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The Role of Ferritin Serum Level as Predictor Sepsis Mortality on Children in Dr. Moewardi Hospital of Surakarta

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ABSTRACT

Background: Sepsis cause death in the worldwide pediatric population. Eestablishing the diagnosis of sepsis in children is challenging because the symptoms are varied and not specific. Serum ferritin is an acute phase protein which can be elevated in sepsis. This study aimed to determine the role of ferritin level as a predictor for sepsis mortality in pediatric patient
Subjects and Method: A cross sectional study was conducted in children aged between 1 months and 18 years old diagnosed with sepsis who were treated at Dr. Moewardi General Hospital, Surakarta from November 2021 to April 2022. The statistical analysis used SPSS 25 with $p<0.05$ was considered significant. The cut off point of serum ferritin level was determined with ROC curve.
Results: A cross sectional study was conducted in children aged between 1 months and 18 years old diagnosed with sepsis who were treated at Dr. Moewardi General Hospital, Surakarta from November 2021 to April 2022. The statistical analysis used SPSS 25 with $p<0.05$ was considered significant. The cut off point of serum ferritin level was determined with ROC curve.
Conclusion: Serum ferritin level can be predictor of mortality in children with sepsis.

Keywords: ferritin, mortality in sepsis, children.

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BACKGROUND

Sepsis causes death in pediatric population worldwide with an estimated insidence of 7.5 million each year. In the United States of 72,000 children hospitalized with sepsis 25% of them died (Matias et al., 2016). The Global Burden of Disease Study stated that children under the 5 years of age who died from sepsis were estimated to be 5 million children each year and 60% - 80% of deaths occured in developing countries (Yo et al., 2018). Globally, it is estimated that there are 22 cases of sepsis in children and 2,202 cases of neonatal sepsis that occur every 100,000 people or live births per year (Weiss et al., 2020).

Making the diagnosis of sepsis in children in daily practice is very difficult becau-

se the symptoms of sepsis in children are varied and not specific, while microbiological culture results takes 48-72 hours and false negative often occur. Using biomarkers can show the presence or absence and severity of sepsis. Biomarkers also play a role in prognosis, therapy and complications of sepsis in the occurrence of organ dysfunction. In the last decade it was known that C-reactive and procalcitonin are good markers of infection and routinely examined in patients, but they are less specific to differentiate between viruses and bacteria infection. There are several new markers that are interesting to study, one of which is ferritin (Sharma et al., 2018).

Ferritin is a protein which plays important role in the body for iron storage and it also describes the condition of iron storage in tissues (Atjo et al., 2015). In the regulation of cellular homeostasis, iron can be stored in a non-toxic form and will be used by cell metabolism if needed and ferritin is the main iron reserve protein in the body. Ferritin in addition to iron reserves, is also a protein in acute inflammation which increases when there are cytokines in the circulation (Aderson et al., 2017; Tonial et al., 2020).

Studies on the effect ferritin on sepsis have been carried out in several countries such as Brazil by Garcia et all and India by Sharman et all that ferritin increase in septic conditions in children, but to the author's knowledge there has not been any study conducted on the effect of ferritin on sepsis in children in Indonesia. Hence, we performed this study in order to determine the role of ferritin in predicting mortality of children with sepsis.

SUBJECTS AND METHOD

1. Study Design

This research used a cross-sectional design. It was performed in Dr. Moewardi General Hospital, Surakarta, Indonesia from November 2021 to April 2022

2. Population and Sample

The population of this study were pediatric patients diagnosed with sepsis aged between 1 month old and 18 years old who were treated at the Pediatric High Care Unit and Pediatric ward. We used consecutive sampling technique. We excluded patients suffering from thalassemia and aplastic anemia receiving routine blood transfusions.

3. Study Variable

The dependent variable was the mortality. The independent was serum ferritin level.

4. Operational Definition of Variables

Sepsis was defined as p-SOFA score $\geq$ 8.

Serun feritin level taken from the blood sample.

Mortalitas was determined as death occuring during hospitalization.

Age was classified into < 1 years, 1-5 years, and >5 years.

Sex was categorized as male and female

5. Study Instrument

The demographic data were obtained by interviewing with the patients or caregivers. The patient's medical status data were taken from medical record of patient. The serum ferritin levels were examined in clinical pathology laboratory of Dr. Moewardi General Hospital, Surakarta, Indonesia

6. Data Analysis

We analysed all the data statistically with SPSS-based statistical software (version 25). Chi-square test was applied for bivariate analisys, and $p < 0.05$ was considered statistically significant. The cut-off point of serum ferritin level was determined with ROC curve.

7. Research Ethics

This study was approved by the Ethics Committee of Dr. Moewardi General Hospital, Surakarta, Indonesia.

