

# Correlation of Troponin Level (Troponin T, Troponin I) With PELOD-2 Score in Sepsis as a Predictive Factor of Mortality

Aileen C. Dauhan<sup>1\*</sup>, Aridamuriyany D. Lubis<sup>1</sup>, Erna Mutiara<sup>2</sup>, Munar Lubis<sup>1</sup>

<sup>1</sup>Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; <sup>2</sup>Faculty of Public Health, Universitas Sumatera Utara, Medan, Indonesia

## Abstract

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**\*Correspondence:** Aileen Clarissa Dauhan, Department of Child Health, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia. E-mail: aileen.clarissa.dauhan@gmail.com

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**BACKGROUND:** Sepsis in children with cardiovascular involvement can increase mortality. Recently, many studies have been conducted to investigate troponin as an early marker of myocardial dysfunction, associated with pediatric sepsis score. Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score is recent scoring to assess organ dysfunction in sepsis children.

**AIM:** To determine the correlation between troponin T, troponin I with PELOD-2 score in sepsis as a predictive factor of mortality.

**METHODS:** A prospective cohort study was conducted on sepsis children in PICU Haji Adam Malik General Hospital, Medan. Assessment of PELOD-2 score, serum troponin T, and troponin I levels performed on the first day and 48 hours after sepsis was diagnosed. Patients were observed until moved to the ward or died.

**RESULTS:** A group of 41 subjects were recruited in this study. Troponin T level at 24 hours did not correlate with PELOD-2 scores. Troponin T level at 48 hours was positively correlated with PELOD-2 score ( $r = 0.771$ ,  $p < 0.001$ ) and had a significant association with the mortality rate ( $p < 0.001$ ). Troponin T at 48 hours could be used as a predictive factor of mortality (AUC 86.4%,  $p < 0.001$ ) with a cut-off point of 40.3 ng/mL (76% sensitivity, 75% specificity, RR 2.48). Troponin I levels at 24 and 48 hours also had strong correlation with PELOD-2 score ( $r = 0.326$ ,  $p = 0.037$ ;  $r = 0.691$ ,  $p < 0.001$ ) and could be used as a predictor of mortality in pediatric patients with sepsis (AUC 74.8%,  $p 0.008$ ; AUC 92.6%,  $p < 0.001$ ). The cut-off point of troponin I at 24 hours was 0.075 ng/mL (68% sensitivity, 68.8% specificity, RR 1.84) and at 48 hours was 0.125 ng/mL (80% sensitivity, 81.3% specificity, RR 3.13).

**CONCLUSION:** Serum troponin T and troponin I levels at 48 hours have positive correlation with PELOD-2 score as a predictive factor of mortality in pediatric patients with sepsis.

## Introduction

Sepsis is a life threatening organ dysfunction that caused by immune dysregulation of infection. Sepsis is the most common cause of morbidity and mortality in children [1]. According to the Sepsis Prevalence Outcomes and Therapies (SPROUT) study in 2015, the most common cause of infection came from the respiratory system (40%), while organ dysfunction occurred in 67% of children with sepsis [2]. Research by Proulx et al found that systemic inflammatory response syndrome (SIRS) occurred in 82% treated patients in a pediatric intensive care unit (PICU), in which 23% of patients had sepsis, 4% of severe sepsis, and 2% of septic shock [3]. In Cipto Mangunkusumo Hospital PICU, as many as 19.3% of 502 pediatric patients treated experienced sepsis with

a mortality rate of 54% [4]. Salim et al., in Haji Adam Malik Hospital PICU (RSHAM), Medan, showed the presentation of sepsis in boys was higher than girls, the highest age was 1 to 50 months, and the mortality rate was 42% [5].

Untreated sepsis can progress to septic shock and end in multi-organ failure such as brain, kidney, liver and cardiovascular system. Sepsis with the involvement of the cardiovascular system will increase mortality by 70% to 90%. Cardiovascular dysfunction in sepsis occurs in 2-3 days after onset of sepsis, which is characterized by decreasing left ventricular ejection fraction (LVEF). Sepsis is associated with acute myocardial damage. Some studies have shown cardiac ventricular dilatation in sepsis [6], [7]. Assessment of cardiac function disorders using echocardiography is most often performed, but requires subjective ability by trained experts. In

addition, there is often difficulty in radiographic support modalities within the first 24 hours [8]. Therefore, the idea arises to use biomarkers of cardiac dysfunction detect myocardial disorders and provide prognostic information in sepsis.

