Correlation of Bacterial Infection Markers with Organ Dysfunction Based on PELOD-2 Scores in Crtitically Ill Children

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Abstract

Background: Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score is the score for organ dysfunction that currently recommended in critically ill children. Laboratory markers that can describe the presence of organ dysfunction in bacterial infections, such as neutrophils, lymphocytes, neutrophil/lymphocyte ratio (NLR), platelet, red blood cell distribution width (RDW), C-Reactive Protein (CRP) and procalcitonin (PCT). **Objective:** to determine the relationship between neutrophil, lymphocyte, NLR, platelets, RDW, PCT, and CRP with organ dysfunction based on PELOD-2 scores in critically ill children. **Methods:** Analytical analysis with cross sectional approach in critically ill patients age ≥ 1 month to 18 years treated at the High Care Unit (HCU) and Pediatric Intensive Care Unit (PICU), Haji Adam Malik General Hospital, Medan, from November 2020 – February 2021. Assessment of PELOD-2 scores as well as neutrophil, lymphocyte, NLR, platelet, RDW, PCT, and CRP were conducted within 24 hours after patient was admitted. **Results:** A total of 52 subjects were analyzed. Neutrophil, lymphocyte, NLR, platelet and RDW values measured in the first 24 hours had no correlation to PELOD-2 scores in critically ill children. PCT and CRP values measured in the first 24 hours had a positive correlation to PELOD-2 scores in critically ill children ($r = 0.463$, $p = 0.001$ for PCT and $r = 0.320$, $p = 0.021$ for CRP). **Conclusion:** PCT and CRP values measured in the first 24 hours were correlate with organ dysfunction based on PELOD-2 scores in critically ill children.

Keyword: Bacterial Infection Markers;PELOD-2 Scores;Critcilly Ill Children

1. Introduction

Multi-organ dysfunction syndrome is generally found in the Pediatric Intensive Care Unit (PICU). The occurrence of multi-organ dysfunction syndrome will increase the mortality of critically ill pediatric patients.[1] The number of critically ill children varies in each hospital. Haji Adam Malik Central General Hospital (RSUP HAM) Medan is one of the central hospitals and referral hospitals in North Sumatra Province. RSUP HAM has a PICU room for the treatment of critically ill children. From 2018 to 2019, there were 352 critically ill children who were treated at the PICU of the HAM Hospital, Medan.[2]

Clinical assessment of the severity of illness is an important element in determining the prognosis and

referral services in PICU patients because it provides an objective assessment and includes a number of clinical data that will provide conclusions that affect the length, quality, and cost of care.[3] Scores have been developed to assess severity organ dysfunction in children, such as pediatric logistic organ dysfunction (PELOD)[3], pediatric risk of mortality (PRISM)[4], and pediatric index of mortality (PIM)[5], with the latest versions being PRISM III and PIM2.[5] The PELOD scoring system is a a good scoring system in estimating the severity of multi-organ dysfunction syndrome in the PICU. The PELOD score can describe the clinical course of the disease and predict the risk strata of death in critically ill children well.[5] Laboratory or organ physiologic markers are needed to describe the presence of organ dysfunction in bacterial infections.[6] In recent decades, measurement of bacterial infection markers/biomarkers such as C-Reactive Protein (CRP) and procalcitonin (PCT) have long been used in clinical practice because they are good markers of inflammation. Other markers of bacterial infection that can be used are neutrophils, lymphocytes, neutrophil/lymphocyte ratio, platelets, and red blood cell distribution width (RDW).[7,8]

2. Method

The design of this study is an analytic study with a cross sectional approach to determine the relationship between the values of neutrophils, lymphocytes, neutrophil/lymphocyte ratio, platelets, RDW, PCT, and CRP (as independent variables) and organ dysfunction based on PELOD-2 scores (as dependent variable). in critically ill children. Measurement of independent variables and dependent variables was carried out once, within 24 hours after being treated.

The study was conducted at the High Care Unit (HCU) and Pediatric Intensive Care Unit (PICU) Haji Adam Malik Hospital (Human Hospital) Medan. The time of the study is November 2020 – February 2021. The target population is all children over the age of 1 month – 18 years. The affordable population is the target population who are treated in the HCU and PICU rooms at the HAM Hospital in Medan, North Sumatra Province. The sample is an affordable population that meets the inclusion and exclusion criteria.

Data processing was carried out using a computerized system of statistical processing software, 95% confidence interval (CI) and a significance level of $P<0.05$. Univariate analysis was used to determine the distribution of sample characteristics. The test used in this study was the Spearman correlation test to assess the relationship between the values of neutrophils, lymphocytes, neutrophil/lymphocyte ratio, RDW, PCT, and CRP with organ dysfunction based on the PELOD-2 score in critically ill children.

