

New PELOD-2 cut-off score for predicting death in children with sepsis

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Abstract

Background According to the most recent *Sepsis-3 Consensus*, the definition of sepsis is life-threatening organ dysfunction caused by dysregulated immune system against infection. Currently, one of the most commonly used prognostic scoring system is pediatric logistic organ damage-2 (PELOD-2) score.

Objective To determine and validate the pediatric logistic organ dysfunction-2 (PELOD-2) cut-off score to predict mortality in pediatric sepsis patients.

Methods A prospective cohort study was conducted in the intensive care units of Cipto Mangunkusumo Hospital, Jakarta. We assessed subjects with PELOD-2 and calculated the predicted death rate (PDR) using SFAR software. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate calibration and the area under the curve (AUC) of the receiver operating characteristic curve (ROC) to estimate discrimination.

Results Of 2,735 children admitted to the emergency department, 52 met the inclusion criteria. Patients had various types of organ dysfunction: 53.8% respiratory, 28.8% neurological, 15.4% cardiovascular, 1.9% hematological. The mortality rate in this study was 38.5%. Mean PELOD-2 score was higher in patients who died than in those who survived [13.9 (SD 4.564) vs. 7.59 (SD 3.025), respectively, $P=0.000$]. The discrimination of PELOD-2 score with the lactate component had an AUC of 85.5% (95%CI 74.5 to 96.5), while PELOD-2 without lactate had an AUC of 85.4% (95%CI 74.5 to 96.3%). We propose a new PELOD-2 cut-off score to predict organ dysfunction and death of 10, with 75% sensitivity, 72% specificity, 62.5% PPV, and 82% NPV. PELOD-2 score > 10 had a moderate, statistically significant correlation to mortality ($r=0.599$; $P<0.001$).

Conclusion A PELOD-2 score > 10 is valid for predicting life-threatening organ dysfunction in pediatric patients with sepsis. [Paediatr Indones. 2021;61:39-45 ; DOI: 10.14238/pi61.1.2021.39-45].

Keywords: PELOD-2 score; diagnostic test; sepsis; pediatric

For the last four decades, there has been a significant increase in the incidence of sepsis in the developed, as well as developing countries. An epidemiological study showed that the prevalence of severe sepsis was 0.56 cases per 1,000 population per year, with mortality rate of 10.3%.¹ In the pediatric intensive care unit (PICU) at Cipto Mangunkusumo Hospital, 19.3% (97/502) of patients suffered from sepsis, with an alarming mortality rate of 54%.²

Most patients hospitalized in ICUs experience organ dysfunction, which increases mortality rates.³⁻⁵ The lowest mortality rate was in patients with no organ dysfunction (9%). The rate progressively increased as dysfunction affected more organs: 26% in patients with dysfunction in 2 organs; 62% in those with dysfunction in 3 organs; and 88% in those with dysfunction in 4 or more organs ($P<0.0001$).⁶

In 1992, the *American College of Chest Physicians/Society of Critical Care Medicine* (ACCP/SSCM)

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Consensus defined sepsis in the general population as systemic inflammatory response syndrome (SIRS) associated with infection. But, in practice, SIRS can be seen with a wide variety of insults. In addition to infectious insults, non-infectious causes such as ischemia, multiple trauma, shock, or immune-mediated organ injury can manifest as SIRS.⁷ The *Surviving Sepsis Campaign* (SSC) 2001 concluded that using SIRS to define sepsis (two out of four criteria) was too sensitive (96.9% sensitivity) and not specific enough (58.3% specificity), thus increasing the risk of antibiotic resistance due to irrational antibiotic use.⁸ In 2005, Goldstein *et al.*⁹ renewed the use of SIRS criteria for the pediatric population according to age-specific vital signs and laboratory data, thus redefining sepsis as SIRS in the presence of suspected or proven infection. The main problem with the old sepsis definition was that SIRS criteria do not necessarily indicate a dysregulated, life-threatening response, whereas sepsis is a dysregulated systemic host response caused by infection, inducing organ dysfunction. The *Third International Consensus for Sepsis* (Sepsis-3) suggested the latest sepsis definition to be life-threatening organ dysfunction caused by a dysregulated immune system against infection.¹⁰