In adult patients, troponin is one of biomarker that have high sensitivity and can even show small myocardial damage. Troponins assessed were troponin T (cTnT) and troponin I (cTnI). Troponin T had sensitivity 99% with specificity 78%, meanwhile for cTnI the sensitivity was 96% with specificity 88%. The cTnT and cTnI levels increased in 3 hours after myocardial injury, but cTnT lasted longer than cTnI [8]. Various studies of troponin in adult sepsis have been carried out, but not much research has been done on children.

Organ dysfunction in sepsis can be assessed by using the pediatric logistic organ dysfunction score (PELODS) which assessed 6 systems organ with 12 variables to assess the degree of diseases [9]. In 2013, Letreutre et al. validated PELODS into PELOD-2. Organ dysfunction was based on PELOD scores -2 level  $\geq 11$  because it is associated with increased mortality as 30.5%. At type B or C health centers, the cut-off for PELOD-2 score is  $\geq 7$  [10].

The objectives of this study were to evaluate correlation between troponins (TnT and TnI) level with PELOD-2 score in children with sepsis as a predictive factor of mortality.

## Methods

A prospective cohort study was conducted at pediatric intensive care unit (PICU) Haji Adam Malik Hospital, Medan, North Sumatera, in October 2017-March 2018. Samples were patients aged 1 month- $\leq 18$  years that treated at PICU and diagnosed with sepsis. The exclusion criteria were patient with heart disease, either congenital or acquired, based from anamnesis, physical findings, or x-ray. Samples were obtain by consecutive sampling. This study was approved by the Health Research Ethical Committee, Medical School, Universitas Sumatera Utara.

After get consent from the parents, blood sampling was done for all subjects. Full blood count, blood culture, blood gas analysis, lactat serum, creatinine, TnT and TnI level at the first 24 hours were examined. All the blood examination except culture were reassess in 48 hours of the PICU stay. Calculation of PELOD-2 score was made for the first 24 hours and 48 hours. Then the subjects were followed up during treatment, until moved into the ward or died.

Data analysis was done with statistical software SPSS 20.0. Univariate analysis was done for

subject characteristic. Spearman's correlations were used to examine the association between troponin level and PELOD-2 score. Differences in the troponin level and mortality were tested with Mann Whitney U-test. Statistical calculation was done at 95% confidence interval and p-level  $< 0.05$  was considered significant. Diagnostic test was done to examine cut off troponin, receiver operator curve (ROC), areas under the curve (AUC), and relative risk (RR) troponin as predictive value of mortality in pediatric sepsis.

## Results

### Study Participants

A total of 43 patients were recruited, 2 patient died at first 24 hours in PICU, 41 patients were analyzed in this study. Patient characteristics distribution can be seen in the Table 1.

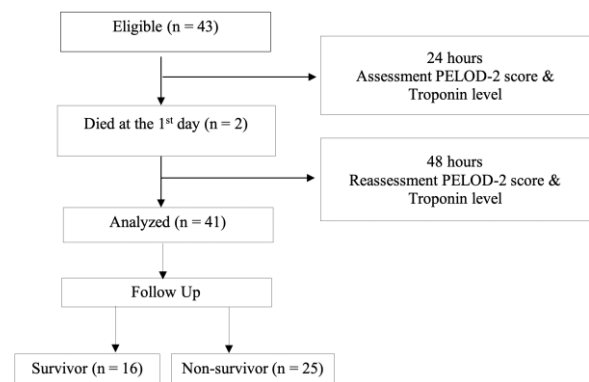


Figure 1. Study flow chart

There were 19 boys and 22 girls with median age 5.5 years old (interquartile range 0.08 to 17). Overall mortality rate was 61%, with central nervous system was the most common primary infection source. Only 19 (39%) patients with sepsis has positive blood culture.

Table 1: Baseline subject characteristics

Charateristics	Samples n = 41
Sex	
Male, n (%)	19 (46.3)
Female, n (%)	22 (53.7)
Age (year), Median (Min-Max)	5.5 (0.08 – 17)
Weight (kg), Median (Min-Max)	18.7 (3 – 70)
Height (cm), Median (Min-Max)	96.3 (43 – 175)
Nutritional status, n (%)	
Malnutrition	7 (17.1)
Underweight	9 (22)
Well nourished	24 (58.5)
Overweight	1 (2.4)
Outcome, n (%)	
Survive/ward	16 (39)
Died	25 (61)
Primary Infection, n (%)	
Kidney	4 (9.8)
Respiratory tract	8 (19.5)
Post operation	12 (29.3)
Central nerve system	14 (34.1)
Infectious and tropical disease	2 (4.9)
Skin	1 (2.4)
Blood culture, n (%)	
Positive	16 (39)
Negative	25 (61)

### Correlation between Troponin Level and PELOD-2 Score

Table 2 shows correlation between troponin level and PELOD-2 score. From this study, there is no correlation between cTnT level and PELOD-2 score at 24 hours. Troponin T level at 48 hours and cTnI level at 24 and 48 hours have positive correlation with PELOD-2 score ( $r = 0.771$ ,  $p < 0.001$ ;  $r = 0.326$ ,  $p = 0.037$ ;  $r = 0.691$ ,  $p < 0.001$ , respectively).