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3. Result

In this study, there were 89 critically ill children. Of these, 8 children were excluded because they suffered from chronic kidney failure, 7 children were excluded because of suspicion of malignancy, 16 children were excluded because of post-surgery and 6 children were excluded because the measurement of variables was carried out over 24 hours. So that this study involved 52 critically ill children who were admitted and treated at the HCU and PICU of the HAM Hospital who had met the inclusion criteria, and an analysis was carried out.

The subjects of the children were male and female with the same number, namely 26 people (50%). The largest age group was children aged < 12 months totaling 18 people (34.6%), followed by children aged 60 - 143 months as many as 12 people (23.1%). The median weight and height of the subjects were 9.05 kg (minimum 2.8 kg and maximum 106 kg) and 78 cm (minimum 40 cm and maximum 170 cm). The median TDS and TDD were 90 mmHg (minimum 55 mmHg and maximum 117 mmHg) and 50 mmHg (minimum 30 mmHg and maximum 100 mmHg). The mean MAP was 63.25 mmHg (SD ± 13.95 mmHg). A total of 29 children (55.8%) were on a ventilator. From the results of pupillary examination, most of them showed reactive results, amounting to 41 children (78.8%).

The results of the oxygen fraction examination showed a median of 50% (minimum 28% and maximum 100%). The mean oxygen tension was 163.13 mmHg (SD ± 32.39 mmHg). The median carbon dioxide pressure was 30 mmHg (minimum 10 mmHg and maximum 76 mmHg). The median oxygen saturation is 100% (minimum 95% and maximum 100%). The complete characteristics of the research subjects are presented in table 1.

Table 1. Demographic Characteristics of Research Subjects

Demography Characteristic	Value
Gender, n(%)	
Male	26 (50)
Female	26 (50)
Age	
< 12 months	18 (34,6)
12 - 23 months	10 (19,2)
24 - 59 months	3 (5,8)
60 - 143 months	12 (23,1)
≥ 144 months	9 (17,3)
Weight, kg	9,05 (2,8-106)*
Height, cm	78 (400-170)*
Systolic BP, mmHg	90 (55-117)*
Diastolic BP, mmHg	50 (30-100)*
MAP, mmHg	63,25 (13,95)
FiO_2, %	50 (28-100)*
PO_2, mmHg	163,13 (32,39)
PCO_2, mmHg	30 (10-76)*
SpO_2,%	100 (95-100)*

Ventilator, n(%)	
Yes	29 (55,8)
No	23 (44,2)
Pupil, n(%)	
Reactive	41 (78,8)
Non-Reactive	11 (21,2)

The patient's mean hemoglobin was 10.22 g/dL (SD ± 2.69 g/dL). The mean leukocyte was 15.8 thousand cells/µl (SD ± 7.22 thousand cells/µl). Platelets with a mean of 312.18 thousand cells/µl (SD ± 163.05 thousand cells/µl). Neutrophils with a median of 77.4% (minimum 30.9% and maximum 93.5%). Lymphocytes with a median of 13.6% (minimum 3% and maximum 57.7%). For the neutrophil/lymphocyte ratio with a median of 5.57 (minimum 0.6 and maximum 31).
For lactate values with a median of 1.4 mmol/L (minimum 0.3 mmol/L and maximum 7 mmol/L). The median creatinine was 0.6 mg/dL (minimum 0.2 mg/dL and maximum 13.56 mg/dL). The median CRP was 1.4 mg/L (minimum 0.7 mg/L and maximum 2.8 mg/L). The median PCT was 4 ng/mL (minimum 0.04 ng/mL and maximum 100 ng/mL). The median RDW was 17.2% (minimum 12.3% and maximum 38.5%). For the PELOD-2 score with a mean of 6.33 (SD ± 4.48).

Table 2. Parameters of Bacterial Infection Markers and PELOD-2 Scores

Parameters	**Value**
Hemoglobin, gr/dL	10,22 (2,69)
Leukocytes, thousand cells/µl	15,8 (7,22)
Platelets, thousand cells/µl	312,18 (163,05)
Neutrophils, %	77,4 (30,9-93,5) *
Lymphocytes, %	13,6 (3-57,7) *
Neutrofil/Limfosit Ratio	5,57 (0,6-31) *
Lactate, mmol/L	1,4 (0,3-7) *
Creatinine, mg/dL	0,6 (0,2-13,56) *
CRP, mg/L	1,4 (0,7-2,8) *
PCT, ng/mL	4 (0,04-100) *
RDW, %	17,2 (12,3-38,5) *
PELOD-2 Scores	6,33 (4,48)

Differences in PELOD-2 scores by age group are presented in table 4.3. There were 31 patients in the <5 years age group, with a mean PELOD-2 score of 6.55 (SD ± 4.48). While the number of patients in the age group 5 years was 21 people, with the mean PELOD-2 score in this group was 6 (SD ± 5). There was no significant difference between the PELOD-2 scores and the differences in the age groups of the studied patients (p>0.05).

