

# Serum Ferritin and PELOD-2 Scores in Critically Ill Septic Children – a Cross-sectional Single-center Study

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## ABSTRACT

**Objective.** This study aims to assess the correlation of ferritin serum level and PELOD-2 score, and determine the effectiveness of ferritin serum level as early indicator of organ dysfunction.

**Methods.** This was a cross-sectional study carried out to pediatric patients with sepsis in the Pediatric Intensive Care Unit Haji Adam Malik and Universitas Sumatera Utara hospital from June 2021 – January 2022. Complete blood work was done, and ferritin serum level and PELOD-2 score were measured on the first and third day of hospital stay of all the sixty participants aged 1-18 years old with sepsis. The correlation was measured using Spearman test, with  $p < 0.05$  indicating a significant correlation.

**Results.** The median level of serum ferritin level was 480 (24.7 – 22652) ng/mL. There were 20% patients with ferritin level  $< 200$  ng/mL, 26.7% with ferritin level 200-500 ng/mL, and 53.3% patients with ferritin  $> 500$  ng/mL. The median score of PELOD-2 was 4. There was a significant correlation of serum ferritin and PELOD-2 score on day 1 of hospital stay.

**Conclusion.** The ferritin serum level is effective as an early indicator of organ dysfunction until PELOD-2 score is established. There is a positive correlation between serum ferritin and PELOD-2 score. There is a link between elevated ferritin and worse disease prognosis.

**Keywords:** ferritin, sepsis, infection, PELOD -2

## INTRODUCTION

Sepsis is a life-threatening condition in which organ dysfunction occur as a result of dysregulated immune as a response to infections.<sup>1</sup> Untreated sepsis can progress to septic shock and result in multiple organ failures such as the brain, kidneys, and cardiovascular system – eventually leading to death. Multiple organ failures are common occurrence in the pediatric intensive care unit (PICU), where mortality is closely related to organ system failure and the extensive organ dysfunction.<sup>2,3</sup>

Scoring systems are usually used to assess the degree of severity of diseases, especially in the intensive care unit (ICU). They provide an overview in the ICU in terms of possible mortality, outcome anticipation, prediction of diseases' severity, and organ failure.<sup>4,5</sup> The Pediatric Logistic Organ Dysfunction (PELOD) score is one of the scoring systems used to assess the severity of diseases in children with critical condition (Appendix). The PELOD score had a good validity to assess patients' outcome in the ICU.<sup>6</sup> Later in 2013, Leteurte et al. developed the PELOD scoring



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system and validated PELOD-2 – as an update to the PELOD score, to determine the degree of severity of the diseases in the PICU by analyzing multi-organ failures.<sup>7</sup> The PELOD-2 score has been established as the diagnosis and prognostication for sepsis in children following the national guideline on medical service (PNPK) for the administrative procedure of sepsis in children in 2016.<sup>8</sup> However, calculation of the PELOD score requires several examinations based on the system organ, which take longer time for the assessment to be established.

Ferritin serum level is known as an acute phase reactant to reflect the degree of acute and chronic inflammation in infections, rheumatology, hematology, and malignancy.<sup>9</sup> There is an iron buildup in the reticuloendothelial system and a decrease in circulating iron in chronic inflammation. As a result, erythropoietin production is disrupted, erythropoiesis is decreased, the erythrocyte life cycle is disrupted, and iron homeostasis is dysregulated. Hyposideremia (lower iron serum) and the changes in iron transport are linked to chronic inflammation. Cytokines produced through inflammatory processes change the pattern of iron distribution in the reticuloendothelial system, lowering erythropoiesis, and increasing iron storage.<sup>10</sup> Bobbio-Pallavicini et al. described ferritin as a potential marker for prognosis in critically ill children and they found that an increase in ferritin serum level was related with a worsening clinical status.<sup>11</sup> The link between ferritin serum level and critical outcomes has also been shown in adults. Ferritin serum levels in critically ill patients are linked to the severity of their illness, and high ferritin serum levels are linked to an increased risk of developing multiple organ failures and acute respiratory distress syndrome.<sup>11,12</sup>

From the existing theory and idea, ferritin serum level can be an early marker of organ dysfunctions in the inflammatory process, especially in patients with sepsis. However, there are very few studies to assess ferritin serum level in the early stage of sepsis diagnosis. Therefore, more research and analysis are needed. This research expects that ferritin serum level that can be easily determined through a blood test can become an early marker of organ dysfunctions in children with sepsis – allowing fast and appropriate disease management to prevent multiple organ dysfunction syndrome and death. This research assesses the association of ferritin level with mortality in septic critically-ill children and determines the correlation of ferritin serum level with PELOD-2 score.