**Table 2: Correlation of troponin level and PELOD-2 score**

	Median (Min-Max)	r	p*
24 hours			
PELOD-2 score	8 (1 – 21)		
Troponin T level	36.6 (0.68-177)	0.137	0.394
Troponin I level	0.1 (0-1.1)	0.326	0.037
48 hours			
PELOD-2 score	9 (1 – 24)		
Troponin T level	42 (1.97-233)	0.771	< 0.001
Troponin I level	0.2 (0-3-1)	0.691	< 0.001

\*Spearman correlation.

### Association of Troponin Level and Mortality

Troponin T level at 24 hours has no association with mortality, but there is significant association cTnT level at 48 hours and TnI level with mortality. From all died subject in this study, both cTnT and cTnI level at 48 hours were higher than survivor children. Table 3. Showed association of troponin level and mortality.

**Table 3: Association of troponin level and mortality**

	Survivor Median (Min-Max)	Non Survivor Median (min-max)	p**
24 hours			
Troponin T (ng/mL)	38 (0.68 – 107)	36.2 (12.9 - 177)	0.968
Troponin I (ng/mL)	0 (0 - 0.93)	0.33 (0 - 1.11)	0.007
48 hours			
Troponin T (ng/mL)	24.2 (1.97- 46)	53 (13 - 233)	< 0.001
Troponin I (ng/mL)	0 (0 - 0.26)	0.7 (0 - 3.11)	< 0.001

p\*\*, Mann-Whitney U-test.

### Troponin Level as a Predictive Factor of Mortality

Troponin level at 48 hours had well power as a predictive factor of mortality in children with sepsis with cTnT level cut-off point at 48 hours was 40.3 ng/mL (76% sensitivity, 75% specificity, RR 2.48), (Fig. 2).

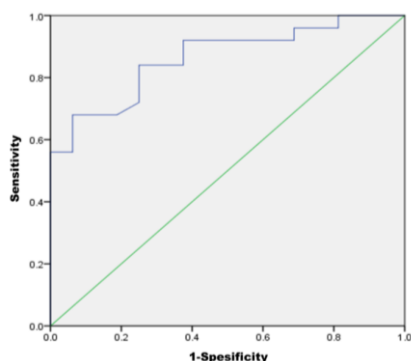


Figure 2: ROC curve of troponin T level at 48 hours (AUC 86.4%,  $p < 0.001$ , 95% CI 0.75-0.97)

Troponin level at 48 hours had well power as a predictive factor of mortality in children with sepsis with cTnI level 0.125 ng/mL (80% sensitivity, 81.3% specificity, RR 3.13), (Fig. 3).

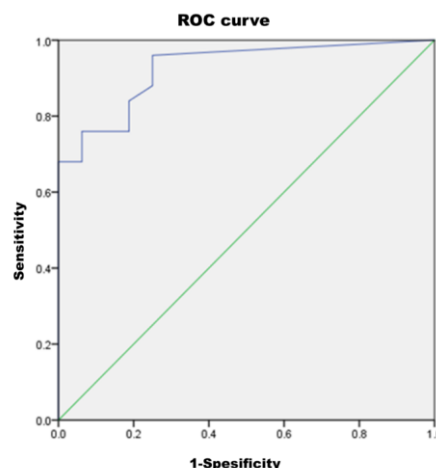


Figure 3. ROC curve of troponin I level at 48 hours (AUC 92.6%,  $p < 0.001$ , 95% CI 0.85-1.0)

## Discussion

Sepsis is the major cause of death in children within last two decades, especially in developing countries. The mortality rate in children with sepsis can reach 5-20%. More than 50% of death from sepsis are associated with severe infections such as pneumonia, diarrhea, and malaria. The high mortality rate in low-income countries is related to the delay in the sepsis diagnosis and treatment [1], [11].