Table 3. PELOD-2 Scores Difference by Age Group

	Age < 5 years	**Age ≥ 5 years**	**p**
Number of patients	31	21	
Average PELOD-2 Score (SD ±)	6,55 (4,17)	6 (5)	0,670*

The correlation between several hematological parameters with PELOD-2 scores is shown in the table. 4.3. Using the Spearman correlation test, it appears that there was no significant correlation between neutrophils, lymphocytes, neutrophil/lymphocyte ratio, and RDW with a PELOD-2 score (p>0.05). However, for PCT and CRP showed a significant correlation (p<0.05). Pearson correlation test was used for platelets and no significant correlation was found between platelets and PELOD-2 score (p>0.05).
Based on the correlation value (r) obtained using the Spearman correlation test, PCT has a moderate level of correlation (r value = 0.4 - <0.6) with a positive direction meaning that an increase in PCT value will be followed by an increase in PELOD-2 score. Meanwhile, for CRP, the value of r = 0.320, which means that CRP has a weak correlation (r value = 0.2 - <0.4) with a PELOD-2 score in a positive direction, an increase in the CRP value will be followed by an increase in the PELOD-2 score. .

Table 4. Correlation of Neutrophils, lymphocytes, Neutrophil/Lymphocyte Ratio, Platelets, RDW, PCT and CRP to PELOD-2 Scores

	Skor PELOD 2	
	r (correlation)	**p**
Neutrophils	0,199	0,158[a]
Lymphocytes	-0,200	0,155[a]
Neutrophil/Lymphocyte ratio	0,222	0,133[a]
Platelets	-0,127	0,371[b]
RDW	-0,121	0,392[a]
PCT	0,463	0,001[a]
CRP	0,320	0,021[a]

The scatterplot graph of the correlation between PCT scores and PELOD-2 scores is shown in Figure 4.1. The PCT value for the X-axis (horizontal line) and the Y-axis PELOD-2 score (vertical line), it can be seen that the higher the PCT value, the higher the PELOD-2 score, as illustrated by the line representing the PCT value and the lower PELOD-2 score. to the right, the value increases.

Figure 1. Scatterplot Graph Correlation PCT and PELOD-2 Score

While the scatterplot graph of the correlation between the CRP value and the PELOD-2 score is shown in Figure 4.2. The CRP value for the X-axis (horizontal line) and the Y-axis PELOD-2 score (vertical line), it can be seen that the higher the CRP value, the higher the PELOD-2 score, as illustrated by the line representing the CRP value and the lower PELOD-2 score. to the right, the value increases.

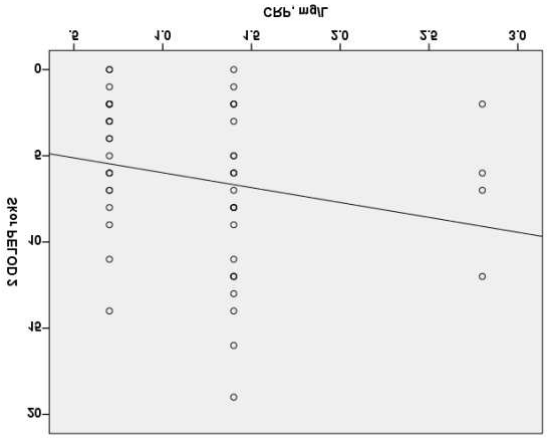
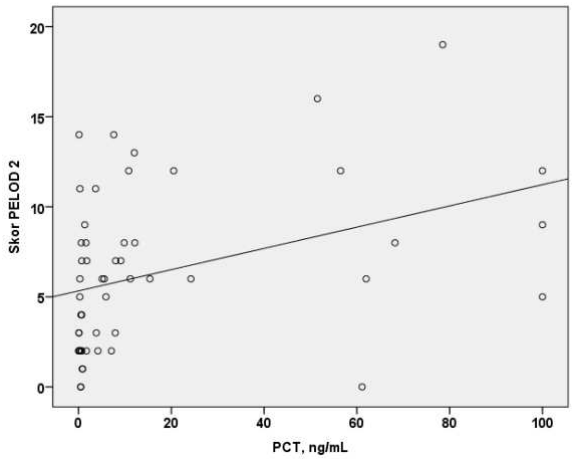


Figure 2. Scatterplot Graph Correlation CRP and PELOD-2 Score



4. Discussion

Critical illness is any disease process that causes physiological instability that can lead to disability or death within minutes or hours and requires intensive care, comprehensive observation, and special care.[9,10] After going through the assessment process according to the specified criteria, 52 critically ill children were found. The number of children subject to male and female is the same, namely 26 people (50%). According to Angele et al., the male gender is more likely to experience a critical condition than the female. This is because in men there is a significant increase in pro-inflammatory mediators, such as tumor necrotizing factor (TNF), IL-6, and IL-10, whereas in women they have more anti-inflammatory mediators. Gender affects the prognosis, where women have a better prognosis than men.[10] Another theory states that the male sex hormone (testosterone) has a suppressive effect on the immune system, while the female sex hormone (estrogen) has an immune-boosting effect on the immune system. immune system. However, this cannot be applied to infants who are beyond puberty, so further research is needed.[11]