There are many scoring systems to assess organ dysfunction, such as SIRS, *Sepsis Related Organ Failure Assessment* (SOFA), *Logistic Organ Dysfunction Score* (LODS), and quick SOFA (qSOFA). In adults, organ dysfunction represented by SOFA or qSOFA scores includes parameters that cannot be used in the pediatric population. The LODS scoring system had high sensitivity and specificity, with AUC of 0.75 (95%CI 0.73 to 0.76).¹¹ The LODS was adjusted for the pediatric population and is called the *Pediatric Logistic Organ Dysfunction* (PELOD) score. The PELOD was designed to determine organ dysfunction in children, with physiologic parameters including cardiorespiratory, neurologic, hepatic, renal, and hematological organ dysfunction, which was developed in 1999 and was updated into PELOD-2 score in 2013. The PELOD score was quantitative, however its value is discontinuous, hence it is difficult to analyze statistically.¹² Schlappbach LJ showed that discrimination of outcomes did not differ much between SOFA and PELOD-2 (AUC 0.829 vs. 0.816, respectively).¹³

Validation of PELOD-2 is lacking in developing

countries, as pediatric patient characteristics differ between developed and developing countries. Most pediatric sepsis in developing countries has been associated with poor nutritional status that worsens infection, leading to poor prognosis. Hence, patient characteristics may influence PELOD-2 score cut-off points for predicting mortality. Therefore, we aimed to determine and validate a new PELOD-2 cut-off score to predict mortality in pediatric sepsis in Indonesia, a developing country with different characteristics from developed countries.

Methods

This prospective cohort study was conducted in the intensive care units at Cipto Mangunkusumo Hospital (PICU/ICU/HCU/Burn Unit/ED), Jakarta, from January to April 2017. All critically ill children aged 1 month to 18 years with organ dysfunction were included in the study by consecutive sampling. Exclusion criteria were: (1) patients with no improvement in vital signs after continuous cardiopulmonary resuscitation; (2) patients who died within 4 hours after admission; (3) patients with multiple congenital anomalies; (4) patients with prior organ failure including nutritional or immune disorders, comorbidities (asplenia, chronic disease, transplantation, or malignancy), or history of therapy (steroid, antibiotic, or invasive procedure) that was not accompanied by acute infection; and (5) patients transferred out to another hospital.

Nutritional status was assessed using subject's body weight (BW) and body height (BH) measured upon hospital admission. We used *World Health Organization* (WHO) growth chart for children < 5-years-old,¹⁴ otherwise the *Centers for Disease Control* (CDC). Nutritional status was then defined using BW/BH as proposed by Waterlow.¹⁶

The dependent variable was the outcome of children with sepsis. Independent variables were the PELOD-2 score components, including central nervous system (consciousness and pupillary reflex), cardiovascular system (mean lactate level and arterial blood pressure), renal system (creatinine level), respiratory system (PO₂ to FiO₂ ratio, pCO₂ level, and use of mechanical ventilation), and hematological system (leukocyte and platelet counts).

Data were processed and analyzed with SPSS 20.0

software. Initial PELOD-2 score and predicted death rate were calculated with SFAR software.¹⁷ PELOD-2 score and mortality rate were analyzed by Spearman's rank correlation test. This study was approved by the Ethics Committee for Health Research, University of Indonesia, Faculty of Medicine.

Results

A total of 2,735 children were admitted to the ED of Cipto Mangunkusumo Hospital between January and April 2017. Of these, 90 children were critically ill. We excluded 9 patients because of death within 4 hours of admission, 17 children transferred out of Cipto Mangunkusumo Hospital, and 8 children due to history of trauma. Out of 56 patients, 4 patients had incomplete laboratory results for PELOD-2 score calculation. Thus, 52 children were included in the final analysis.

