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Original Article

Validation of PELOD-2 score as a predictor of life-threatening organ dysfunction in pediatric sepsis

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Abstract

Background *The Third International Consensus Definitions for Sepsis and Septic Shock* (Sepsis-3) defined sepsis as life-threatening organ dysfunction due to immune dysregulation against infection. It recommends the *Sequential (sepsis-related) Organ Failure Assessment* (SOFA) score to evaluate life-threatening organ dysfunction. But the SOFA tool has not been adjusted for pediatric patients. The *Indonesian Pediatrics Society* (IPS) uses the same sepsis definition and recommends using the PELOD-2 score as an indicator of life-threatening organ dysfunction in children.

Objective To evaluate the validity of the PELOD-2 score for predicting life-threatening organ dysfunction in pediatric sepsis.

Methods A prospective cohort study was conducted in children with sepsis who were admitted to the PICU. Subjects were taken consecutively with inclusion criteria of 1 month-18 years of age, with organ dysfunction, having two or more symptoms of systemic inflammatory response syndrome (SIRS), and suspected or proven infection. PELOD-2 score, with and without lactate result, of each subject were plotted to receiver operating characteristic (ROC) curve, then we determined the most optimal cut off point to predict the life-threathneing organ dysfunction in pediatric sepsis based on the sensitivity and specificity of each score.

Results Sixty-six patients were analyzed, with 40 males and 26 females aged 2 to 183 months (median 11 months). Twenty patients died while in the PICU. A PELOD-2 score (with lactate) cut-off ≥ 7 was determined by (ROC) curve, with sensitivity of 80% and specificity of 78%. The area under the curve (AUC) of PELOD-2 score (with lactate) was 84.8% (95%CI 74.7 to 95.9%). A PELOD-2 score (without lactate) ≥ 7 was the most optimum cut off based on its Youden index, it had 70% of sensitivity and 80% of specificity.

Conclusion PELOD-2 score ≥ 7 , with or without lactate component is the optimal cut-off for predicting life-threatening organ dysfunction in pediatric sepsis. **[Paediatr Indones. 2020;60:227-32 ; DOI: 10.14238/pi60.4.2020.227-32]**.

Keywords: *PELOD-2 score, pediatric sepsis*

Sepsis is a leading cause of mortality and morbidity in infants and children. There is no gold standard for the diagnosis of sepsis, so the experts continue to refine the definition of sepsis.[1] *The First International Consensus of Sepsis* (Sepsis-1) defined sepsis as a systemic inflammatory response syndrome (SIRS) caused by suspected or proven infection. Severe sepsis was defined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension.[2] This definition was later refined in 2001, with the acknowledgement of the predisposition, infection, response, and organ dysfunction (PIRO) system. Since then, several assessment systems have been developed to determine the severity of organ dysfunction.[3] Neither Sepsis-1 nor Sepsis-2 put forward specific parameters for children, so in 2005 a *Pediatric Sepsis Consensus Congress* (PSCC) was held to standardize the definition of sepsis in children by considering physiology and age-specific vital signs.[4]

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In 2016, the latest international consensus on sepsis (Sepsis-3) was issued; it defined sepsis as life-threatening organ dysfunction caused by immune dysregulation against infection. The consensus recommended that the sequential (sepsis-related) organ failure assessment (SOFA) score be used to evaluate life-threatening organ dysfunction.1 However, the SOFA score can only be applied to adults, due to the absence of special parameters for pediatric patients. Several studies have been conducted to adapt this score for children.[5] In the same year, the *Indonesian Pediatrics Society* (IPS) also issued a consensus statement on the diagnosis and management of pediatric sepsis. It refers to the definition of Sepsis-3, however, IPS recommended a different scoring system to assess organ dysfunction, the *Pediatric Logistic Organ Dysfunction-2* (PELOD-2) score. A PELOD-2 cut-off point of ≥ 11 was set as the criterion for predicting life-threatening organ dysfunction.[6]

A study at Cipto Mangunkusumo Hospital found that PELOD-2 score ≥ 10 was a predictor for life-threatening organ dysfunction for sepsis patients,[7] in contrast to a multicenter study in Europe who reported PELOD-2 score ≥ 8 as a cut-off point.[8] Differing cut-off points may have been due to differences in patient characteristics, facilities, and staff capability at each center. The aim of this study was to assess the validity of PELOD-2 scoring for predicting life-threatening organ dysfunction in children with sepsis.

Methods

This prospective cohort study was done in the Pediatric Intensive Care Unit, Mohammad Hoesin Hospital, Palembang, South Sumatera, from March to September 2019. All patients aged 1 month to 18 years who had organ dysfunction and two of the SIRS criteria, as well as infection according to the 2005 PSCC criteria[4] were included. Exclusion criteria were patients who died within the first 4 hours of PICU admission, or had multiple congenital anomalies, HIV infection, or neutropenia due to a medical condition other than SIRS.