Of the 52 critically ill patients, the largest age group was children aged <12 months. The study by Melda et al. with research subjects as many as 140 critically ill pediatric patients, also showed similar results where the age group 1 – 11 months (42 patients) was the largest age group.[12] The age group 1 – 11 months to 5 years had a risk of critical illness due to an immature immune system. perfect so that they are more susceptible to bacterial infections and cause high morbidity and mortality.[13,14]

Death in critically ill pediatric patients is closely related to multiple organ dysfunction syndrome. According to the systematic review of Tantalean et al. Showed that 97% of patients who died in the Pediatric Intensive Care Unit (PICU) had previously met the criteria for multi-organ dysfunction syndrome. Currently, a score system (score) has been developed that is used to estimate organ dysfunction in critically ill children, one of which is the Pediatric Logistic Organ Dysfunction (PELOD)-2 score.[15,16] The Indonesian Pediatric Association (IDAI) recommends the PELOD-2 score to assess organ dysfunction. in children. Thus, in this study the PELOD-2 score was used as a modality to assess organ dysfunction in critically ill children.[17]

Of the 52 critically ill children analyzed in this study, a mean PELOD-2 score was found to be 6.33 (SD ± 4.48) and there was no significant difference in the mean PELOD-2 score between patients in the <5 years age group (mean score PELOD-2 6.55 [SD ± 4.48]) compared to the age group 5 years (mean PELOD-2 score 6 [SD ± 5]), with a p-value of 0.67. In this study, it was found that the lowest PELOD-2 score was 0 and the highest was 19. In this study, this result is not too different from the research of Natasukma et al at Moewardi Hospital Surakarta in 2019, with a mean PELOD-2 score of 6.62 (SD ± 0 ,84).[18] Another study by Dewi et al in 2016 at Hasan Sadikin Hospital Bandung found the mean PELOD-2 score in critically ill children was 5.9.[19] Research by Dauhan et al. at the PICU of the HAM Hospital in Medan in 2019, the lowest PELOD-2 score was 1 and the highest was 21, which was carried out in the first 24 hours after the patient was admitted.[20] Where the results of this study can describe the PELOD-2 score in critically ill children in Indonesia.

The mean PELOD-2 score in this study is smaller than the cut-off value of previous studies and still reflects the presence of organ dysfunction in critically ill pediatric patients studied. This is because the patient has been given therapy at the first hospital when the patient was treated before being referred to the Medan HAM Hospital, so there has been an improvement in the parameters that can be measured through the PELOD-2 score. The value of the PELOD-2 score if measured when the patient first came to the hospital, is likely to be even greater. Research by Suari et al. at RSUPN dr. Cipto Mangunkusumo Jakarta found that patients with dysfunction in one organ had a mean PELOD-2 score of 3.25 (SD ± 1.25), with a mean mortality of 0.7% (SD ± 0.4%). The mean PELOD-2 score for dysfunction in the two organs was 6.5 (SD ± 2.46), with a mean mortality of 5% (SD ± 7.4%). Dysfunction in three organs had a mean PELOD-2

score of 9.78 (SD ± 4.81) with a mean mortality of 21.9% (SD ± 33.03%). Dysfunction in four organs the mean PELOD-2 score was 11.5 (SD ± 3.55) with a mean mortality of 30.2% (SD ± 30.28%). Meanwhile, dysfunction in five organs had a mean PELOD-2 score of 14.36 (SD ± 38.28) with a mean mortality of 51.2% (SD ± 32.7%).[21] In this study, the researcher did not analyze the value of PELOD-2 cut-off score and mortality in critically ill pediatric patients.

Neutrophils and lymphocytes are components of white blood cells. Neutrophils are the body's first defense mechanism if there are damaged body tissues or foreign objects enter the body. Neutrophils are closely related to the activation of antibodies and the complement system which will increase the ability of cells to carry out phagocytosis and decompose particles. Lymphocytes undergo differentiation and proliferation to become B cells that mediate humoral immunity or antibody-mediated immunity and T cells that mediate cellular immunity.[22]

This study is the first study to discuss the correlation between neutrophils and lymphocytes on the PELOD-2 score. In this study, there was no significant correlation between neutrophils and lymphocytes on the PELOD-2 score through the Spearman test (r value = 0.199; p value = 0.158 for neutrophils and r = -0.2; p = 0.155 for lymphocytes). inversely proportional to the PELOD-2 score, that is, if the lymphocyte value decreases, the PELOD-2 score will be higher. Until now, there has been no study that discusses the relationship between the value of neutrophils and lymphocytes on the PELOD-2 score. In this study, neutrophil values increased from normal (median 77.4%) and lymphocyte values decreased from normal (median 13.6%) in critically ill pediatric patients suspected of having bacterial infection. This is in accordance with the study by Dai et al. who stated that an increase in the neutrophil value indicated an acute bacterial infection process and the study of Hotchkiss et al. which indicates the presence of low lymphocyte values in bacterial infections.[23,24]