RESULTS

There were 20 septic patients with the pSOFA score ≥ 8 who were treated in the Children's HCU and Pediatric Ward of Dr. Moewardi General Hospital during the study period. Sixty five percent of subjects were male. The study subjects were dominated by children aged > 5 years old (65%). The most common comorbidity was pneumonia (40%) followed by peritonitis (35%) and encephalitis (10%). Moreover 65% subjects had bacterial growth in their culture examination (Table 1).

Table 1. The Subjects characteristics

Characteristics	Frequency	Percentage (%)
Gender		
Male	13	65
Female	7	35
Age		
≤1 years	5	25
1-5 years	2	10
>5 years	13	65
Comorbidity		
Pneumonia	8	40
Peritonitis	7	35
Encephalitis	2	10
Uremic encephalopathy	1	5
Cancer	1	5
Burn Injury	1	5
Bacterial Culture		
Growth	13	65
No growth	5	25
No Culture	2	10

Table 2. Ferritin Serum Results

Ferritin Serum Level	Survival	Mortality
< 500	6	1
500 – 1000	5	1
1000 – 1500	4	3
> 1500	5	3

Table 3. Serum Ferritin Levels

	Serum Ferritin Levels				
Outcome	**N**	**Min**	**Max**	**Mean**	**SD**
Survival	12	50	1675	703.66	586.16
Mortality	8	201	2000	1257	550.12
Total	20	50	2000	925	622.712

Of all 8 subjects who died, 75% of them had ferritin levels of more than 1000 (Table 2). Statistical analysis of ferritin levels as a predictor of mortality in septic patients. The numbers of patients who died during the study period were 8 patients with the mean ferritin level of 1257 ng/ml and a standard deviation of 550.12 ng/ml (Table 3).

The comparison of ferritin levels between the survival and mortality group was demonstrated in Figure 1. in which the

distribution of ferritin level was higher in subjects who died than that of who survived.

T-test analisys obtained, the T value of -2.118 with a probability value of 0.048 indicating a significant difference in ferritin levels between the survival and the mortality groups.

We analyzed serum ferritin data on mortality in sepsis patients using the receiver operating characteristic (ROC) curve. Obtaining area under curve (AUC) of 0.760 and the best cut-off for ferritin levels to predict mortality in sepsis patients was 975 ng/ml with a sensitivity of 87.5% and a specificity of 75%. Based on this the cut-off , 7 patients (70%) who died had ferritin levels higher than 975 ng/ml, and only 1 patient (10%) who died had serum ferritin levels under 975 ng/ml. Chi-square test obtained significant differences mortality rate of patients with ferritin levels of more than 975 ng/ml compared to that of patients with serum ferritin levels under 975 ng/ml (p = 0.006).

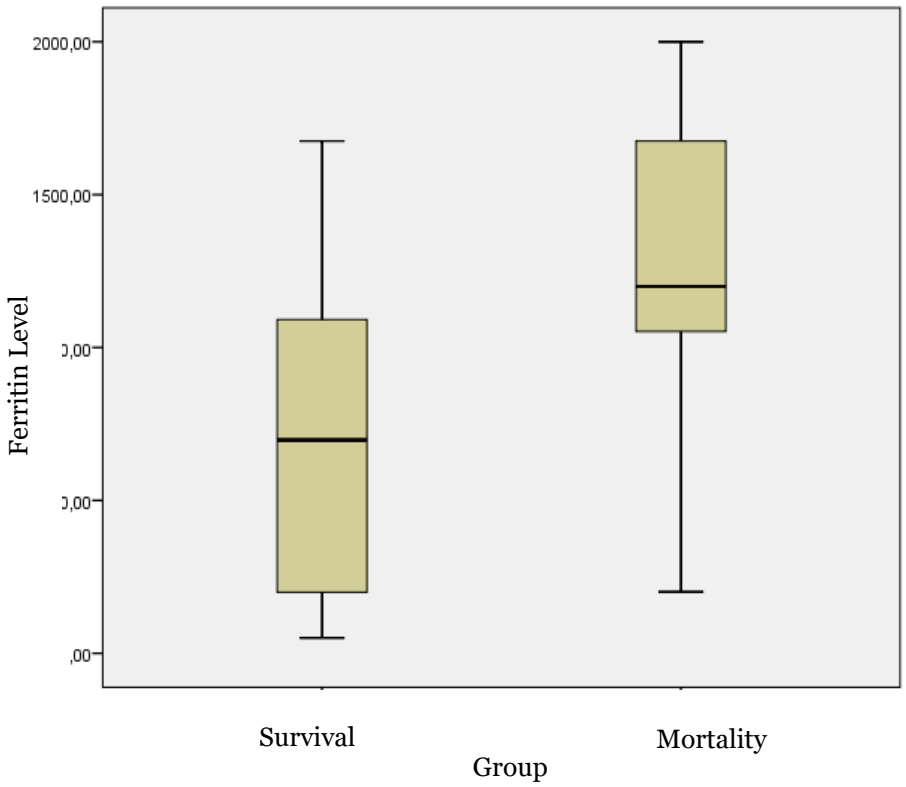

Figure 1. Box and Whisker Plots

Table 4. T-test Analysis Results

Group	Mean	SD	T value	P value	95%CI	
					Lower Limit	Upper Limit
Survival	703.66	586.16	-2.118	0.048	4.418	1102.24
Mortality	1257	550.12				