The study by Wang et al., found that children with sepsis and severe sepsis in China the mortality rate approximately 34.6%, and two-thirds of deaths occurred within 72 hours of treatment [12]. Another study conducted by Jaramillo-Bustamante et al., said that there were 50% of pediatric patients treated in PICU with septic shock and 40% of them experienced MODS, with a high mortality rate of 34% [13]. Large-scale research by SPROUT in 2015 found the mortality rate due to sepsis in children worldwide was 25% [14].

From this study, 41 patients with sepsis who were treated in PICU Haji Adam Malik Hospital, 25 patients (61%) died. The most causes of sepsis are central nervous system infections (34.1%) and infections after surgery (29.3%). Mortality rate in this study was higher than the previous study conducted in PICU Haji Adam Malik Hospital in 2012 by Salim et al., with mortality rate was 42% [5].

Pediatric logistic organ dysfunction scores are used to assess organ dysfunction in pediatric

population. The latest version that has been revised and validated in large-scale research with good calibration is PELOD-2 [10]. Karam et al., in his study found that changes in PELOD-2 scores assessed serially were related to the probability of death [15]. Assessment of PELOD-2 scores in this study was carried out within first 24 hours after diagnosis of sepsis in PICU and after 48 hours of therapy. The PELOD-2 score assessed at 24 hours and 48 hours had a significant relationship with mortality ( $p = 0.008$ ;  $p < 0.001$ ). The PELOD-2 score in sepsis patients who died was higher than that of survive patients. Assessment of PELOD-2 scores in this study was conducted in addition to predicting the occurrence of mortality, and also to evaluate therapy progress through biomarkers of myocardial dysfunction in sepsis. Klag et al., found that evaluation for successful antimicrobials therapy in septic patients can be done after 48 hours, which is one of its sign characterized by a decrease in sepsis biomarkers [16].

Troponin T and troponin I are cardiac myofibrin compounds that studied with regard to myocardial dysfunction in sepsis. Myocardial dysfunction, characterized by left ventricular systolic and diastolic disorders, is a complication of early sepsis, especially in patients with sepsis shock [17]. In addition, the cardiovascular system itself is part of the calculation of the scores of new PELOD-2 organ dysfunction [10]. Physiological and metabolic changes occur in sepsis patient, such as impaired coronary blood flow, decreased oxygen levels, hypokinetic heart wall, and ventricular dilatation [18]. Macrocirculation of cardiac blood flow will increase in septic shock, while microcirculation decreases. The disruption of blood flow will result in a decrease in perfusion of the heart muscle, resulting in myocardial dysfunction and troponin release from cardiac myocytes [19], [20].

This study showed that troponin T from 24-hour assessment did not had a significant correlation with the PELOD-2 score. Meanwhile troponin T and troponin I levels showed a statistically significant correlation with the PELOD-2 score if measured at 48 hours. The results from this study were the same as the case control study by Hassan et al., where cTnT levels were related to the severity of patients and had a positive correlation with PIM2 scores ( $r = 0.67$ ;  $p < 0.05$ ) [21]. Lodha et al., study showed serial cTnI levels at 24 hours, 48 hours, and 96 hours higher in pediatric patients with sepsis. Also, the level of cTnI at the time of admission had a positive correlation with the PIM2 score ( $r = 0.51$ ,  $p = 0.03$ ) [22].

Differences in type of infection, methods of troponin levels examination, significant intersection points for troponin, and timing of blood sampling will affect troponin results. In addition, a decrease in blood pressure is a further manifestation of low cardiac-output in children with septic shock. Heart blood flow will be maintained in the initial phase by vasoconstriction, increased heart rate, and reduced

peripheral perfusion. In untreated sepsis, there will be a hemodynamic disruption so that the perfusion of the heart muscle will decrease and stimulate troponin release [23]. Increased troponin levels in blood correlate with impaired heart function, increase the needed for inotropic drugs, and the severity of the disease in critically ill pediatric patients with sepsis shock [24].

In a prospective study by Eldeen et al. in adult patients with sepsis treated in the ICU, cTnI levels correlated with the Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score with  $r = 0.71$ ,  $p = 0.0001$ . Assessment of organ dysfunction using the Sequential Organ Failure Assessment (SOFA) score on the first and second days of treatment also showed a significant correlation with cTnI ( $r = 0.69$ ,  $r = 0.64$ ;  $p = 0.0001$ ). APACHE II and SOFA scores can be used as predictor scores for mortality ( $p = 0.0001$ ), while cTnI alone cannot be predicted as a mortality ( $p = 0.29$ ) [25]. Abnormalities of troponin levels in sepsis are associated with increased morbidity and mortality. Data from meta-analysis by Sheyin et al., obtained from 1857 patients, death occurred in 60.5% of sepsis patients and 38.9% of septic shock patients with elevated troponin levels. Increased troponin levels will increase almost twice the risk of death [26].