The neutrophil/lymphocyte ratio (NLR) is a laboratory parameter that has the potential to be a predictor of bloodstream infection/bacteremia in patients with suspected infection.[25] In this study, the neutrophil/lymphocyte ratio did not show a significant relationship (r = 0.222; p = 0.133) with a median of 5.57, which is an increase from the normal value. This is in accordance with the study by Dursun et al. who stated that the neutrophil/lymphocyte ratio was increased in children with sepsis compared to children without sepsis. The cut-off value of the neutrophil/lymphocyte ratio was 1.97 with a sensitivity of 75.6% and a specificity of 38.4%.[26] In the study by Dewi et al. at RSUPN dr. Cipto Mangunkusumo (RSCM) Jakarta in 2021 through the Spearman correlation test, it was found that the neutrophil/lymphocyte ratio had a relationship but was not significant (r = 0.021; p = 0.857) with the PELOD-2 score. The cut-off value of the neutrophil/lymphocyte ratio is >3.5 with a sensitivity of 14.3% and a specificity of 79.4%.[27]

Platelets are blood components that are formed in the bone marrow and have a life span of about 7-10 days. Thrombocytopenia is often found in patients with sepsis.[28] The mechanism of thrombocytopenia is due to megakaryocyte hypoplasia, decreased platelet production, increased platelet destruction due to splenomegaly and reticuloendothelial cells, disseminated intravascular coagulation and direct activation of platelets by endotoxins and proinflammatory cytokines.[29] Through the Pearson test, platelets show a high value. the correlation is not significant and inversely proportional to the PELOD-2 score (r = -0.127; p = 0.392) where if the platelet value decreases, the PELOD-2 score will also be higher. There is still no research on the relationship between platelets and PELOD-2 scores. However, there was a study by Puspitasari et al., which described the relationship of the mean platelet volume (MPV) to the PELOD-2 score. MPV can describe the overall platelet size. The study obtained significant results in increasing the MPV value in line with changes in the PELOD-2 score (r = 0.51; p = <0.001). The measurement results at 72 hours showed the MPV value above the normal value with a higher level of correlation (r = 0.703; p = <0.001). Changes in MPV values (ΔMPV) were also tested in this study to be associated with changes in the PELOD-2 score, the results were also significant (r = 0.668; p = <0.001).[30]

Red Cell Distribution Width (RDW) is a hematological parameter that indicates heterogeneity in size or volume of peripheral erythrocytes.[31] In this study, the correlation between RDW and PELOD-2 scores showed insignificant and inversely proportional results (r = -0.121; p = 0.392) with a median of 17.2%. Unlike adults, research on RDW in children is limited and the results are inconclusive. Research by Devina et al. get a median of 14.8% with a range of 11.2 – 27.8%. Mortality rates in normal and elevated RDW were 40% and 45%, respectively.[8] Another study by Warouw et al. showed a significant relationship between an increase in RDW and the incidence of neonatal sepsis with a p value = 0.048 and a median of 17.8% (range 16.0 – 19.8%).[32]

In sepsis, the acute systemic inflammatory response can also affect erythropoiesis and erythrocyte maturation. The increase in RDW describes the degree of inflammation and oxidative stress that occurs. Inflammation that occurs can increase hormones in the body such as adrenaline, noradrenaline, angiotensin. Inflammatory factors can affect bone marrow hematopoietic and iron metabolism in the body. An increase in RDW also indicates cytomembrane instability which can lead to multi-organ dysfunction which can worsen the prognosis and increase the risk of death.[33]

To detect the presence of bacterial infection, procalcitonin (PCT) and C-Reactive Protein (CRP) can be used. In this study, it was found that PCT and CRP showed a significant association with PELOD-2 scores. From the Spearman test, for PCT the value of r = 0.463 (p = 0.001), which indicates a moderate level of correlation, with a median of 4 ng/mL (range 0.04 – 100 ng/mL) to the PELOD-2 score. Meanwhile, for CRP through the Spearman test, the value of r = 0.320 (p = 0.021), which indicates a weak correlation level, with a median of 1.4 mg/L (range 0.7 – 2.8 mg/L) against the PELOD-2 score. The higher the PCT and CRP scores, the higher the PELOD-2 score.

