

# Interleukin-6 as an early marker mortality prediction in the first day of pediatric septic shock in the Pediatric Intensive Care Unit

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## Abstract

**Introduction:** Early identification of infection severity and organ dysfunction is crucial in improving outcomes for patients with sepsis.

**Objective:** We aimed to develop an early marker that can early predict mortality in pediatric patients with septic shock.

**Method:** Prospective observational study of 6 months -18 years pediatric patients with septic shock who were admitted to the Pediatric Intensive Care Unit (PICU), Dr. Soetomo General Academic Hospital Surabaya. The measurement of interleukin 6 (IL-6) levels was carried out by Human IL-6 ELISA test on days 1, 2, and 3 after entering the PICU. The lactate levels and Pediatric Logistic Organ Dysfunction (PELOD) 2 score were also used as predictors of mortality.

**Results:** A total of 19 pediatric patients with septic shock were included in the inclusion cri-

teria of this study. Subjects were divided into the survivor (n=9) and the non-survivor group (n=10). There was a significant difference in IL-6 levels between the survivor and non-survivor groups on day 1 ( $p<0.05$ ). However, the levels of IL-6 on day 2 and day 3 did not show a significant difference as a predictor of mortality at the cut-off value of 593.34 pg/ml with a sensitivity of 60% and specificity of 100%. This study showed that IL-6 levels on day 1 had a positive correlation with mortality outcomes ( $p<0.05$ ). The PELOD 2 score showed a significant difference, but the lactate levels did not show a significant difference between the survivor and nonsurvivor groups.

**Conclusions:** IL-6 levels measured at admission can be used as an early marker for predicting first-day mortality in pediatric septic shock in the PICU.

**Key words:** IL-6, mortality, septic shock, PICU.

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## Introduction

Sepsis is a condition with life-threatening organ dysfunction caused by dysregulation of the immune response to infection. (1,2) The mortality of critically ill pediatric patients with sepsis ranges from 4% to 50%, depending on disease severity, risk factors, and geographic location. Most mortality in septic children is due to refractory or septic shock and multi-organ failure syndrome, with the highest mortality occurring 48-72 hours after initial treatment. (3)

Sepsis involves the complex effects of systemic inflammation, immune dysfunction, and the dysfunction of multiple organ systems in the body. (2) The pathophysiological process in sepsis is determined by the activation of pro and anti-inflammatory cascades controlled by cytokines, mediators, and cellular components of the immune system. (4) Interleukin-6 (IL-6) is one of the cytokine cascades that can

cause cell damage and organ failure, which significantly correlates with the prognosis of septic patients. (2,5)

Classical laboratory parameters examinations, such as lactate on admission, base deficit, and pH, have been extensively studied to assess the prognosis of sepsis in various conditions leading to organ dysfunction or death. (6) Several studies evaluating different septic biomarkers such as interleukin (IL)-1b, IL-6, IL-8, IL-10, procalcitonin (PCT), and C-reactive protein have been carried out, and IL-6 is more reliable in diagnosis and risk stratification. However, the sensitivity and specificity of IL-6 show varying values concerning the severity of infection. Until now, there have not been many studies evaluating the role of cytokines in pediatric septic shock patients on the severity of the disease and outcome. (7)

This prospective observational study was conducted to evaluate the role of IL-6 in the early diagnosis of septic shock in pediatric patients admitted to a pediatric intensive care unit and to predict the outcome.

### **Subjects and methods**

This prospective observational study was conducted on patients admitted to the Pediatric Intensive Care Unit (PICU) at Dr. Soetomo General Academic Hospital, Surabaya, Indonesia. All procedures in this study involving human participants followed the ethical standards of institutional research committees and were carried out by the most recent version of the Declaration of Helsinki. All parents/guardians of the children were well informed about the purpose of the study and gave informed consent. This research was conducted with the approval of the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya (No. 0166/105/3/VIII/2020).

#### *Study population*

The subjects were critically ill children between 6 months - 18 years old who were admitted to the Pediatric Intensive Care Unit (PICU) of Dr. Soetomo General Academic Hospital in September 2020-December 2021 who met the inclusion criteria for septic shock according to the Consensus on the Diagnostic and Management of Sepsis in Children in 2016. The diagnosis of septic shock is sepsis with cardiovascular dysfunction that has been given adequate fluids. Patients with congenital heart disease and incomplete data were excluded from the study. All subjects were provided with timely early intervention, including appropriate antibiotics, hemodynamic resuscitation, and organ support therapy using mechanical ventilation according to

the 2016 Surviving Sepsis Campaign (SSC) guideline recommendations.