## MATERIALS AND METHODS

This research was a cross-sectional study carried out to pediatric patients with sepsis in the PICU Haji Adam Malik and Universitas Sumatera Utara hospitals and was conducted in June 2021 to January 2022. The research subjects were patients aged between 1 and 18 years old admitted to the PICU with sepsis – including severe sepsis and septic shock condition from June 2021 to January 2022. Exclusion criteria were patients with malignancy, patients receiving blood

transfusion in the last three months, and patients refusing to participate in this study. There were complete blood work, ferritin serum level check, and PELOD-2 score calculation based on the vital signs and laboratory results which were carried out on the first and third day of hospital stay to all the research subjects.

## Ethical approval

This study was approved by the Research Ethics Committee of Universitas Sumatera Utara No 668/KEP/USU/2021.

## Data analysis

The correlation of ferritin serum level and PELOD-2 score was measured using Spearman correlation test with  $p < 0.05$  indicating a significant correlation. Kolmogorov Smirnov normality test was conducted to determine the distribution data. Significance level and confidence interval used were  $p < 0.05$  and 95%, respectively.

## RESULTS

Sixty patients aged between 1 and 18 years old admitted to the PICU with sepsis were involved in this study where 61.7% were male (Figure 1).

The underlying diseases were acute respiratory distress syndrome, central nervous system infection, gastrointestinal diseases, congenital heart failure, and acute kidney injury. The characteristics of subjects were mentioned in Table 1. Over half of the research subjects had good nutritional status, while 12 patients (20%) have severe malnutrition and one patient (1.7%) with obesity. The majority of patients received treatment in the hospital for less than 7 days. There were 9 deaths (15%) recorded, while the rest of the patients (85%) were discharged from PICU to the inpatient ward.

Ferritin serum level showed a median value of 480 ng/mL (24.7 – 22652 ng/mL). From all the patients treated in PICU, there were 32 patients (53.3%) with ferritin serum level above 500 ng/mL, 16 patients (26.7%) with ferritin serum level between 200 and 500 ng/L, and 12 patients (20%) with ferritin serum level below 200 ng/mL (Table 2). Using Spearman correlation test showed a significant correlation

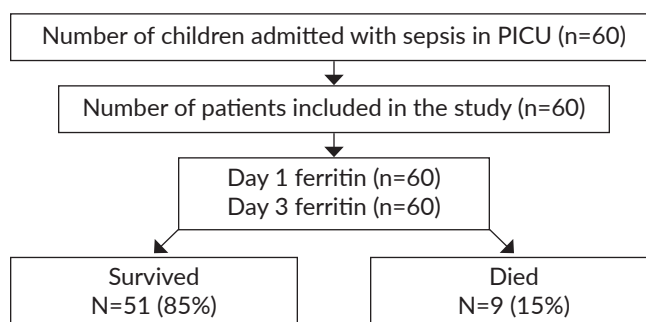


Figure 1. Study flow.

**Table 1.** Characteristics of Subjects

Characteristics	n (Percentage)
<b>Gender</b>	
Boys	37 (61.7%)
Girls	23 (38.3%)
<b>Age</b>	
1-5 years old	15 (25%)
6-10 years old	27 (45%)
11-18 years old	18 (30%)
<b>Length of hospital stay</b>	
<7 days	51 (85%)
≥7 days	9 (15%)
<b>Nutritional status</b>	
Normal	38 (63.3%)
Moderate malnutrition	9 (15%)
Severe malnutrition	12 (20%)
Obesity	1 (1.7%)
<b>Outcome</b>	
Died	9 (15%)
Discharged to ward	51 (85%)
<b>PELOD-2 score<sup>†</sup></b>	4 (0-9)

<sup>†</sup>median (min-max)

**Table 2.** Serum Ferritin Level of Patients

Serum ferritin levels (ng/ml)	n (Percentage)
<200	12 (20%)
200-500	16 (26.7%)
>500	32 (53.3%)

**Table 3.** Correlation of Serum Ferritin Level and PELOD-2 Score

Hospital stay	Variable	Median (range)	p	r
<b>Day 1</b>	PELOD-2 score	4 (0-9)	0.027*	0.36
	Ferritin (ng/mL)	480 (24.7 - 22652)		
<b>Day 3</b>	PELOD-2 score	4 (0-12)	0.075	0.18
	Ferritin (ng/mL)	302.3(98 - 2000)		

\*p<0.05

(p=0.027) between ferritin serum level and PELOD-2 score on day 1 hospital stay and statistically insignificant correlation (p=0.075) between ferritin serum level and PELOD-2 score on day 3 hospital stay (Table 3).