Based on a study by Dewi et al. at RSUPN dr. Cipto Mangunkusumo Jakarta using the Spearman correlation test, for PCT the value of r = 0.206 (p = 0.076) which means that PCT has a weak but significant correlation level (r value = 0.2 - <0.4) to the PELOD-2 score with positive direction, where an increase in the PCT value will be followed by an increase in the PELOD-2 score. The PCT cut-off value was found to be >0.7 ng/mL with a sensitivity of 100% and a specificity of 35.3%. Meanwhile, for CRP, the value of r = 0.134 (p = 0.250), where CRP has a very weak and insignificant correlation level (r value = 0 – 0.2) to the PELOD-2 score where the cut-off is >3.5 mg/dL with a sensitivity of 85.7% and a specificity of 17.6%.[27]

PCT semi-quantitative examination is very practical and can be used bed-side. A significant increase in PCT occurs in bacteremic conditions where systemic inflammatory reactions are caused by bacterial endotoxins, exotoxins, and several types of cytokines.[33] PCT values are also increased in patients with fungemia.[34]

In conditions of chronic inflammation and autoimmune diseases, viral infections, and local infections, PCT levels <0.5 ng/mL, whereas in SIRS and multiple trauma, PCT levels are 0.5–2 ng/mL and PCT levels >2 ng/ml. (most often 10 – 100) ng/mL is a predictor of severe infection, sepsis, and multiple organ failure.[35] According to Hoeber et al. with a PCT cut-off value of 0.5 ng/mL, PCT had an accuracy of bacteremia with an area under the curve of 0.79 with a sensitivity and specificity of 76% and 69%, respectively.[36] In the study by Runtunuwu et al., PCT sensitivity was obtained. 80% and PCT specificity 11.54%, but no cut-off value was obtained because the specimen was taken only once.[37] Another study by O'Connor et al. found that in early infection with sepsis, PCT gave a sensitivity of 83%–100% and specificity 70%–100% and in late infection sepsis lasting 3–30 days, PCT gave a sensitivity and specificity of 100% in the identification of bacterial sepsis.[38]

CRP is an inflammatory cytokine that is one of the markers in pediatric sepsis. CRP levels increased significantly in cases of invasive bacterial infection and decreased with improvement in inflammatory conditions.[39] According to Lanziotti et al., the diagnostic accuracy of CRP for bacterial infections in children who were not hospitalized had a sensitivity and specificity of 77% and 79, respectively. %. If

periodic measurements are made, the predictive value is increased and is useful in management.[40] A study by Lai et al., showed that an increase in CRP <10 mg/L over 24 hours can rule out a diagnosis of infection and/or suspicion of sepsis.[41] Another study by Lubis et al. obtained a median CRP of 2.8 mg/dL (0.5 – 22.4) in sepsis patients who died and a cut-off of 2.05 mg/dL.[42]

When compared with CRP and other markers of sepsis, circulating PCT levels are considered superior because they are not affected by the administration of anti-inflammatory therapies, such as glucocorticoids.29 CRP can be affected by the use of systemic corticosteroids. Compared with PCT, CRP levels were not affected by renal dysfunction or dialysis.[36,41,43]

Research by Lubis et al. conducted at the HAM Hospital in Medan discussed CRP, PCT, PELOD-2 scores, and their combination as predictors of mortality in sepsis and showed that CRP alone could not be an independent predictor of mortality. PCT has a high accuracy in predicting mortality in children with sepsis where the area under the curve is 0.95 when compared to CRP with an area under the curve 0.8. PCT has a higher prognostic value for bacterial infection and mortality than other SIRS markers such as temperature, tachycardia, tachypnea, and elevated leukocytes.[42] A similar study by Luzzani et al. who compared PCT and CRP as markers of sepsis also stated that PCT was a better marker for sepsis than CRP. This is evidenced by the value of the area under the PCT curve of 0.925 when compared to the CRP which is only 0.677.[44]

Research by Dewi et al. which discusses the correlation between PCT and CRP on the PELOD-2 score at Hasan Sadikin Hospital Bandung showed significant results on the 3rd day of examination in cases of septic shock. On day 3, the PCT variable on the PELOD-2 score was found to be p = <0.001 and the CRP to the PELOD-2 score was p = 0.018. However, this study did not include the value of r.[19] This is in accordance with this study which also showed significant results between PCT and CRP on the PELOD-2 score.

5. Conclusion

The value of neutrophils, lymphocytes, neutrophil/lymphocyte ratio, platelets and RDW measured in the first 24 hours had no correlation with PELOD-2 scores in critically ill children. The PCT and CRP values measured in the first 24 hours had a positive correlation with the PELOD-2 score in critically ill children, namely the increase in PCT and CRP scores was in line with the increase in the PELOD-2 score.

PCT and CRP values can be an alternative examination to estimate the occurrence of organ dysfunction in critically ill children.

Further research by measuring markers of bacterial infection periodically / serially (such as measuring within 24 hours, then continuing measurements at 48 hours and 72 hours after the patient is admitted), analyzing the results of the gold standard examination for bacterial infection, namely specimen culture, linking mortality in critically ill pediatric patients, examination of other biomarkers (such as ferritin) against the PELOD-2 score or other scoring system, and a larger sample size should be performed.

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References

1. Tantaleán JA, León RJ, Santos AA, Sánchez E. Multiple organ dysfunction syndrome in children. Pediatr Crit Care Med. 2003; 4(2):181-5.