#### *Data collection*

Data collection includes the patient's name, age, gender, vital signs, and primary diagnosis. Blood samples were taken within 24 hours after entering the PICU on days 1, 2, and 3. Venous blood samples were collected in tubes containing heparin or ethylenediaminetetraacetate. The samples were then stored and analyzed within 24 hours for routine inspection, and the remaining pieces were stored at -800 °C for measurement of IL-6 levels. Complete blood leukocyte count, results of blood gas analysis, blood biochemical parameters, and chest X-ray findings were recorded. The Pediatric Logistic Organ Dysfunction (PELOD) 2 score was calculated based on neurologic variables (Glasgow coma scale and pupil), cardiovascular (lactate, mean arterial pressure), kidney (creatinine), respiratory (the ratio of partial pressure of oxygen to fractional inspired oxygen [PaO<sub>2</sub>/FiO<sub>2</sub>], partial pressure of carbon dioxide [PaCO<sub>2</sub>], mechanical ventilation), hematology (leukocytes, platelets) at the time when the patient entered the PICU. Patients with septic shock were classified into survivors and non-survivors according to the outcome.

#### *IL-6 examination*

Peripheral blood samples were taken from individuals in septic shock using a 3 ml sterile syringe (Terumo), put in a 5 ml project plain, and then centrifuged at 1000 rpm for 15 minutes to separate the serum from the precipitate/pellet within 30 minutes after collection. The serum should be stored at -200 °C, if not analyzed immediately. After that, an ELISA test was carried out to determine the levels of IL-6 using Human IL-6 ELISA Kit no. catalog E-EL-H6156 and quantification using ELISA Reader (iMark Microplate Absorbance Reader).

#### *Data analysis*

The collected data were analyzed using SPSS for Windows 20.0 software (IBM, Armonk, NY, USA). Numerical data were tested for normality with Shapiro Wilk, where data with normal distribution were presented in terms of mean and standard deviation (SD), and data with non-normal distribution were given in median and minimum, and maximum range values. The two means, which were normally distributed, were analyzed using the T-test, and the Mann-Whitney test analyzed those that were not normally distributed. Correlation between variables was carried out by bivariate analysis; data that were normally distributed were analyzed using Pearson's

correlation, while abnormal data were analyzed using Spearman's correlation.

The receiver operating characteristic (ROC) curve was used to find the optimal cut-off value and calculate the sensitivity and specificity for examining IL-6, lactate, and PELOD 2 score. A p-value of less than 0.05 ( $p < 0.05$ ) was considered a statistically significant difference.

## Results

A total of 19 pediatric patients with septic shock were included in the inclusion criteria of this study. In the observation, 19 pediatric patients with septic shock were divided into the survivor group ( $n=9$ ; 5 boys and 4 girls) and the non-survivor group ( $n=10$ ; 3 boys and 7 girls). A comparison between the survivor and non-survivor groups showed a statistically significant difference in PELOD 2 scores (survivor vs non-survivor: 7 (5-8) vs  $8.70 \pm 2.4$ ,  $p < 0.05$ ), while age and gender did not show any significant difference between the two groups. The comparison between the survivor and non-survivor is depicted in **Table 1**.

**Table 2** shows that the IL-6 levels on days 1, 2, and 3 in the non-survivor group increased. There was a significant difference in IL-6 levels between the survivor and non-survivor groups on day 1 ( $p=0.02$ ). However, the levels of IL-6 on day 2 ( $p=0.278$ ) and day 3 ( $p=0.13$ ) did not show a significant difference. The lactate levels on days 1, 2, and 3 were increase in the non-survivor group; however it was not significantly different.

