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Original Article

# The clinical and biomarker approach to predict sepsis mortality in pediatric patients

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## *Abstract*

***Background*** Sepsis is a leading cause of pediatric morbidity and mortality. The prevalence of sepsis mortality in Indonesia varies between 22.5 to 52%.

***Objective*** To identify the clinical criteria for predicting sepsis mortality and evaluate the performance of the PELOD-2 score.

***Methods*** This retrospective cohort study included pediatric patients admitted to the emergency department or pediatric intensive care unit (PICU) of Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from January 2015 to May 2020. Demographic characteristics (age and sex), clinical manifestations [nutritional status, presence of shock, need for intubation, source of infection, inotrope use, mean arterial pressure, pulse rate, respiratory rate, and *Glasgow Coma Scale* (GCS) score], laboratory [leukocyte, platelet, neutrophil, and lymphocyte counts, neutrophil-to-lymphocyte count ratio (NLCR), procalcitonin, C-reactive protein (CRP), and lactate profile], PELOD-2 score, and mortality data were recorded as outcomes.

***Results*** We analyzed data from 241 sepsis subjects. The overall mortality rate was 65%. Shock [OR 3.2; 95%CI 1.80 to -5.55; P<0.001)], GCS <9 [OR 2.4; 95%CI 1.30 to 4.23; P=0.005)], inotrope use [OR 3.1; 95%CI 1.74 to 5.5; P<0.001)], CRP >33.5 mg/L [OR 2.5; 95%CI 1.14 to 5.35; P=0.02)], and lactate level >2.85 [OR 2.1 (95%CI 1.02 to 4.56, P=0.04)] were considered significant predictors of mortality. A PELOD-2 cut-off score of >8 had optimal sensitivity (81.2%) and specificity (72.9%) to predict mortality, with an OR of 11.6 (95%CI 5.72 to 23.5; P<0.001).

***Conclusion*** Shock, GCS score, inotrope use, CRP, and lactate level can serve as clinical biomarkers to predict mortality in pediatric sepsis. A PELOD-2 score of >8 can predict mortality with reasonably good sensitivity and specificity. **[Paediatr Indones. 2023;63:37-44; DOI: 10.14238/pi63.1.2022.37-44** ].

***Keywords:*** *mortality; pediatric sepsis; PELOD-2 score; clinical predictor*

Sepsis is a leading cause of morbidity and mortality for children worthwhile and a major post of healthcare utilization. Globally, an estimated 22 cases of childhood sepsis per 100,000 person-years and 2,202 cases of neonatal sepsis per 100,000 live births translate into 1.2 million cases of childhood sepsis per year.[1] The prevalence of severe sepsis has reportedly increased in recent years[2-4] due to reasons such as increase in comorbidities,[5,6] increase in multidrug-resistant organisms and opportunistic infections,[7,8] as well as better sepsis surveillance and diagnostics.[7,9,10]

Mortality in children with sepsis ranges from 4% to as high as 50%, depending on illness severity, risk factors, and geographic location.[4,11-13] Early identification and appropriate resuscitation and management are critical to optimizing outcomes for children with sepsis.[14] In 2005, the *International Pediatric Sepsis Consensus Conference* published definitions and

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criteria for sepsis, severe sepsis, and septic shock in children based on prevailing views of adult sepsis at the time, with physiology-based modifications for age and maturation.[15] In 2016, new adult definitions and criteria were published (*Sepsis-3*), with "sepsis" defined as life-threatening organ dysfunction caused by a dysregulated host response to infection and "septic shock" defined as the subset of sepsis with circulatory and cellular/metabolic dysfunction associated with a higher risk of mortality.[16] Early identification, appropriate resuscitation, and critical care management are needed to optimize outcomes for children with sepsis. In 2020, the *Surviving Sepsis Campaign* (SSC) developed evidence-based guidelines and recommendations for children separate from adult recommendations. The recommendations consist of screening, diagnosis, and systematic management of pediatric sepsis.[14]

Many sepsis studies have been conducted in Indonesia, but with small numbers of subjects. Sepsis mortality in Indonesia has been reported to be between 22.5% and 52%.[17-19] The mortality rate of pediatric sepsis in the Pediatric Intensive Care Unit (PICU) at Dr. Cipto Mangunkusumo Hospital, Jakarta, in 2009 was 19.3%.20 In 2014, the *Indonesian Pediatric Intensive Care Working Group* recommended the *Pediatric Logistic Organ Dysfunction-2* (PELOD-2) score as a tool to define life-threatening organ dysfunction, with a cut-off point of 10. Unfortunately, many hospitals in Indonesia were unable to perform PELOD-2 score at admission because of limited resources and lack of facilities, therefore, patients were referred late to the ICU with severe conditions. The objectives of this study were to identify clinical criteria and biomarkers to predict sepsis mortality in pediatric patients and evaluate the performance of PELOD-2 score.