## DISCUSSION

High serum ferritin levels are observed in children with sepsis. In this research, from all the patients treated in PICU, there were 32 patients (53.3%) with ferritin serum level above 500 ng/mL, 16 patients (26.7%) with ferritin serum level between 200 and 500 ng/L, and 12 patients (20%) with ferritin serum level below 200 ng/mL. In Brazilian children with severe sepsis and septic shock, ferritin level <200 ng/ml was associated with 23% mortality, while ferritin 200-500 ng/ml was associated with 9% mortality, and a hyperferritinemic response where the level of serum

ferritin >500 ng/ml was associated with 58% mortality. The study in Seattle Children’s hospital stated that ferritin serum level ≥1,000 ng/ml and ≥3,000 ng/ml had an elevated risk of intensive care admission and death over the next five years.<sup>13-16</sup> The mortality rate in this research was 15% with a median PELOD-2 score of 4 ranging from 0 – 9. Generally, the cut-off value of serum ferritin level in sepsis cases is above 500 ng/mL. This condition is defined as hyperferritinemic, and the level greater than 1,000 ng/mL was associated with a five-fold increase in mortality risk.<sup>17</sup>

The association between ferritin level and outcome in children has not been reported before. This research showed that ferritin levels were significantly correlated with PELOD-2 score. The data may indicate that some patients had improved disease prognosis, while some had worsened prognosis. This finding was consistent with the previous reports in adults showing an association between ferritin and severity of diseases with sepsis diagnosis.<sup>11</sup> In spite of the data, Williams et al. concluded that serial serum ferritin level predicted neither organ dysfunction nor mortality in pediatric sepsis with tropical infections. Daily PELOD-2 and PRISM-III predicted unfavorable outcomes better than ferritin.<sup>18</sup> Serum ferritin has emerged as an independent marker predicting the outcome of critically ill patients when it was associated with septic shock and severe sepsis that affected the mortality.<sup>19</sup> Serum ferritin level may still become an early marker of organ dysfunction in the intensive care unit until PELOD-2 or PRISM-III diagnosis are established. Early indication may allow better disease management to provide better prognosis and lower mortality.

In intensive care unit, early diagnosis and sepsis stratification is important to initiate timely and specific treatment and provide prognostication. Proinflammatory cytokines such as IL-6, IL-8, and tumor necrosis stimulate the synthesis of ferritin. The hyperferritinemic sepsis then leads to iron-induced hydroxyl radical formation leading to oxidative damages.<sup>20</sup> Serum ferritin rose significantly in patients with septic shock despite iron deficiency and it seemed to correlate with the severity of inflammation and organ dysfunction.<sup>21</sup> It is reasonable for iron deficiency anemia to be considered as one of factors which may also affect the ferritin levels in sepsis.<sup>22</sup>

To the extent of this study to be implemented in the intensive care units, iron deficiency anemia prevalence needs to be taken into account. In Indonesia, one of the low-middle income countries, the prevalence of iron deficiency anemia (IDA) in 50 school-aged children was at 32%, while a retrospective study involving 709 laboratory records of Indonesian children and adolescents showed the prevalence of 16% in the 5 - 11.9 years old age group and 15.2% in the 12 - 18 years age group.<sup>23</sup> The effect of iron deficiency and infection on the ferritin level may lead to a higher ferritin threshold to identify iron depleted stores among infected patients (30-100 ng/ml to identify iron depleted storage among infected patients, while <12-15 ng/ml in non-infected patients).<sup>21</sup>

There are some potential limitations in our study. First, this is a single-center study with the limitation of sample size. Second, we did not exclude the patients with hepatic abnormality that may affected the serum ferritin level.

## CONCLUSION

Ferritin serum level is effective to be an early indicator of organ dysfunction until PELOD-2 score assessment is established. Ferritin serum level showed positive correlation with PELOD-2 score and there was a link between elevated serum ferritin and worse disease prognosis.

## Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

## Author Disclosure

All authors declared no conflicts of interest.

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## APPENDIX

### Appendix. PELOD-2 Scoring System

Organ dysfunctions and variables	Points by severity levels						
	0	1	2	3	4	5	6
<b>Neurologic</b>							
Glasgow coma score	SII	5-10			3-4		
Pupillary reaction	Both reactive					Both fixed	
<b>Cardiovascular</b>							
Lactatemia (mmol/L)	<5.0	5.0-10.9			SII.0		
Mean arterial pressure (mmHg) (months)							
0-<1	S46		31-45	17-30			≤16
1-11	S55		39-54	25-38			≤24
12-23	S60		44-59	31-43			≤30
24-59	S62		46-61	32-44			≤31
60-143	S65		49-64	36-48			≤35
SI44	S67		52-66	38-51			≤37
<b>Renal</b>							
Creatinine (mmol/L) (months)							
0-<1	≤69		S70				
1-11	≤22		S23				
12-23	≤34		S35				
24-59	≤50		S51				
60-143	≤58		S59				
SI44	≤92		S93				
<b>Respiratory</b>							
PaO <sub>2</sub> (mmHg) / FiO <sub>2</sub>	S61		≤60				
PaCO <sub>2</sub> (mmHg)	≤58	59-94		S95			
Invasive ventilation	No			Yes			
<b>Hematologic</b>							
WBC count (x10 <sup>9</sup> /L)	>2		≤2				
Platelets (x10 <sup>9</sup> /L)	SI42	77-141	≤76				

PELOD-2 score ≥11 = sepsis