The ROC curve analysis was used to calculate the cut-off value, sensitivity, and specificity of IL-6 as predictors of mortality in septic shock. Youden's index with the highest sum of sensitivity and specificity was used to determine the optimal cut-off value for differentiation. Based on ROC curve analysis and **Table 3**, IL-6 levels on day 1 showed AUC 0.811 (95% CI 0.609-1.0;  $p=0.022$ ) (**Figure 1**), on day 2 AUC 0.656 (95% CI 0.395-0.916;  $p=0.253$ ) (**Figure 2**), and on day 3 AUC 0.722 (95% CI 0.475-0.969;  $p=0.102$ ) (**Figure 3**). There was a significant difference in IL-6 levels between the survivor and the non-survivor groups on day 1. As a predictor of mortality at the cut-off value of 593.35 pg/ml IL-6 on day 1 showed a sensitivity of 60% and specificity of 100%. IL-6 on day 2 with the cut-off value of 46.51 pg/ml showed a sensitivity of 80% and specificity of 55.6%, while on day 3 IL-6 with the cut-off value of 2126.69 pg/ml showed a sensitivity of 50% and specificity of 100% (**Figure 1**). The PELOD 2 score was also evaluated. It showed that AUC with a cut-off value of 8.5 was 0.767 ( $p=0.05$ ), a sensitivity of 50%, and a specific-

ity of 100% (**Figure 4, Table 4**).

Correlation analysis has been carried out with Spearman correlation to analyze the association of IL-6 levels and mortality outcome over three days. It was found a sign that the IL-6 levels were positively correlated with mortality outcome on day 1 ( $r=0.539$ ;  $p=0.017$ ; **Table 1**). IL-6 levels on day 2 ( $r=0.269$ ;  $p=0.265$ ; **Table 1**) and IL 6 levels on day 3 ( $r=0.385$ ;  $p=0.104$ ; **Table 2**) were positively correlated with mortality outcome; however, it was not significant. The correlation between PELOD 2 score and mortality outcome ( $r=0.471$ ;  $p=0.04$ ) showed a significance that PELOD 2 score was positively correlated with mortality outcome (**Table 2**). The trend levels of IL-6 and lactate were also measured. **Figure 5** shows that the trend levels of IL-6 decrease with an increasing number of days. This condition also existed in lactate levels whose levels only increase on the first day and will decrease the day after in septic shock children (**Figure 6**).

The trend levels of IL-6 and lactate were measured on days 1, 2, and 3 in the survivor and the non-survivor groups of septic shock children. This study found that there was an increasing number of IL-6 levels on the first day in the survivor group, followed by a significant decrease on day 2, and a slight increase on day 3. In the non-survivor group, IL-6 levels did not increase significantly on days 1, 2, and 3. However, lactate levels measured on days 1, 2, and 3 showed a linear trend in both groups, where there was an increasing number on day 1, a significant decrease on day 2, and a slight increase on day 3.

## Discussion

The development of an ideal pediatric prognostic score in critically ill patients remains a challenging objective.

In this study, we compared serum levels of IL-6 and lactate and PELOD 2 scores in critically ill pediatrics with septic shock. Of the three parameters, only IL-6 identified of the severity of organ dysfunction, according to the PELOD 2 scores. In the analysis of time-course changes, the highest parameter values were frequently found on day 1 for IL-6 and the PELOD 2 score. We found that IL-6 levels and PELOD 2 scores on day 1 were good predictors of mortality in the overall PICU population. The median IL-6 levels on day 1 were significantly higher in non-survivors compared to survivors, while IL-6 levels decreased on day 2 and increase on day 3 in non-survivors and survivors. Moreover, the IL-6 levels had a good AUC of 0.811 for the prediction of 28-day mortality. The mean PELOD 2 scores on

day 1 were significantly higher in non-survivors compared to survivors ( $8.70 \pm 2.4$ ) and PELOD 2 scores had a good AUC of 0.767 for the prediction of 28-day mortality. The median lactate levels on day 1 were not significantly higher in non-survivors compared to survivors, while it decreased on day 2 and increased on day 3 in non-survivors and survivors.

Cytokines are inflammatory markers that can help identify and guide specific treatments in patients with septic shock. IL-6 is thought to be significant in the progression of sepsis, particularly as an early marker of the inflammatory state. (8) However, at present, only a few studies have evaluated the profile of IL-6 levels in children with septic shock. (4) In this study, we found that higher levels of IL-6 on the first day of septic shock were significantly associated with mortality.