## Methods

This retrospective cohort study was conducted in the PICU of Dr. Cipto Mangunkusumo Hospital, a tertiary care hospital affiliated with Universitas Indonesia Faculty of Medicine, Jakarta, Indonesia. The hospital is also a teaching hospital for pediatric residency training and pediatric intensive care subspecialty training. The study period was between January 2015 and May 2020. The study was approved by The Ethics Committee of the Faculty of Medicine, Universitas Indonesia as a retrospective study with anonymity of subjects. The study setting was a 12-bed medical-surgical PICU providing care to patients aged 1 month to 18 years.

Medical records of PICU patients admitted during the study period were reviewed for clinical manifestations and laboratory results. At the time of hospital admission, subjects were evaluated using quick PELOD-2 (qPELOD-2) score, which includes *Glasgow Coma Scale* (GCS) score, mean blood pressure, heart rate, and systolic blood pressure. The full PELOD-2 score was then evaluated, with a cut-off score of 10. The full PELOD-2 score includes ten variables corresponding to five organ system dysfunctions (neurologic, cardiovascular, renal, respiratory, and hematologic systems). Sepsis was defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Septic shock was defined as a subset of sepsis that involves profound circulatory, cellular, and metabolic abnormalities.[21]

The dependent variable in the model was in-hospital mortality, presented as a percentage. The independent variables were categorized based on demographic characteristics (age and sex), clinical features [nutritional status, presence of shock, need for intubation, source of infection, inotrope use, mean arterial pressure (MAP), pulse rate, respiratory rate, and GCS score], and laboratory parameters [leukocyte count, platelet, neutrophil, and lymphocyte counts, neutrophil-to-lymphocyte count ratio (NLCR), procalcitonin, C-reactive protein (CRP), and lactate profile]. These variables were considered as potential clinical predictors of mortality besides the PELOD-2 criteria.

Data analysis was performed using *SPSS version 26.0* (*IBM*, Armonk, New York). P values (two-tailed) $<0.05$ were considered as statistically significant. Mean and median PELOD-2 scores were calculated for mortality outcome. Potential clinical predictors were analyzed by univariate analysis and the results presented as odds ratio (OR) with 95% confidence interval (95%CI). We also performed bivariate analysis to evaluate for possible associations between patient characteristics and outcome (survival or death). To analyze for potential associations between two categorical variables, we used the Chi-square test,

or the Fisher's exact test if the number of subjects in a category did not reach 20% of total subjects. To analyze for possible associations of numeric variables with categorical variables, we used the independent t-test for normally distributed data or the Mann-Whitney test for non-normally distributed data. We ran a sensitivity analysis for PELOD-2 score to assess the sensitivity, specificity, and prognostic accuracy of different thresholds.

## Results

From January 2015 to May 2020 there were 270 pediatric sepsis patients, out of which 241 met inclusion criteria. Out of these, only 110 patients had complete data for all variables. Most cases were referred from other hospitals or health care facilities. Overall mortality was 65%. Each patient was given antibiotics within one hour of diagnosis of sepsis. A comparison of survivors and non-survivors per year is shown in **Figure 1**.

Univariate analysis of certain characteristics revealed that septic shock patients had an OR of 3.2 (95%CI 1.80 to 5.55; P<0.05) for mortality compared to those without septic shock, while inotrope use had an OR of 3.1 (95%CI 1.20 to 1.75; P<0.05) for mortality compared to no inotrope use (**Table 1**). Certain clinical characteristics included in qPELOD-2 scoring and biomarkers for sepsis showed increased mortality in the same analysis (**Table 2**).

**Table 3** shows the ORs of potential mortality risk factors in this study. Of note, those with GCS <9 had an OR of 2.35 (95%CI 1.30 to 4.23; P<0.05) for mortality compared to those with higher GCS. In addition, lactate >2.85 mmol/L, absolute lymphocyte count <2592/mm$^3$, and CRP >33.5 mmol/L were significant risk factors for mortality, with ORs of 2.14, 2.16, and 2.47, respectively.