The characteristics of subjects are shown in **Table 1**. The majority of critically ill children were male (63.5%), aged 1-11 months (44.2%), and underweight (76.9%). In addition, 53.8% of subjects suffered respiratory dysfunction, followed by neurologic (28.8%), cardiovascular (15.4%), hematologic (1.9%) dysfunction. Most subjects had septic shock (75%) and were in intensive care for less than 14 days (69.2%). The mortality rate in this study was 38.5%.

Subjects who survived had mean PELOD-2 score of 7.59 (SD 3.025), while those who died had mean score of 13.9 (SD 4.564). The relationship between organ dysfunction, PELOD-2 score, and subjects' outcome is shown in **Table 2**. The sepsis consensus released by the Indonesian Pediatric Society uses two PELOD-2 cut-off scores: 11 in type A hospitals, and 7 in type B and C hospitals. In Indonesia, referrals

Table 1. Characteristics of subjects

Characteristics	(N=52)
Gender, n (%)	
Male	33 (63.5)
Female	19 (37.5)
Age, n (%)	
1-11 months	23 (44.2)
12-23 months	6 (11.5)
24-59 months	9 (17.3)
60-143 months	7 (13.5)
>144 months	7 (13.5)
Nutritional status, n (%)	
Underweight	40 (76.9)
Normoweight	6 (11.5)
Overweight	4 (7.7)
Obese I	1 (1.9)
Obese II	1 (1.9)
Axillary temperature, n (%)	
36.5°C	2 (3.8)
36.6-37.4°C	9 (17.4)
37.5-38.4°C	18 (34.6)
38.5°C	23 (44.2)
Organ dysfunction, n (%)	
Neurological/CNS	15 (28.8)
Respiratory	28 (53.8)
Cardiovascular	8 (15.4)
Renal	0 (0)
Hematological	1 (1.9)
Sepsis, n (%)	
Shock	39 (75)
Mean predicted death rate (SD), %	25.1 (31.04)
Outcomes, n (%)	
Length of stay < 14 days	36 (69.2)
Mortality	20 (38.5)

to hospitals are based on hospital classification. This study was conducted in a type A hospital, thus, the standard cut-off was considered to be 11. The number of patients who died according to the PELOD-2 score cut-off of > 11 was 14/52 (27.0%).

The PELOD-2 cut-off value was taken from the intersection between sensitivity and specificity

Table 2. Organ dysfunction, PELOD-2 score, and predicted death rate

Organ dysfunction	Number of patients	Mean PELOD-2 score (SD)	Mean PDR (SD), %
1	4	3.25 (1.25)	0.7 (0.4)
2	12	6.5 (2.46)	5.0 (7.4)
3	9	9.78 (4.81)	21.9 (33.03)
4	16	11.5 (3.55)	30.2 (30.28)
5	11	14.36 (38.28)	51.2 (32.7)

PDR=predicted death rate

by tracing the AUC value and determining the coordinates from the ROC curve. The AUC value of the PELOD-2 score was 85.5% (95%CI 74.5 to 96.5) to predict mortality. The intersection in the PELOD-2 score coordinate was > 10, with sensitivity and specificity of 75% and 72%, respectively. We also analyzed the PELOD-2 score without the lactate component by ROC curve, resulting in AUC of 85.4% (95%CI 74.5 to 96.3). **Figure 1** shows that comparison of PELOD-2 score ROC curves with and without lactate measurement resulted in a difference of 0.1% (P<0.05).

Table 3 shows a comparison of the number of subjects who survived and died with PELOD-2 score of 10 as the cut-off, with and without the lactate test. The optimal cut-off coordinate of the PELOD-2 score without lactate was 10, with 75% sensitivity and 75%

specificity. **Table 4** shows that the sensitivity and specificity of PELOD-2 score, with and without the lactate test were similar, with good positive predictive value (PPV) and similar positive likelihood ratio (PLR).

Spearman's test was used to analyze for correlations, as the PELOD-2 scores with and without lactate test were numerical and abnormally distributed by Kolmogorov-Smirnov test (P<0.05). The correlation value (r) of mortality and PELOD-2 score with lactate test was r=0.599 (P<0.001), while that of the PELOD-2 score without lactate was r=0.598 (P<0.001).