IL-6 is a cytokine secreted by activated monocytes and macrophages. The average serum concentration of IL-6 is  $<5$  pg/ml with a plasma half-life of fewer than six hours. Plasma IL-6 concentrations are elevated in sepsis and associated with the development of shock and death. Reinhart et al. (2001) found that IL-6 immunostrip assay could identify two different septic populations with significantly different mortality rates in studies with anti-tumor factors. (9)

A study reported that plasma levels of IL-6 were found to be elevated earlier than C-reactive protein and could be used as a diagnostic marker for sepsis. (10) A part from being used as a diagnostic test for the presence of sepsis, it is also used as a prognostic factor to predict outcomes in these patients. (11)

Duramaza et al. found that at 0 hour IL-6 value was considerably more significant in the septic shock group than in the systemic inflammatory response syndrome (SIRS) group ( $p=0.025$ ). The IL-6 level at 24 hours was substantially more significant in the septic shock group than in the sepsis and SIRS groups ( $p=0.048$  and  $p=0.043$ , respectively). At 72 hours, IL-6 readings did not differ significantly across the septic shock, sepsis, and SIRS groups. In PICU patients, elevated IL-6 levels may suggest septic shock. At 0, 24, and 72 h, mean CRP, PCT, and IL-6 values were considerably higher in the SIRS, sepsis, and septic shock groups than in the control group. (12)

Several studies have developed prognostic scores to objectively measure disease severity and predict the risk of mortality in PICU admission, which can assist in treatment planning. (4) The PELOD score is one of the scores used to determine the severity of organ dysfunction in critically ill children. (13) The Sequential Organ Failure Assessment (SOFA) score (originally known as the Sepsis-Related Or-

gan Failure Assessment) is one of the most widely used scores to measure organ dysfunction in critically ill adults and is currently being studied extensively in critically ill children. (14)

The Carta and colleagues study found that SOFA scores were consistently higher in the high IL-6 group, although not significantly due to the limited number of patients included in the study. The development of multiple organ dysfunction syndromes (MODS) has a survival-related impact. It is most likely related to the increased need for ventilatory support and length of stay in the intensive care unit. (4) Similarly, Cuschieri and colleagues (2010) in patients with hemorrhagic shock found elevated IL-6 levels to be associated with a higher risk of organ failure, more ventilator days, and more time spent in the hospital. (15)

Machado and colleagues in 2011 found higher baseline levels of IL-6, IL-8, and IL-10 to be associated with unfavorable organ dysfunction in patients with septic shock, (16) while a 2011 study by Vincent and colleagues reported severe and persistent organ dysfunction. (17)

Advances in diagnostic modalities and therapeutic strategies (improved resuscitation, appropriate infection control, and better support critical care therapy) have improved outcomes in children with sepsis. Nonetheless, the morbidity and mortality from sepsis remain high, especially in resource-limited settings. Early identification of patients with severe sepsis with higher disease severity and increased risk of death is critical. This can provide maximum individualized care for optimizing organ function and better survival.

To date, many studies have not evaluated the relationship of IL-6 with outcomes in children with septic shock. In our study, IL-6 levels had a better AUC than PELOD 2 scores measured on day 1. This research study was one of the studies in a developing country that considered IL-6 levels in septic shock children in terms of mortality.

Further research studies measuring cytokine serials are needed to provide a better indicator of pediatric septic shock patients. A limitation of this study is the inability to stratify cytokine levels to predict outcomes due to the small sample size. Despite this limitation, serum IL-6 measurement in the early phase of acute illness might be useful to assess the severity of organ dysfunction earlier than the PELOD 2 score.

## Conclusions

This study concluded that IL-6 concentrations measured at admission (within 24 hours of the patient developing septic shock) could assist in plan-

ning appropriate interventions to reduce mortality and predict mortality and risk stratification of patients with septic shock. Given the complexity of the host response to infection and the diversity of organisms, no single sepsis biomarker appears ideal for diagnosing sepsis or predicting mortality. Therefore, further research should evaluate biomarker assays and clinical markers in managing septic shock.