In addition, we also evaluated the performance of PELOD-2 score in predicting mortality in critically ill pediatric patients. The sensitivity and specificity of different cumulative score cut-off points are shown in **Table 4**. The PELOD-2 cut-off score of 8 had 81.2% sensitivity and 72.9% specificity, which was considered to be the optimall cut-off point to predict mortality. With this new cut-off point, pediatric sepsis patients with a PELOD-2 score of 8 or higher have a mortality risk of 11.6 times (95%CI 5.72 to 23.51; P<0.05) those with a score below 8.

## Discussion

The mortality of severe sepsis in children varies across studies, possibly explained by differences in study population, diagnostic criteria, and/or time period.9 The SPROUT study reporting global epidemiology of severe sepsis in children aged <18 years in 2015 across both developing and developed countries, found a prevalence of 8.2% in ICU settings.[22] A previous study noted that the incidence of severe sepsis hospitalizations in children significantly increased from 0.67 in 2003 to 1.59 in 2014, a 2.5-fold increase. School-age children (age 6-15 years) were the least affected compared to older teens in whom severe sepsis rates were highest.[9] Similarly, a study reported a 30% increase in severe sepsis rates in the 15 to 19-year-old age group over a span of 11 years.[2] In our study, gender, age, and nutritional status were

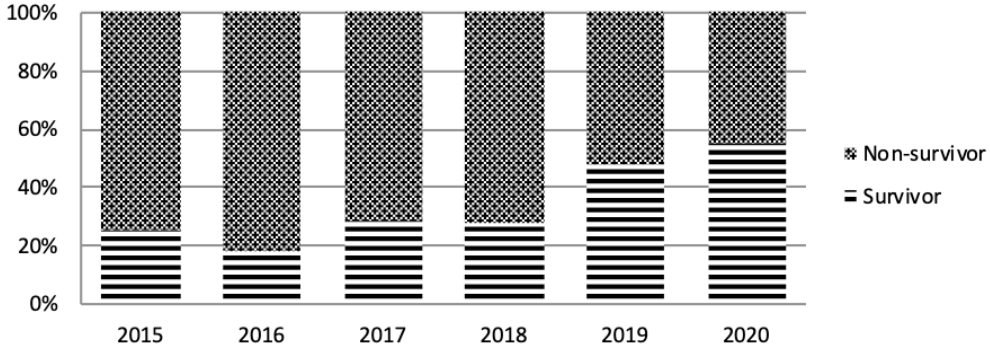


**Figure 1**. Comparison of sepsis survivors and non-survivors each year

**Table 1**. Subjects' characteristics

| Characteristics | Survivors | Non-survivors | OR | P value |
|---|---|---|---|---|
| Sex (N=241), n (%) | n=82 | n=159 | | |
| Male | 49 (59.8) | 85 (53.5) | | 0.41 |
| Female | 33 (40.2) | 74 (46.5) | | |
| Age (N=241), n (%) | n=82 | n=159 | | |
| 1 mo-<1 yr | 35 (42.6) | 70 (44.0) | | 0.57 |
| 1-5 yrs | 29 (35.4) | 48 (30.2) | | |
| 6-10 yrs | 8 (9.8) | 12 (7.6) | | |
| > 10 yrs | 10 (12.2) | 29 (18.2) | | |
| Nutritional status (N=234), n (%) | n=79 | n=155 | | |
| Severe malnutrition | 24 (30.4) | 35 (22.6) | | 0.21 |
| Underweight | 21 (26.6) | 51 (32.9) | | |
| Normal | 28 (35.4) | 61 (39.4) | | |
| Overweight | 5 (6.3) | 3 (1.9) | | |
| Obese | 1 (1.3) | 5 (3.22.1) | | |
| Shock (N= 238), n (%) | n=81 | n=157 | | |
| Yes | 26 (32.1) | 94 (59.9) | 3.2 | 0.00 |
| No | 55 (67.9) | 63 (40.1) | | |
| Intubation (N=237), n (%) | n=82 | n=155 | | |
| Yes | 40 (48.8) | 83 (53.5) | | 0.49 |
| No | 42 (51.2) | 72 (46.5) | | |