This study showed troponin T and troponin I levels at 48 hours correlated with mortality. The ROC and AUC curves showed that troponin T levels at 24 hours could not be used as a predictor factor for mortality of children with sepsis (AUC 50.04%,  $p = 0.97$ ). Whereas in the 48-hour measurement, troponin T levels could be used as predictors of mortality in children with sepsis (AUC 86.4%,  $p < 0.001$ ). Troponin I levels at 24 hours and 48 hours can be used as predictors of mortality (AUC 74.8%,  $p = 0.008$ ; AUC 92.6%,  $p < 0.001$ ). For both troponins, it is better to examine troponin levels in the first 48 hours because statistically having a good AUC ( $> 80\%$ ). Same result was stated in meta-analysis study by Bessière et al., that troponin could be a prognostic factor in septic patients and increase in troponin levels was associated with an increase in mortality rate, with AUC 68% (CI 0.63–0.71) [27]. This meta-analysis of 13 studies with 1227 samples had not been able to determine the optimal cut-off point for adult patients, while research on children are still limited.

The cTnT level at 48 hours in this study, which could predict mortality, was more than 40.3 ng/mL (76% sensitivity and 75% specificity) and cTnI level was more than equal to 0.125 ng/mL (sensitivity 80%, specificity 81.3%). Gurkan et al., study, in pediatric patients treated in PICU, concluded that cTnI measurements could evaluate the presence of myocardial dysfunction in cut-offs  $\geq 0.6$  ng/ml (sensitivity 93.3%, specificity 46.2%) [28]. However, that study found that there was no significant association between cTnI levels and mortality of pediatric patients with sepsis. Whereas there have

been no studies to determine cTnT levels as predictors of mortality in children.

Meta-analysis study by Sheyin et al., found 38.9% of septic patients with increased troponin were died compared with 22.1% of sepsis patients without elevated troponin (RR 1.91; 95% CI: 1.65-2.22) [26]. This was similar to a meta-analysis study by Bessiere et al., [17]. Increased troponin levels will increase the risk of death in patients with sepsis (OR 1.92; CI 1.35-2.47). According to John et al., patients with positive troponin had a mortality of 32.2% in 28 days, which was greater than negative troponin 13.2% ( $p < 0.0001$ ) [29]. Multivariate analysis showed that troponin was an independent prognostic factor of mortality with OR 2.02.

In this study, the likelihood of mortality in septic patients with troponin T levels at 48 hours more than 40.3 ng/mL was 2.48 times greater (95% CI 1.26-4.89). Whereas troponin I measurements at 48 hours had relative risk (RR) 3.13 (95% CI 1.46-6.70). This means that at a 48-hour examination, patients with troponin I levels greater than 0.125 ng/mL would have a 3.13 times greater mortality than those with troponin I levels less than 0.125 ng/mL.

Some limitations in this study are variations in the course of the disease and the severity of the disease when the patient firstly diagnosed with sepsis was very broad, resulting in a wide range of data. This study also performed troponin examination only twice, at the beginning of PICU treatment and at 48 hours. In addition, measurements of troponin should be followed by examination of myocardial dysfunction such as echocardiography or other hemodynamic assessments. Assessment of myocardial dysfunction with various modalities is expected to be one of the references for the provision of optimal interventions for cardiovascular system disorders in sepsis.

Research on the level of troponin in the pediatric population is still very limited, therefore one of the advantages of this study is that it can provide a cut-off point for troponin levels that can be referred to in a population of children with sepsis. This study also investigated the correlation of troponin level as a marker of myocardial dysfunction with PELOD-2 score that currently used to assess organ dysfunction in pediatric sepsis, and it has never been studied before.

With repeated measurements, this study can show the course of the severity of an illness in children suffering from sepsis including predicting mortality. Although the variation in the course of the disease and the severity of the disease when diagnosed with sepsis were limitation for this research, but also became an advantage, because it is appropriate and can be used in daily clinical practice. Repeated measurements can also be used to evaluate therapy progress. Consideration for treatment changes can be done by physician with reference of increased troponin levels and PELOD-2 scores in pediatric patients with sepsis.

In conclusion, serum troponin T and troponin I levels at 48 hours have positive correlation with PELOD-2 score as a predictive factor of mortality in pediatric patients with sepsis.

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