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**Table 1.** Subject characteristics

	Survivor	Non-survivor	p-value
Age (months)	24 (12-168) <sup>a</sup>	66 (15-192) <sup>a</sup>	0.11
Gender			
- Boy, n	5	3	0.49
- Girl, n	4	7	
PELOD 2 scores	7 (5-8) <sup>a</sup>	8.70±2.4 <sup>b</sup>	0.04*

Legend: PELOD=Pediatric Logistic Organ Dysfunction.

<sup>a</sup>median (interquartile range); <sup>b</sup>mean±SD; \* significantly different.

**Table 2.** Distribution of biomarkers in survivor and non-survivor patients

Biomarker	Survivor	Non-survivor	p-value
IL-6 day 1 (pg/ml)	56.33 (17.4-382.2) <sup>a</sup>	1041.02 (29.3-94132.1) <sup>a</sup>	0.02*
IL-6 day 2 (pg/ml)	44.64(15.5-3791.7) <sup>a</sup>	99.26 (34.3-13277.1) <sup>a</sup>	0.28
IL-6 day 3 (pg/ml)	51.06 (25.8-1926.7) <sup>a</sup>	1614.0 (23.3-16410.6) <sup>a</sup>	0.13
Lactate day 1 (mmol/l)	2.30 (1.09-10.12) <sup>a</sup>	4.57±2.2 <sup>b</sup>	0.29
Lactate day 2 (mmol/l)	0.81 (0.42-6.7) <sup>a</sup>	2.56±1.97 <sup>b</sup>	0.37
Lactate day 3 (mmol/l)	1.99±1.46 <sup>b</sup>	0.98 (0.5-7.5) <sup>a</sup>	0.78

Legend: IL-6=interleukin 6.

<sup>a</sup>median (interquartile range); <sup>b</sup>mean±SD; \* significantly different.

**Table 3.** Comparison of area under the curve (AUC) value of IL-6 levels on days 1, 2, and 3 to mortality

Biomarker	Area	p-value
IL-6 day 1 (pg/ml)	0.81	0.022*
IL-6 day 2 (pg/ml)	0.66	0.253
IL-6 day 3 (pg/ml)	0.72	0.126

Legend: IL-6=interleukin 6.

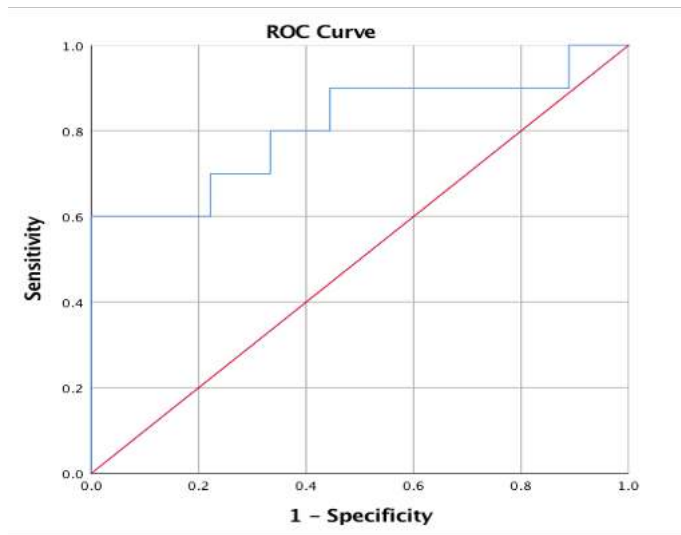
\* significantly different.

**Table 4.** The area under the curve (AUC) value of PELOD 2 score to mortality

Variable	Area	p-value
PELOD 2 scores	0.767	0.05

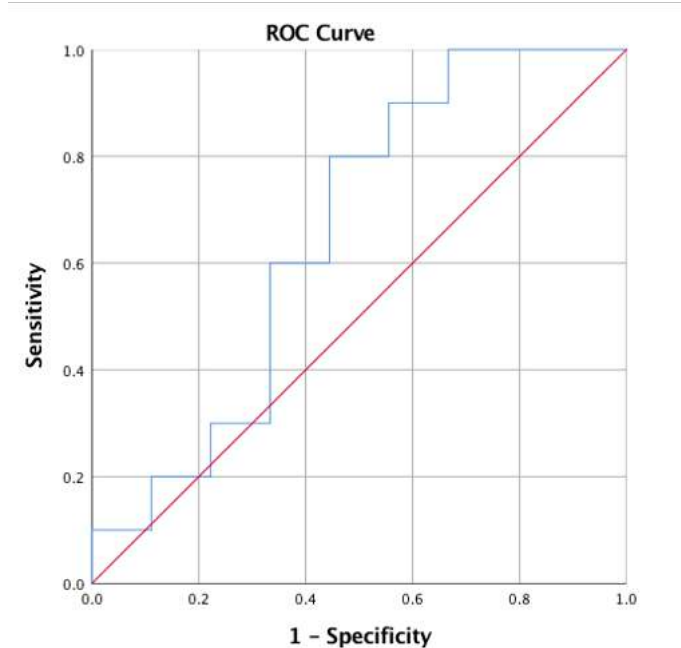
Legend: PELOD=Pediatric Logistic Organ Dysfunction.