| Etiology of Infection (N=225), n% | n=78 | n=147 | | |
| Central nervous system | 9 (11.5) | 21 (14.3) | | 0.56 |
| Respiratory | 43 (55.1) | 84 (57.1) | | 0.77 |
| Gastrointestinal tract | 23 (29.5) | 51 (34.7) | | |
| Urinary tract | 3 (3.8) | 2 (1.4) | | |
| Other | 14 (17.0) | 16 (10.9) | | |
| Number of sources of infection (N=217), n (%) | n=71 | n=146 | | |
| 1 | 55 (77.5) | 114 (78.167.1) | | 0.44 |
| 2 | 14 (19.7) | 31 (21.268.9) | | |
| 3 | 2 (2.8) | 1 (0.7) | | |
| Inotropic use (N=244), n (%) | n=85 | n=1598 | | |
| Yes | 29 (34.1) | 93 (58.5) | 3.1 | 0.00 |
| No | 56 (65.9) | 66 (41.5) | | |
| Vasoactive agent use (N=119), n (%) | n=26 | n=93 | | |
| Dobutamine | 19 (73.0) | 44 (47.3) | | 0.07 |
| Epinephrine | 5 (19.2) | 30 (32.3) | | |
| Dopamine | 1 (3.9) | 14 (15.0) | | |
| Norepinephrine | 0 | 5 (5.4) | | |
| Milrinone | 1 (3.9) | 0 | | |
| Number of inotropes used (N=115), n (%) | n=25 | n=90 | | |
| 1 | 17 (68) | 40 (44.4) | | 0.08 |
| 2 | 6 (24) | 28 (31.1) | | |
| 3 | 2 (8) | 22 (24.4) | | |
| PELOD-2 score (N=213), n (%) | n=69 | n=144 | | |
| ≤9 | 605 (87) | 82 (57) | | 0.00 |
| >9 | 94 (13) | 62 (43) | | |
| Lactate (N=112), n (%) | n=37 | n=75 | | |
| ≤2 | 24 (64.9) | 29 (38.7) | | 0.01 |
| >2 | 13 (35.1) | 46 (61.3) | | |

*median (range)

not significantly different between survivors and non-survivors. Thamvamani *et al.*[9] also found no gender-related differences in incidence rates.

Mortality for children with sepsis ranges from 4% to as high as 50%, depending on illness severity, risk factors, and geographic location.[4,11-13] Our

**Table 2**. Clinical signs based on qPELOD-2 and biomarkers of pediatric sepsis

| Variables | Survivors | Non-survivors | P value |
|---|---|---|---|
| qPELOD-2 | | | |
| Median GCS (IQR) (N=230) | 12 (3-15) | 9 (3-15) | 0.001 |
| Mean MAP (SD) (N=151) | 66 (16.7) | 63 (16.8) | 0.284 |
| Median heart rate (IQR) (N=237) | 154 (90-208) | 160 (50-220 | 0.413 |
| Biomarkers | | | |
| Leukocyte, /mm$^3$ (N=232) | 14,700 (1640-29,400) | 13,700 (800-116,000) | 0.32 |
| Absolute neutrophil count, /mm$^3$ (N=209) | 8,512 (520.4-87,865) | 7,785 (48.9-68,440) | 0.02 |
| Absolute lymphocyte count, /mm$^3$ (N=206) | 3,690 (109-31,356) | 2,592 (67-34,784) | 0.08 |
| NLCR (N=197) | 2.24 (0.08-46.0) | 3.18 (0.01-166.6) | 0.02 |
| Lactate (N=241) | 1.95 (1-16) | 2.85 (1-14) | 0.02 |
| C-reactive protein, mg/L (N=116) | 12 (0.3-370.2) | 33.5 (0.3-371.2) | 0.01 |
| Procalcitonin, ng/mL (N=174) | 6.4 (0.02-1150) | 19.3 (0.07-2862) | 0.02 |

*median (range)