A minimum required sample size of 62 patients would provide 80% power with a 95% level of significance. Six additional patients were included to allow for an estimated 10% drop out rate (patients transferred to other PICUs).

Subjects underwent physical and laboratory examinations. The PELOD-2 scores were calculated under supervision of a pediatric intensivist consultant. All subjects were followed until PICU treatment was completed. The outcomes were categorized as death in PICU or improvement (transferred to the ward).

Statistical analysis was performed using *SPSS software version 22.0*. Analysis by ROC curve was done to determine the optimal cut-off point of PELOD-2 score, both with and without lactate, for predicting life treathning organ dysfunction in pediatric sepsis. Regarding that not every health facilities were able to carry out lactate examination, we also aimed to revalidate the previously recommended cut-off point from the IPS consensus, which were score ≥11 for PELOD-2 with lactate and score ≥7 if lactate examination was excluded.

The Ethics Committee of Universitas Sriwijaya Medical School, Palembang, Indonesia approved this study. Informed consent was obtained from all parents.

Results

Of 70 patients who fulfilled the inclusion criteria, 66 enrolled in this study. Two children were excluded because of dengue shock syndrome (DSS) diagnosis, and two had incomplete data. Characteristics of subjects are reported in **Table 1**. The median age was 11 months (range 2-183) months, and 61% of subjects were male. Respiratory dysfunction occurred in 73% of subjects and the most common underlying infectious disease was pneumonia (41%).

The PICU mortality rate was 30%. **Table 2** shows the mortality distribution based PELOD-2 components. Glasgow coma scale (GCS), mean arterial pressure (MAP), lactate, and serum creatinine level had significant differences between the outcome groups.

The discrimination of PELOD-2 score was evaluated by calculating the AUC, by the result was 84.8% (95% CI: 74.7% to 95.9%). It means a moderate level of discrimination. An optimal cut-off point was determined by ROC analysis. This study found that PELOD-2 score (with lactate) ≥ 7 has

Table 1. Subjects' characteristics

Characteristics	Outcomes	
	Died in PICU (n=20)	Improved (n=46)
Age group, n		
1-11 months	11	22
12-23 months	1	7
24-59 months	1	9
60-143 months	3	4
≥144 months	4	4
Gender, n		
Male	13	27
Female	7	19
Nutritional status weight for height, n		
Severely wasted	5	6
Mild to moderately wasted	4	13
Normal	10	24
Overweight	1	3
GCS, n		
<11	14	19
≥11	6	27
Mean arterial pressure (MAP), n		
Hypotensive	13	9
Non-hypotensive	7	37
Pulse, n		
Normal	6	37
Tachycardic	12	9
Bradycardic	2	0
Temperature, n (%)		
< 36°C	0	1
36-37.9°C	12	23
> 37.9°C	8	22
Organ dysfunction*		
Cardiovascular	12	15
Respiratory	19	29
Neurologic	16	21
Hematologic	3	3
Renal	9	2
Hepatic	8	1
Underlying infection		
Pneumonia	10	17
Intracranial infection	4	15
Intraabdominal infection	1	5
Acute diarrhea with severe	1	4
dehydration	0	3
Surgical site infection	4	2
Others		
PICU length of stay, n		
< 48 hours	10	12
≥ 48 hours	10	34

*Subjects could suffer from more than one organ dysfunction

80% of sensitivity and 78% of specificity in predicting life threatening organ dysfunction (**Figure 1**). The AUC of the PELOD-2 score (without the lactate component) was 83.3% (95%CI 72.9 to 93.8) and a cut-off value ≥ 6 had 75% sensitivity and 72% specificity (**Figure 2**).

We observed that IPS's recommended cut-off point as a predictor of life-threatening organ dysfunction in children with sepsis (score ≥11, with lactate component) had 50% sensitivity and 98% specificity, with 91% positive predictive value (PPV) and 82% negative predictive value (NPV). A PELOD-2 score cut-off point ≥ 7 without lactate had 70% sensitivity and 80% specificity, with 61% PPV and 86% NPV.

Discussion

The median age of study subjects was 11 (range 2-183) months, with most subjects (50%) in the 1-11 month age group. Children in this age group have a higher risk of sepsis due to their immature immune system.[9] The majority of subjects (61%) were male. A previous study hypothesized that male sex hormones suppress the immune system, while female hormones actually trigger it. However, this explanation would not apply to infants far from puberty, so further investigation is needed.[10]

Pneumonia was the most common (41%) underlying infection found in this study. Endothelial damage in sepsis is caused by attachment and migration of pro-inflammatory cytokines to vasculature. This process must be preceded by an interaction between activated PMNs and endothelium. In certain organs, such as the lung, adhesion and migration through the endothelium can occur independently. Hence, the most common organ dysfunction in sepsis patients related to the respiratory system.[11]

The PELOD-2 scores were analyzed by ROC curve. The AUC was 84.8% (95%CI 74.7 to 95.9%), indicating a moderate level of discrimination in PELOD-2 score for predicting life-threatening organ dysfunction in pediatric sepsis. The IPS set a PELOD-2 score ≥ 11 for diagnosis and management of pediatric life-threatening organ dysfunction.5 We found that PELOD-2 score ≥ 11 had sensitivity of 50% and a specificity of 98%.