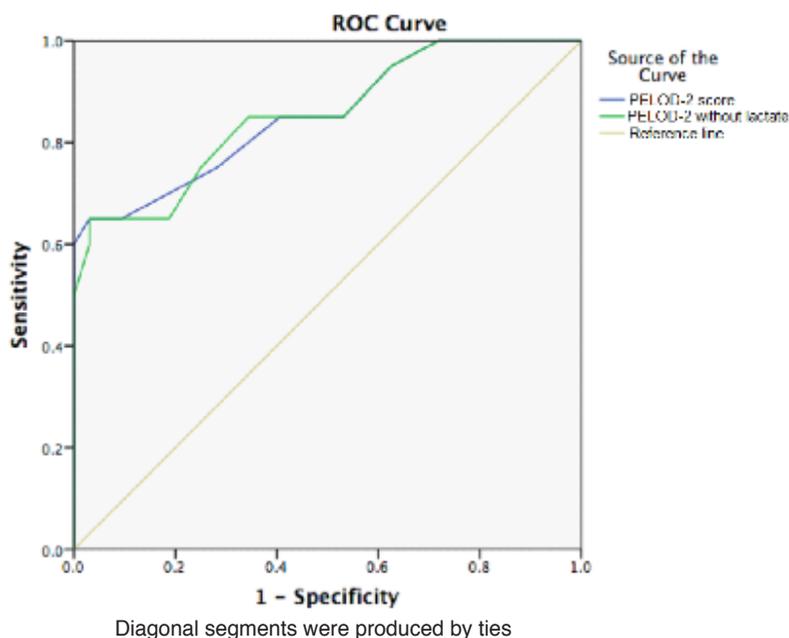


Figure 1. Comparison of PELOD-2 score ROC curves with and without the lactate component

Table 3. PELOD-2 score and mortality (2x2)

Variables		Outcome		Total
		Died	Survived	
PELOD-2 score with lactate	> 10	15	9	24
	< 10	5	23	28
PELOD-2 score without lactate	> 10	15	8	23
	< 10	5	24	29

Table 4. Comparison of PELOD-2 score cut-offs

Variables	Sn (%)	Sp (%)	PPV (%)	NPV (%)	Acc (%)	PLR (%)	NLR (%)
> 11 (IPS)	81.3	70	81.3	70	76.9	2.7	0.27
> 7 (IPS)	37.5	95	92	48	56.9	7.5	0.66
>10 (with lactate)	75	72	62.5	82	73	2.7	0.35
> 10 (without lactate)	75	75	65	83	73	2.5	0.23

Sn=sensitivity; Sp=specificity; PPV=positive predictive value; NPV=negative predictive value; Acc=accuracy; PLR=positive likelihood ratio; NLR=negative likelihood; IPS=Indonesian Pediatric Society

Discussion

Previous PICU studies in France, South America, and England revealed that male patients had higher mortality rates (57.1-59%) compared to females.^{12,18,19} Similarly, the majority of septic children were male (63.5%) in our study. Gender may affect mortality rate and severity of disease, due to differences in immune responses. Male subjects often had more severe disease due to a significant increase in pro-inflammatory mediators, including TNF, IL-6, and IL-10, while female subjects had more anti-inflammatory mediators. Thus, prognosis was generally better for females than for males.²⁰

In our study, the majority of subjects were in the 1-11 months age group. Other studies noted that more than half of subjects were in a similar age range. Children less than 5 years of age have immature immune systems, thus, they are more susceptible to severe infections and even sepsis.^{9,21} More than half of our subjects were undernourished. This condition can affect the body's systemic functions, especially immune response, atrophy, or increased permeability of the gastrointestinal epithelium which facilitates bacterial translocation and infection. In addition to hypermetabolic conditions and increased catabolism in sepsis, children with malnutrition are more likely to suffer from organ dysfunction.²² The more severely malnourished the child, the more susceptible that child is to infections.