2. Adilla NR, Lubis AD. Hubungan Prokalsitonin dan Rasio Neutrofil Limfosit dengan Angka Mortalitas Pasien Pneumonia Anak di PICU RSUP Haji Adam Malik Medan Tahun 2018-2019. Fakultas Kedokteran Universitas Sumatera Utara. 2021.
3. Leteurtre S, Duhamel A, Grandbastien B, Proulx F, Cotting J, Gottesman R, et al. Daily estimation of the severity of multiple organ dysfunction syndrome in critically ill children. Cmaj. 2010; 182(11):1181-7.
4. Pollack MM, Patel KM, Ruttimann UE. PRISM III: an updated Pediatric Risk of Mortality score. Crit Care Med. 1996; 24(5):743-52.
5. Lacroix J, Cotting J. Severity of illness and organ dysfunction scoring in children. Pediatr Crit Care Med. 2005; 6(3): S126-S134.
6. Aird WC. The hematologic system as a marker of organ dysfunction in sepsis. Elsevier. 2003; 78(7):869-88.
7. Zadeh MT, Nia SR, Shahmoradi S, Sanatkar S, Eftekhari SS. Diagnostic Value of Hematologic and Inflammatory Profile in Asjunction to Blood Culture in Patients Suspected to Septicemia. Int J Pediatr. 2018; 6(49): pp. 6903-10.
8. Devina T, Lubis M, Mutiara E, Yanni GN, Saragih RAC, Trisnawati Y, et al. Red cell distribution width and mortality in pediatric sepsis. Paediatr Indones. 2016; 56(6): pp.320-4.
9. Frost P, Wise MP. Recognition and early management of the critically ill ward patient. Br J Hosp Med (Lond). 2007;68(10):M180-3.
10. Angele MK, Pratschke S, Hubbard WJ, Chaudry IH. Gender differences in sepsis: cardiovascular and immunological aspects. Virulence. 2014; 5: 12-9.
11. Taneja V. Sex Hormones Determine Immune Response. Front Immunol. 2018; 1931(9): pp. 1-5.
12. Melda M, Triasih R, Nurnaningsih. Modifying the PELOD-2 score to predict mortality in critically ill patients. Paediatrica Indonesiana. 2021; 61(2): 61-8.
13. Wynn J, Cornell TT, Wong HR, Wheeler DS. The Host Response to Sepsis and Developmental Impact. Pediatrics. 2010;125:1031-41.
14. Simon AK, Hollander GA, McMichael A. Evolution of the immune system in humans from infancy to old age. Proc Biol Sci. 2015; 282:1-9.
15. Gulla KM, Sachdev A. Illness severity and organ dysfunction scoring in pediatric intensive care unit. Indian J. Crit. Care Med. 2016; 20(1):27.
16. Leteurtre S, Martinot A, Duhamel A, Proulx F, Grandbastein B, Cotting J, et al. Validation of the pediatric logistic organ dysfunction (PELOD) score: prospective, observational, multicentre study. Lancet 2003;362:192-7.
17. Wulandari A, Martuti S, Pudjiastuti. Perkembangan Diagnosis Sepsis pada Anak. Sari Pediatri. 2017; 19(4): 237-44.
18. Natasukma LY, Pudjiastuti, Martuti S. Peran Delta Neutrophil Index sebagai Prediktor Sepsis pada Anak. Sari Pediatri. 2019; 21(2): pp. 115-20.
19. Dewi R, Somasetia DH, Risan NA. Procalcitonin, C-reactive protein and its correlation with severity based on pediatric logistic organ dysfunction-2 (PELOD-2) score in pediatric sepsis. American Journal of Epidemiology and Infectious Disease. 2016; 4(3): 64-7.
20. Dauhan AC, Lubis AD, Mutiara E, Lubis M. Correlation of Troponin Level (Troponin T, Troponin I) with PELOD-2 Score in Sepsis as a Predictive Factor of Mortality. Maced J Med Sci. 2019; 7(23): 4072-7.
21. Suari NMR, Latief A, Pudjiadi AH. New PELOD-2 cut-off score for predicting death in children with sepsis. Paediatrica Indonesiana. 2021;61(1):pp. 39-45.
22. Thomas N, Sreejith V. August. A Review on White Blood Cells Segmentation. IOP Publishing. 2018; 396(1): 012-038.
23. Dai J, Jiang W, Min Z, Yang J, Tan Y, Ma T, et al. Neutrophil CD64 as a diagnostic marker for neonatal sepsis: Meta-analysis. Adv Clin Exp Med. 2017; 26(2): 327-32.
24. Hotchkiss RS, Moldawer LL, Opal SM, Reinhart K, Turnbull IR, Vincent JL. Sepsis and septic shock. Nat. Rev. Dis. Primers. 2016; 2: p.16045.
25. Saputra IMY, Gustawan W, Utama MGD, Arhana BNP. Rasio neutrofil dan limfosit (nlcr) sebagai faktor risiko terjadinya infeksi bakteri di ruang rawat anak RSUP Sanglah Denpasar. Sari Pediatri. 2019; 20(6): 354-9.
26. Dursun A, Ozsoylu S, Akyildiz BA. Neutropil-to-lymphocite ratio and mead platelet volume can be useful markers to predict sepsis in children. Pak J Med Sci. 2018; 34(4): pp.918-22.
27. Dewi R, Imanillah R. Hubungan antara nilai leukosit, rasio jumlah neutrofil-limfosit (NLR), C-reactive protein (CRP) dan prokalsitonin dengan skor pediatric logistic organ dysfunction (PELOD-2) sebagai prediktor derajat keparahan penyakit pada anak sakit kritis. J Indon Med Assoc. 2021; 71(1): 30-5.
28. Kara S, Emeksiz Z, Alioğlu B, Dallar Bilge Y. Effects of neonatal sepsis on thrombocyte tests. J Matern Fetal Neonatal Med. 2016; 29(9): pp.1406-8.
29. Wilar R, Antolis Y, Tatura SNN, Gunawan S. Jumlah trombosit dan mean platelet volume sebagai faktor prognosis pada sepsis neonatorum. Sari Pediatri. 2010; 12(1): 53-7.
30. Puspitasari R. Korelasi mean platelet volume dengan skor PELOD-2 sebagai faktor prognostik sepsis pada anak. Fakultas Kedokteran Universitas Sumatera Utara. 2018.
31. Hakiem F, Yuniati T, Susanah S. Hubungan antara nilai C-reactive protein, immature to total neutrophil ratio, dan red distribution width dengan kejadian sepsis neonatorum bayi premature. Sari Pediatri. 2019; 21(4):218-25.
32. Warouw R, Susanah S, Yuniati T. Hubungan antara red cell distribution width dan kejadian sepsis neonatorum bayi prematur. Sari Pediatri. 2020; 22(2): 104-8.
33. Sukewanti NM, Artana IWD, Kardana IM, Sukmawati M, Putra PJ. Red cell distribution width (RDW) sebagai prediktor mortalitas pada sepsis neonatorum. Medicina. 2019; 50(3): 522-6.
34. McMaster P, Park DY, Shann F, Cochrane A, Morris K, Gray J, et al. Procalcitonin versus C-reactive protein and immature-to-total neutrophil ratio as markers of infection after cardiopulmonary bypass in children. Pediatr Crit Care Med. 2009; 10(2): pp.217-21.