Mortality rates due to sepsis remain high. Late initiation of therapy because of late detection of sepsis leads to rapid deterioration, and eventual septic shock. To detect sepsis early, sensitive diagnostic criteria are

Table 2. Mortality distribution in association with each component of PELOD-2 score

PELOD-2 score criteria	Outcomes		Total	P value
	Died in PICU (n=20)	Improved (n=46)		
Neurologic				
GCS				0.032
<11	14	19	33	
≥11	6	27	33	
Pupillary reaction				0.133
Both reactive	17	44	61	
Both fixed	3	2	5	
Cardiovascular				
Lactatemia, mmol/L	16	45	61	0.012
<11	4	1	5	
≥11				
MAP				0.001
Hypotensive	13	9	22	
Non-hypotensive	7	37	44	
Renal				
Creatinine				0.000
Increased	9	2	11	
Normal	11	44	55	
Respiratory				
PaO2/FiO2				0.117
≥61	16	43	59	
≤60	4	3	7	
PaCO2, mmHg				0.198
≤58	15	40	55	
>58	5	6	11	
Invasive ventilation				0.064
Yes	17	29	46	
No	3	17	20	
Hematologic				
White blood count, x10^9/L				0.712
>2	19	46	65	
≤2	0	1	1	
Platelet count, x10^9/L				0.269
≥142	15	39	54	
< 142	5	7	12	

needed to avoid underdiagnoses.[12] The optimal cut-off point from our study was ≥ 7, with 80% sensitivity and 78% specificity. This cut-off point is more appropriate for predicting life-threatening organ dysfunction in pediatric sepsis than a value ≥ 11, which had only 50% sensitivity, based on our findings.

The positive predictive value of PELOD-2 score (with lactate) ≥11 was 91%, indicating that more than 90% of patients who had a score of ≥ 11 were expected to die. The PELOD-2 score ≥ 7 (without lactate) was able to predict mortality in 62% of sepsis patients, and predict no event of death by 90%, thus, using this cut-off to diagnose sepsis will increase early detection and provide better opportunities to prevent death.

A retrospective study at 9 PICUs in Europe reported an AUC of 91%, which had a high accuracy to assess the ability of the PELOD-2 score in discriminating outcomes of patients with infection. They found that the PELOD-2 score with lactate ≥ 8 had 85% sensitivity and a 88.4% specificity; a score ≥ 11 in subjects with hypotension and hyperlactatemia had a 97.83% sensitivity and 69.6%specificity.[8] The main difference in our study was the operational definition of infection: they established infection based on the clinical decision of the physician, while we used the PSCC (2005) sepsis criteria.[4] Median age, sex, and most organ dysfunction types were similar to those in our study.