**Figure 1.** ROC curve of IL-6 levels day 1 towards mortality prediction



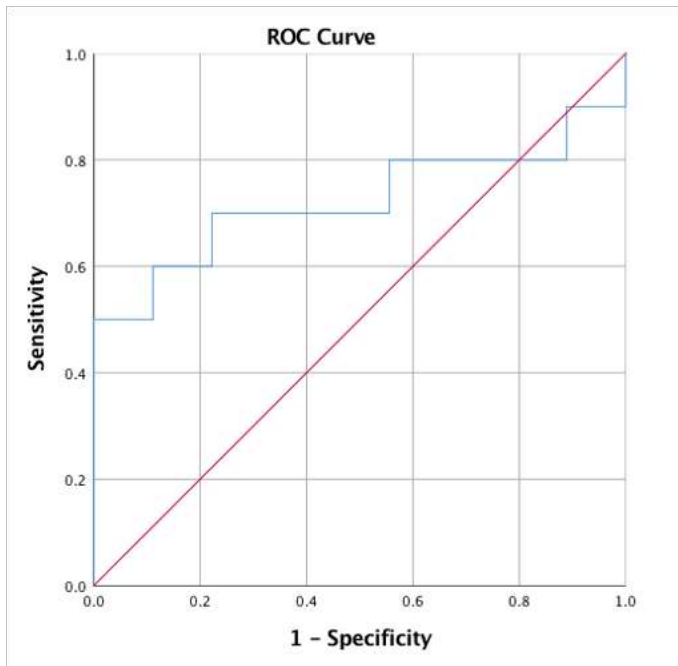
Legend: ROC=receiver operating characteristic; IL-6=interleukin 6. IL-6 cut-off value with mortality outcome 593.35 pg/ml.

**Figure 2.** ROC curve of IL-6 levels day 2 towards mortality prediction



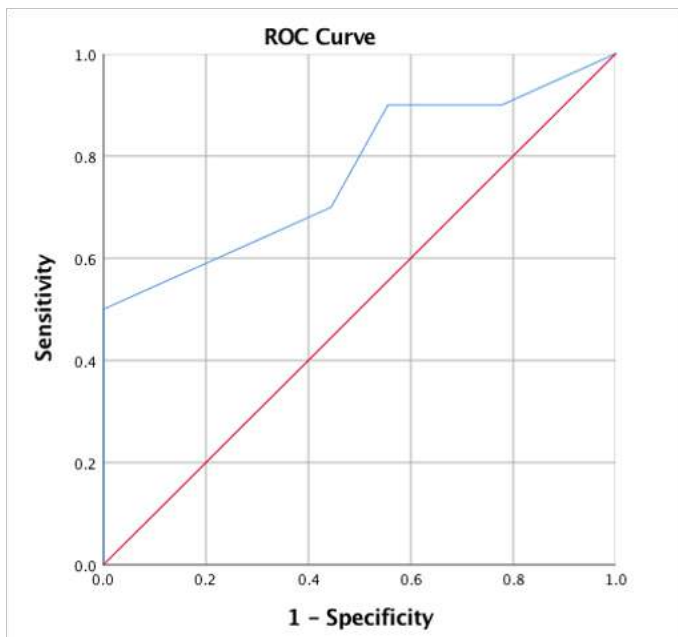
Legend: ROC=receiver operating characteristic; IL-6=interleukin 6. IL-6 cut-off value with mortality outcome 46.51 pg/ml.