**Table 3**. Analysis of potential mortality risk factors in pediatric sepsis

| Variables of qPELOD-2 | Survivors | Non-survivors | OR (95%CI) | P value |
|---|---|---|---|---|
| GCS (n=241), n (%) | | | | |
| ≥9 | 56 (68.3) | 79 (49.7) | 2.35 (1.30 to 4.23) | 0.005 |
| <9 | 26 (31.7) | 80 (50.3) | | |
| Respiratory rate (n=219), n (%) | | | | |
| <44/minute | 49 (22.4) | 68 (48.6) | 1.73 (0.99 to 3.04) | 0.055 |
| ≥44/minute | 30 (13.7) | 72 (51.4) | | |
| MAP (n=151), n (%) | | | | |
| ≥63 mmHg | 31 (55.4) | 41 (43.2) | 1.63 (0.84 to 3.18) | 0.178 |
| <63 mmHg | 25 (44.6) | 54 (56.8) | | |
| Heart rate (/bpm) (n=237), n (%) | | | | |
| <160/bpm | 45 (55.6) | 77 (49.4) | 1.28 (0.75 to 2.19) | 0.365 |
| ≥160/bpm | 36 (44.4) | 79 (50.6) | | |
| Lactate (n=140), n (%) | | | | |
| <2.85 mmol/L | 30 (68.2) | 48 (50) | 2.14 (1.01 to 4.54) | 0.044 |
| ≥2.85 mmol/L | 14 (31.8) | 48 (50) | | |
| Leucocyte (n=232), n (%) | | | | |
| <13,700 /mm$^3$ | 36 (45.6) | 76 (49.7) | 0.85 (0.49 to 1.46) | 0.553 |
| ≥13,700 /mm$^3$ | 43 (54.4) | 77 (50.3) | | |
| Absolute neutrophil count (n=209), n (%) | | | | |
| <7,785/mm$^3$ | 31 (46.3) | 74 (52.1) | 0.79 (0.44 to 1.42) | 0.430 |
| ≥7,785/mm$^3$ | 36 (53.7) | 68 (47.9) | | |
| Absolute lymphocyte count (n=206), n (%) | | | | |
| >2,592 cells/μL | 43 (66.2) | 67 (47.5) | 2.16 (1.17 to 3.98) | 0.013 |
| ≤2,592 cells/μL | 22 (33.8) | 74 (52.5) | | |
| NLCR (n=197), n (%) | | | | |
| <3.18 | 39 (61.9) | 67 (50) | 1.62 (0.88 to 2.99) | 0.118 |
| ≥3.18 | 24 (38.1) | 67 (50) | | |
| Procalcitonin (n=173), n (%) | | | | |
| <19.3 ng/mL | 32 (59.3) | 63 (52.9) | 1.29 (0.674 to 2.48) | 0.439 |
| ≥19.3 ng/mL | 22 (40.7) | 56 (47.1) | | |
| C-reactive protein (n=116), n (%) | | | | |
| <33.5 mg/L | 37 (71.2) | 32 (50) | 2.47 (1.14 to 5.35) | 0.024 |
| ≥33.5 mg/L | 15 (28.8) | 32 (50) | | |

pediatric sepsis mortality was very high at 65%. These conditions may have been due to lack of awareness of the early symptoms of sepsis or lack of laboratory diagnostic facilities, so cases tended to be referred to our hospital in a more severe condition. However, we noticed that in the last 2 years of observation,

**Table 4**. The sensitivity and specificity of PELOD-2 score with different cut-off points

| PELOD-2 cut-off | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | AUROC (95% CI) | OR (95% CI) | P value |
|---|---|---|---|---|---|---|---|
| ≥10 | 94.2 | 22.9 | 36.9 | 89.2 | 0.63 (0.54-0.72) | 4.8 (1.64 to 14.25) | 0.00 |
| ≥9 | 84.5 | 52.7 | 46.0 | 87.3 | 0.67 (0.59-0.74) | 5.9 (2.86 to 12.14) | 0.00 |
| ≥8 | 81.2 | 72.9 | 59.0 | 88.9 | 0.74 (0.67-0.81) | 11.6 (5.72 to 23.8) | 0.00 |
| ≥7 | 68.1 | 81.9 | 64.4 | 84.3 | 0.74 (0.67-0.81) | 9.7 (5.0 to 18.77) | 0.00 |

PPV=positive predictive value, NPV=negative predictive value, AUROC=area under the receiver-operator curve

mortality rates have decreased (**Figure 1**).[2-4,9]

Early identification, as well as appropriate resuscitation and care management are critical to optimizing outcomes for children with sepsis.[14] Systematic screening for sepsis in children is very important to improve morbidity and mortality. To date, no optimal method or tool for screening has been agreed upon. *Surviving Sepsis Campaign* (SSC) *2020* suggests that screening tools be adapted to the type of patients, resources, and processes within each institution.[14] Institutions should monitor and evaluate their practice following the implementation of sepsis screening.[23] We used PELOD-2 score as an initial screening for pediatric sepsis patients, which consists of Glasgow coma scale, mean blood pressure, and heart rate parameters.