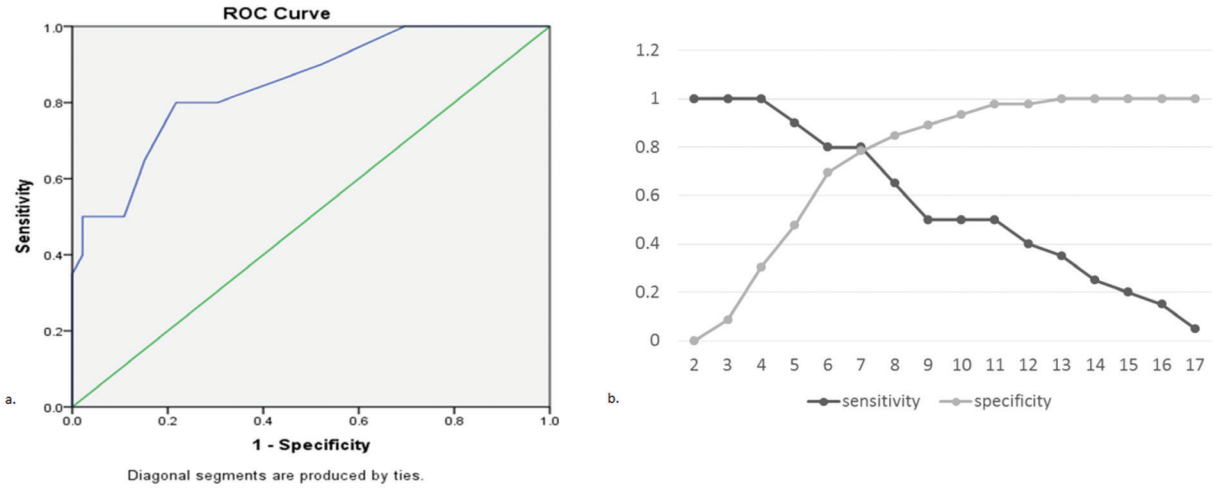

Figure 1. a) ROC curve for PELOD-2 score with lactate, b) cut-off point diagram

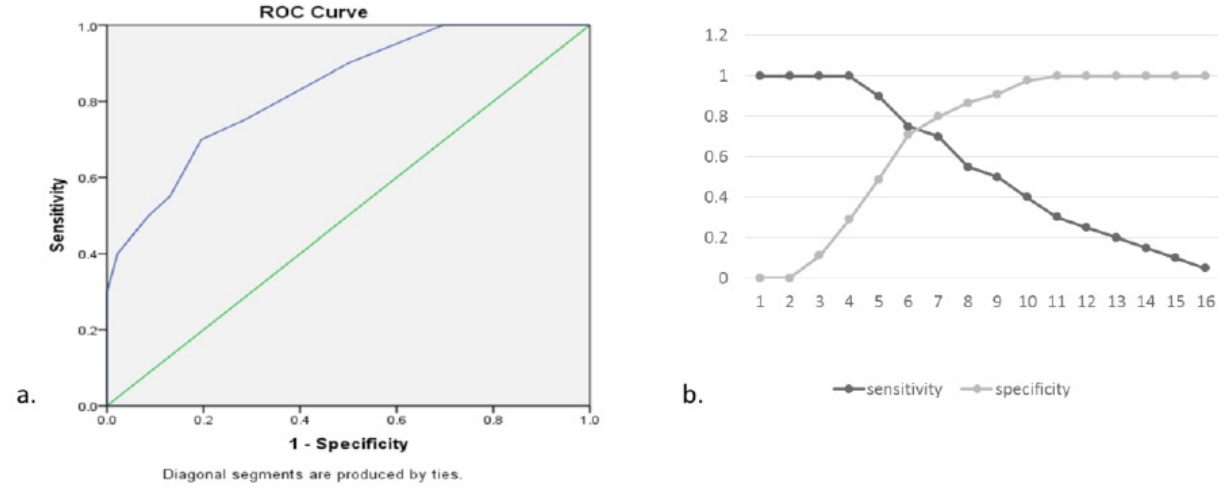

Figure 2. a) ROC curve for PELOD-2 score without lactate, b) cut-off point diagram

Suari[7] assessed the validity of PELOD-2 scores for predicting life-threatening organ dysfunction in pediatric sepsis patients at Cipto Mangunkusumo Hospital and noted an AUC of 85.5%, which was similar to ours. This study found the optimal cut-off point was ≥ 10, with 74% sensitivity and 76% specificity.[7] Subjects' characteristics of age, sex, and major organ dysfunction were similar to ours. However, the difference in cut-off points (≥10 *vs.* ≥7) may have been due to differences in sample size and the operational definition of infection used in subject selection. Supporting facilities and infrastructure as well as human resource capabilities can also affect patient outcomes, so the criteria used should be based on individual facilities.

Laboratory examinations such as lactate may not be available in areas with limited facilities, therefore, IPS also established the PELOD-2 cut-off score ≥7 without lactate.[5] The PELOD-2 score without lactate ≥7 had sensitivity of 70% and specificity of 80%. The ROC curve analysis revealed that PELOD-2 cut-off point ≥6 without lactate had sensitivity of 75% and specificity of 72%. Analysis with ROC assesses the optimal cut-off value based on a balance between sensitivity and specificity. The PELOD-2 cut-off values of ≥6 and ≥7 yielded similar results. Another method to determine the best cut-off value is the Youden index. A Youden index close to 1 or higher

is interpreted as optimal.[12] The Youden index for PELOD-2 score ≥ 7 was 0.504, while that for ≥ 6 was 0.467, indicating that the cut-off score ≥ 7 (without lactate) is more optimal to be used for predicting life-threatening organ dysfunction in pediatric sepsis.

We included only patients with sepsis at PICU admission, while patients who got sepsis during PICU treatment were not studied, so our results might not be applicable to overall sepsis in the PICU. We also validated for PELOD-2 score without the lactate component, for the purpose of use in hospitals with limited facilities, not for a center like our hospital. Differences in facilities and staff capability may also affect patient outcomes.

In conclusion, PELOD-2 score ≥ 7, with or without the lactate component, is the optimal cut-off point to predict life-threatening organ dysfunction in pediatric sepsis. Multicenter revalidation is needed to determine the most optimal cut-off point for general use in Indonesia.

Conflict of Interest

None declared.

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