**Figure 3.** ROC curve of IL-6 levels day 3 towards mortality prediction



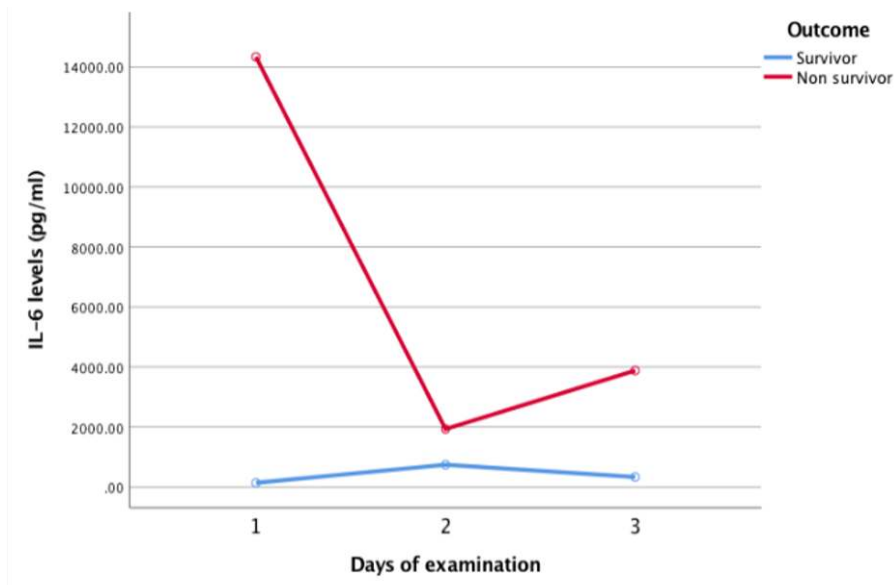
Legend: ROC=receiver operating characteristic; IL-6=interleukin 6. IL-6 cut-off value with mortality outcome 2126.69 pg/ml.

**Figure 4.** ROC curve of PELOD 2 score against mortality prediction with a cut-off value of 8.5



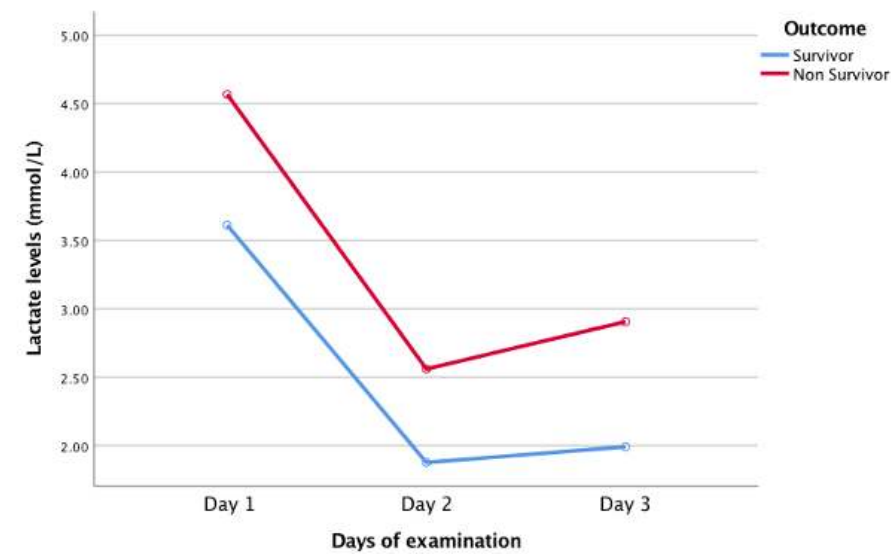
Legend: ROC=receiver operating characteristic; PELOD=Pediatric Logistic Organ Dysfunction.

**Figure 5.** IL-6 levels on days 1, 2, and 3 in both survivor and non-survivor groups



Legend: IL-6=interleukin 6. There was a significant difference between the survivor and non-survivor groups on day 3 of the examination ( $p=0.04$ ).

**Figure 6.** Lactate levels on days 1, 2, and 3 in both survivor and non-survivor groups



Legend: There was a significant difference between the survivor and non-survivor groups on day 3 of the examination ( $p=0.04$ ).

