
PCT + MPV		0.688	0.000
NLR + MPV		0.453	0.002
PCT + NLR + MPV		0.744	0.000
PCT + NLR	Mortality	0.748	0.000
PCT + MPV		0.733	0.000
NLR + MPV		0.280	0.111
PCT + NLR + MPV		0.739	0.000

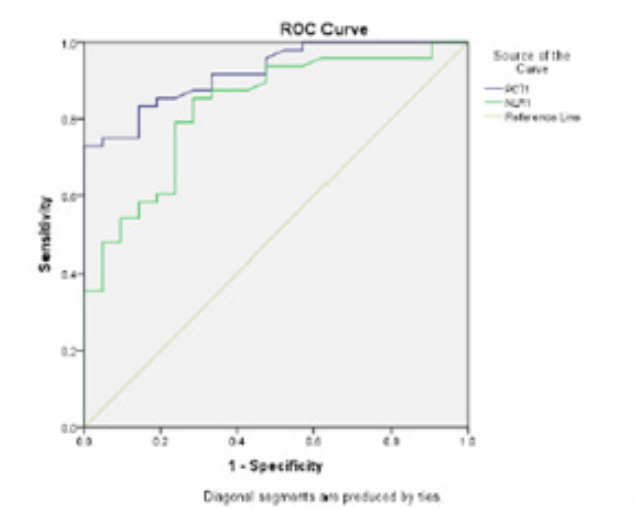


Figure 1. ROC curve of PCT (AUC 0.922; P=0.000) and NLR (AUC 0.829; P=0.000) as organ dysfunction predictors

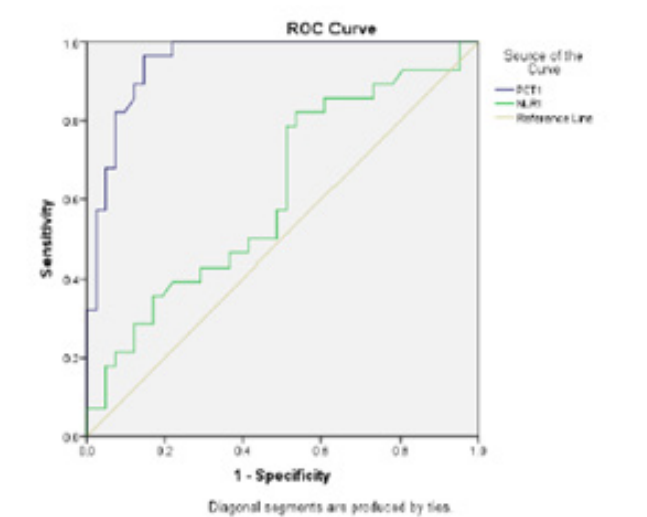


Figure 2. ROC curve of PCT (AUC 0.958; P=0.000) and NLR (not significant) as mortality predictors

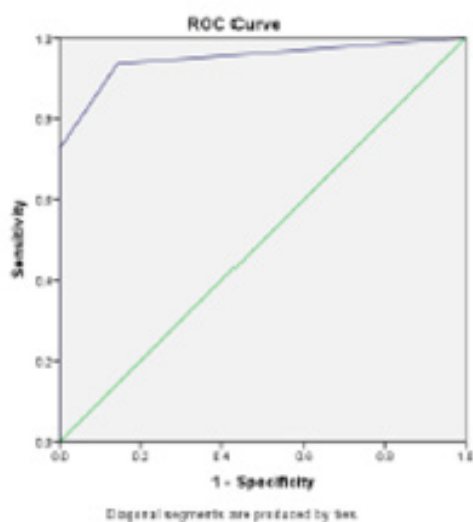


Figure 3. ROC curve of PCT level and NLR simultaneously as organ dysfunction predictor (AUC 0.948; P=0.000)