Five organ systems are assessed in the PELOD-2: neurological, respiratory, cardiovascular, renal, and hematological. During the study period, the most common organ dysfunction in our subjects was respiratory. Similar results were found in several PICU studies, in which 46.6% experienced respiratory dysfunction.²³ Furthermore, the WHO stated that the four major causes of death in children worldwide

include pneumonia. Pneumonia is known to be one of the primary causes of sepsis, which was consistent with the majority of subjects having respiratory dysfunction. Septic shock was predominant, since our facility is a national referral hospital which handles more severe cases of sepsis.

We used PELOD-2 scores to calculate a PDR. Subjects with severe illness have high PDR values, meaning the more severe the disease, the higher the likelihood of death in the near term. The mean PDR in our study was 25.1% (SD 31.04), while the overall mortality rate was 38.5%. Other studies reported much lower mortality rates of 4.7-6.1%.^{12,17} This condition might be related to the fact that Cipto Mangunkusumo Hospital, Jakarta, is a national referral hospital.

The mean PELOD-2 score in subjects who survived was approximately half that of those who died. A previous study reported that higher PELOD-2 scores are indicative of more organ dysfunction and higher mortality rate.¹ Another study reported that a mean PELOD score of 9.78 (SD 4.81) indicated 3 dysfunctional organ systems and 21.9% mortality (SD 33.03).¹²

Further analysis was carried out to determine the optimal PELOD-2 cut-off score, by looking at sensitivity, specificity, PPV, NPV, accuracy, PLR, and NLR values. The PELOD-2 cut-off score (without lactate) of 7 had 95% specificity and 37.5% sensitivity. Specificity values close to 100 mean that the score was good for detecting organ dysfunction, but not for screening, as the sensitivity was quite low. A PLR value of 7.5 means that it has moderately good diagnostic ability.

In our study, the optimal PELOD-2 cut-off score was determined by ROC coordinates. The PELOD-2 score AUC without lactate test was 85.4%, while the PELOD-2 score AUC with lactate test was 85.5%.

Our AUC values were slightly lower than 2 previous studies.^{12,24} The optimal PELOD-2 cut-off score in our analysis, with or without lactate, was 10. A PELOD-2 score >10 had PPV of 62.5 and 65% and NPV of 82 and 83%, with and without lactate, respectively. The PLR were 2.7 for PELOD-2 >10 and 2.5 for PELOD-2 without lactate, which translates to low clinical importance (PLR < 10).

The discrimination value obtained from the AUC was 0.84/0.85, which means the PELOD-2 score of >10 had good discrimination. The calibration value was analyzed by Hosmer and Lemeshow test, revealing the significance probability of 0.728 (>0.05), meaning PELOD-2 score was valid for predicting life-threatening organ dysfunction in pediatric patients with sepsis. The significant influence test on PELOD-2 score was good with P value <0.05, and the prediction accuracy was 69.2%.

There is a considerable difference in the optimal PELOD-2 cut-off scores recommended by Indonesian Pediatric Society, depending on the presence of supporting facilities in the hospital, especially lactate test. We analyzed if the results differed with or without lactate test for our study. The AUC difference of 0.1% between PELOD-2 score of >10 with or without lactate test indicated no significant difference in predicting life-threatening organ dysfunction in children with sepsis.

We noted that 84.6% of subjects had lactate levels <5 mmol/L, had no relationship to mortality (P=0.12). Similarly, a study in Colorado noted that lactate had 20% sensitivity (95%CI 8.9 to 39.1%) and 92.3% specificity (95%CI 90.7 to 93.7%). They concluded that lactate test was not effective for screening and should only be used to identify the level of patient risk of death.²⁵

A limitation of our study was that it was done in a single center, thus, it may not be representative of sepsis outcomes in all Indonesian children. In conclusion, the diagnostic value of PELOD-2 score >10 has good discrimination and is valid for predicting life-threatening organ dysfunction and mortality in children with sepsis. The new optimal PELOD-2 cut-off value of > 10 shows similar results in predicting mortality outcome, with or without the lactate test.

Conflict of Interest

None declared.

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