35. Iskandar HR, Pudjiadi A, Mulyo D, Pratiwi A, Suryatin Y. Sensitifitas dan spesifisitas pemeriksaan procalcitonin, C-reactive protein (CRP), dan hitung leukosit untuk memprediksi infeksi bakterial pada sindrom syok dengue di pediatric intensive care unit. Sari Pediatri. 2010; 12(4): 99-102.
36. Hoeboer SH, van der Geest PJ, Nieboer D, Groeneveld AJ. The diagnostic accuracy of procalcitonin for bacteraemia: a systematic review and meta-analysis. Clin Microbiol Infect. 2015; 21(5) pp.474-481.
37. Runtunuwu AL., Manoppo JIC, Rampengan TH, Rampengan NH, Kosim S. Efektivitas pemeriksaan prokalsitonin sebagai petanda dini sepsis pada anak. Sari Pediatri. 2008; 9(5): 319-22.
38. O'Connor E, Venkatesh B, Lipman J. Procalcitonin in critical illness. Crit Care and Resusc 2001; 3:236-43.
39. Yang Y, Xie J, Guo F, Longhini F, Gao Z, Huang Y, et al. Combination of C-reactive protein, procalcitonin and sepsis-related organ failure score for the diagnosis of sepsis in critical patients. Ann. Intensive Care. 2016; 6(1): p.51.
40. Lanziotti VS, Póvoa P, Soares M, Silva JRL, Barbosa AP, Salluh JIF. Use of biomarkers in pediatric sepsis: literature review. Rev Bras Ter Intensiva. 2016; 28(4): pp.472-82.
41. Lai MY, Tsai MH, Lee CW, Chiang MC, Lien R, Fu RH, et al. Characteristics of neonates with culture-proven bloodstream infection who have low levels of C-reactive protein (≦ 10 mg/L). BMC Infect. Dis. 2015; 15(1): 320.
42. Lubis M, Lubis AD, Nasution BB. The usefulness of C-reactive protein, procalcitonin, and PELOD-2 score as a predictive factor of mortality in sepsis. The Indonesian Biomedical Journal. 2020; 12(2): 102-8.
43. Bal ZŞ, Özdemir NK, Şen S, Karapınar DY, Azarsız E, Aydemir Ş, et al. Diagnostic accuracy of interleukin-6, interleukin-8, and interleukin-10 for predicting bacteremia in children with febrile neutropenia. Turk. J. Hematol. 2017; 34(3): 254.
44. Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A. Comparison of procalcitonin and C-reactive protein as markers of sepsis. Crit Care Med. 2003 Jun;31(6):1737-41