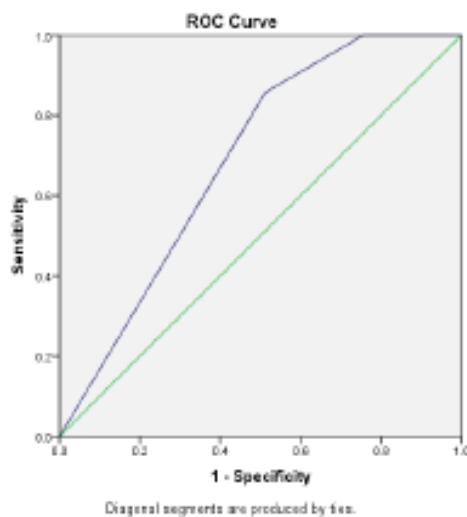


Figure 4. ROC curve of PCT and NLR simultaneously as mortality predictor (AUC 0.690; P=0.008)

and APACHE II score (P=0.036) in adult patients. Regarding its usefulness to predict mortality, a study reported higher NLR level in patients who did not survive (P=0.03). A contradictive result showed by another study that noted there was no correlation between NLR level and 28 days mortality in sepsis patients. All the study above used adult patients as the subjects.¹⁰⁻¹²

We recommend that NLR should not be used alone as organ dysfunction and or mortality predictor in pediatric sepsis considering elevated neutrophils and or lymphopenia can be caused by various conditions other than infection. What should be taken into consideration is that NLR had good sensitivity to predict organ dysfunction so this parameter can be used as a screening tools for patients

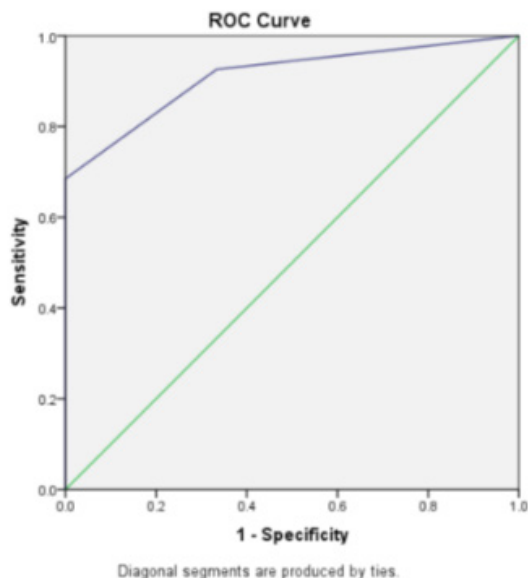


Figure 5. ROC curve of PCV, NLR, and MPV, as an organ dysfunction predictors (AUC 0.910; P=0.017)

that need further septic work up or organ dysfunction observation. Our study failed to show MPV usefulness in predicting organ dysfunction and mortality. The correlation coefficients (0.696 vs. 0.639) and AUCs (0.948 vs. 0.922) of this study shows that PCT level and NLR simultaneously can act as better predictors of organ dysfunction than PCT level alone. A good performance as organ dysfunction predictor also shown by all three parameters combined (PCT level, NLR, and MPV) (R 0.744; AUC 0.910). Vice versa, combination of PCT level and NLR (R 0,748 vs. 0,747; AUC 0,690 vs. 0,958) or of all three parameters altogether (R 0,748 vs. 0,747; AUC 0,690 vs. 0,958) did not show better performances as mortality predictors compared to PCT level alone.

One of limitation of this study was conducted by retrospective method so not all confounding factors that influence organ dysfunction and mortality can be controlled. One of the main confounding factors was sepsis management itself. We suggest to conduct a cohort study with appropriate sepsis management protocols be used to minimize confounding factors that may influence organ dysfunction and mortality of pediatric sepsis patients.

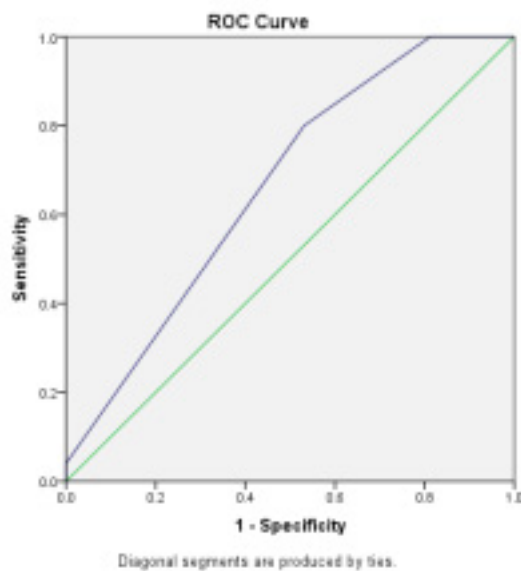


Figure 6. ROC curve of PCV, NLR, and MPV, as a mortality predictors (AUC 0.664; P=0.035)

Conflicts of interest

None declared.

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