In our study, the median lactate level among the non-survivors was 2.85 mmol/dL (**Table 2**). The variables of GCS <9 (OR 2.3; 95%CI 1.30 to 4.23) and lactate >2.85 mmol/L (OR 2.1; 95%CI 1.01 to 4.54) can be used to predict mortality in pediatric sepsis patients. Blood lactate levels provide a valuable indirect marker of tissue hypoperfusion.[24] The optimal threshold to define "hyperlactatemia" remains unclear. In children, several observational studies have demonstrated an association between elevated blood lactate levels and adverse outcomes in septic shock.[24] The *SSC 2020* was unable to issue a recommendation about the use of blood lactate values to stratify children with suspected septic shock or other sepsis-associated organ dysfunction into low- versus high-risk of having septic shock or sepsis.[14,26,27] To date, no RCTs have tested whether initial or serial measurement of blood lactate is directly related to the evaluation and/or management in children. Lactate levels should therefore be interpreted as a part of a more comprehensive assessment of clinical status and perfusion.[14]

There is no data from RCTs supporting specific hemodynamic targets in children, though, evidence suggests that targeting a MAP of approximately 65 mmHg (5$^{th}$ percentile) in adults with septic shock may be beneficial.[28] The *SSC 2020* targets MAP between the 5$^{th}$ and 50$^{th}$ percentile or greater than the 50$^{th}$ percentile for age.[14] In our study, we found that mean MAP was 66 (SD 16.7) mmHg among survivors and 63 (SD 16.8) among non-survivors, but the difference was not statistically significant.

Vasoactive infusions begin after 40-60 mL/kg of fluid resuscitation if the patient continues to have evidence of abnormal perfusion, or sooner if fluid overload develops or other concerns for fluid administration are present. Epinephrine and norepinephrine both have vasopressor and inotropic effects, are widely used, and are effective in treating children with fluid - refractory septic shock (RSS). Epinephrine was associated with a lower risk of mortality (RR 0.63; 95%CI 0.40 to 0.99) and more organ failure-free days among survivors by day 28 (MD 4 more days; 95%CI 2.0 to 6.0).[29,30] In our study, dobutamine and epinephrine were the most commonly used vasoactive agents when children experience fluid resistance. There was insufficient evidence to recommend either epinephrine or norepinephrine as the initial vasoactive agent for children with fluid-RSS.

We used leukocyte, neutrophil, and lymphocyte counts, procalcitonin, and CRP as biomarkers to confirm sepsis diagnosis. These biomarkers are standard blood biomarkers for clinical practice for sepsis. We found that absolute lymphocyte count was higher among survivors, but procalcitonin and CRP were higher among non-survivors (P<0.05) (**Table 2**). A CRP value of >33.5 has a 2.5-fold mortality risk (95% CI 1.14 to 5.35; P<0.05) compared to those <33.5 (**Table 3**).

In our study, the PELOD-2 score cut-off point of 8 showed the best sensitivity (81.2%) and specificity

(72.9%). With this new cut-off point, pediatric sepsis patients with PELOD-2 scores >8 have a 11.6-fold mortality risk (95%CI 5.24 to 20.32; P<0.05) compared to those with lower PELOD-2 scores.

The *SSC 2020* recommends empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.[14] Broad-spectrum therapy refers to the use of single- or multi-drug antimicrobial therapy with activity against multiple groups of bacteria/pathogens. Broad-spectrum therapy was recommended for initial empiric therapy of children with septic shock or sepsis-associated organ dysfunction to increase the likelihood that the initial empirical therapy is effective against causative pathogens. All subjects were given broad-spectrum antibiotics within the first 1 hour after diagnosis of sepsis was established.

Our study had several limitations. As it is a retrospective study, information bias is a possibility that we attempted to control by going over carefully the primary information source that was recorded. Second, the analysis was limited due to incomplete data.

Finally, we conclude that pediatric sepsis patients with GCS <9, septic shock, inotrope use, lactate levels >2.85 mmol/L, and CRP values >33.5 mg/L were at higher risk of mortality than those without. A PELOD-2 score of 8 or more can predict mortality in pediatric sepsis pstients with a sensitivity of 81.2% and specificity of 72.9%. These findings will help in early identification as well as decision making in resuscitation and critical care management to optimize outcomes for children with sepsis.

## Conflict of interest

None declared.

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