## References

1. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43:304-77.
2. Liu J, Bai C, Li B, Shan A, Shi F, Yao C, et al. Mortality prediction using a novel combination of biomarkers in the first day of sepsis in intensive care units. *Sci Rep* 2021;11:1275.
3. Weiss SL, Peters MJ, Alhazzani W, Agus MSD, Flori HR, Inwald DP, et al. Executive summary: Surviving sepsis campaign international guidelines for the management of septic shock and sepsis-associated organ dysfunction in children. *Pediatr Crit Care Med* 2020;21:186-95.
4. Carta A, de Lucca MG, Pires MD, Lobo SM. Sepsis-associated organ dysfunction and increased supportive care are associated with high serum interleukin-6 levels. *J Bras Patol Med Lab* 2016;52:367-73.
5. Costa RT, de Araújo OR, Brunialti MKC, Assunção MSC, Azevedo LCP, Freitas F, et al. T helper type cytokines in sepsis: time-shared variance and correlation with organ dysfunction and hospital mortality. *Brazilian J Infect Dis* 2019;23:79-85.
6. Billeter A, Turina M, Seifert B, Mica L, Stocker R, Keel M. Early serum procalcitonin, interleukin-6, and 24-hour lactate clearance: Useful indicators of septic infections in severely traumatized patients. *World J Surg* 2009;33:558-66.
7. Kandaswamy P, Hemlata, Singh GP, Ahmad MK. Comparative evaluation of procalcitonin and interleukin-6 as diagnostic and prognostic biomarkers for sepsis. *J Clin Diagnostic Res* 2018;12:UC17-21.
8. Vivas MC, Villamarin Guerrero HF, Tascon AJ, Valderrama-Aguirre A. Plasma interleukin-6 levels correlate with survival in patients with bacterial sepsis and septic shock. *Interv Med Appl Sci* 2021;11:224-30.
9. Reinhart K, Menges T, Gardlund B, Harm Zwaveling J, Smithes M, Vincent JL, et al. Randomized, placebo-controlled trial of the anti-tumor necrosis factor antibody fragment afelimomab in hyperinflammatory response during severe sepsis: The RAMSES study. *Crit Care Med* 2001;29:765-9.
10. Pfeiffer KA, Reinsberg J, Rahmun A, Schmolling J, Krebs D. Clinical application of maternal serum cytokine determination in premature rupture of membranes--Interleukin-6, an early predictor of neonatal infection? *Acta Obstet Gynecol Scand* 1999;78:774-8.
11. Hack CE, De Groot ER, Felt-Bersma RJ, Nuijens JH, Van Schijndel RJS, Eerenberg-Belmer AJ, et al. Increased plasma levels of interleukin-6 in sepsis. *Blood* 1989;74:1704-10.
12. Duramaz BB, Ankay N, Yesilbas O, Kihitir HS, Yozgat CY, Petmezci MT, et al. Role of soluble triggering receptor expressed in myeloid cells-1 in distinguishing SIRS, sepsis, and septic shock in the pediatric intensive care unit. *Arch Pediatr* 2021;28:567-72.
13. El-Nawawy A, Mohsen AA, Abdel-Malik M, Taman SO. Performance of the pediatric logistic organ dysfunction (PELOD) and (PELOD-2) scores in a pediatric intensive care unit of a developing country. *Eur J Pediatr* 2017;176:849-55.
14. Lalitha AV, Satish JK, Reddy M, Ghosh S, George J, Pujari C. Sequential organ failure assessment score as a predictor of outcome in sepsis in pediatric intensive care unit. *J Pediatr Intensive Care* 2021;10:110-7.
15. Cuschieri J, Bulger E, Schaeffer V, Sakr S, Nathens AB, Hennessy L, et al. Early elevation in random plasma IL-6 after severe injury is associated with development of organ failure. *Shock* 2010;34:346-51.
16. Machado FR, Sanches LC, Azevedo LCP, Brunialti M, Lourenço D, Noguti MA, et al. Association between organ dysfunction and cytokine concentrations during the early phases of septic shock. *Rev Bras Ter Intensiva* 2011;23:426-33.
17. Vincent J-L, Nelson DR, Williams MD. Is worsening multiple organ failure the cause of death in patients with severe sepsis? *Crit Care Med* 2011;39:1050-5.