Table 5. Cut-off value of ferritin serum on mortality in sepsis patients

Variable	AUC	Cut-off	Sensitivity	specificity	P value
Ferritin Level	0.760	975	0.875	0.750	0.006

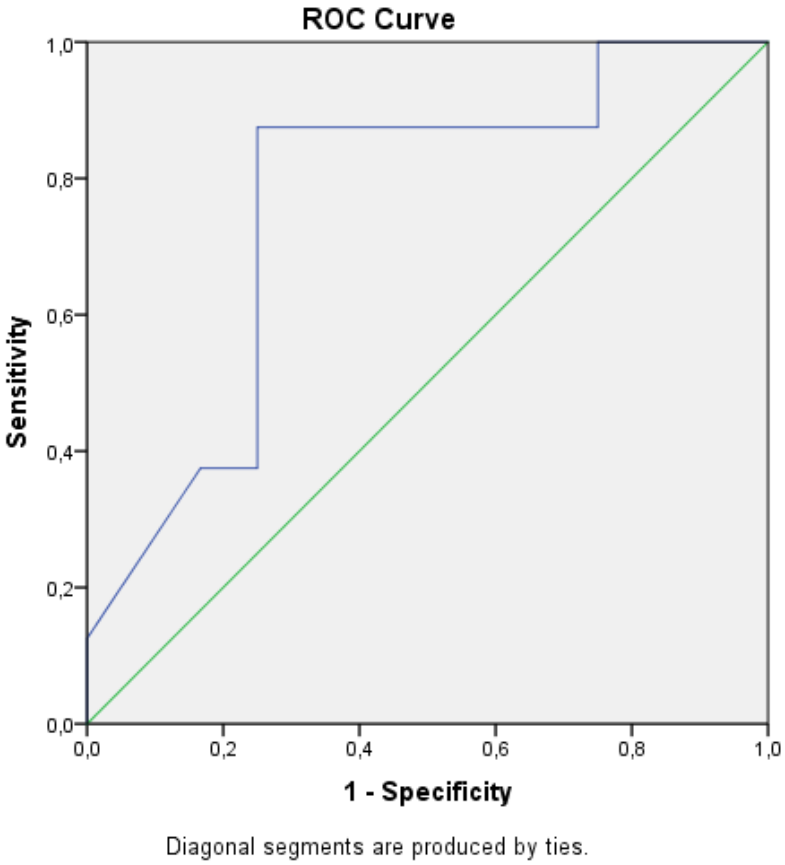

Figure 2. ROC Curve of ferritin serum level in Sepsis patients who died

DISCUSSION

The mechanism of ferritin synthesis in inflammation is through cytokine responses on transcription and translation levels of various cells including mesenchymal, hepatocytes, monocytes and macrophages cells. Ferritin is an acute phase reactant with acute and chronic levels of inflammation in infectious diseases, rheumatology, hematology and malignancy diseases (Kernan et al, 2017).

Previous studies on hyperferritinemia reported that serum ferritin level is indirectly associated with sepsis mortality in children. A study by Garcia et al also revealed that children with sepsis who had ferritin levels of > 500 ng/L were associated with 58% mortality. Bennett et al, in their a single center retrospective study showed an increase mortality rate in children with sepsis with ferritin levels > 1000 ng/dL and > 3000 ng/dL. Moreover Carcillo et al reported that plasma ferritin of 1980 ng/L and over is associated with a very high mortality rate in children with severe sepsis (kernan, 2017; Wiliam et al, 2020). These findings are accordance with our study, in which the mean serum ferritin level in all pediatric patients with sepsis who died was 1257 ng /ml.

This study demonstrates an increase in serum ferritin level of children with sepsis, whereas patients who did not survive had higher ferritin levels than those who survived. This elevation of serum ferritin level is likely due to acute phase inflammation that triggered by pro-inflammatory factors such as TNF-α, IL-2 and IL-10. The source of ferritin production in acute inflammation result from secretion by macro-

phages and cell damage. During viral infections, IL-18 is released inducing an increase in ferritin and stimulating TH-1 immune response which can induce IFN-γ to protect the host from intracellular microorganisms. In contrast to bacterial infection, it is usually associated with extensive over expression of IL-1β effecting an IL-6 to trigger hepatocytic CRP, which acts as an initial host defense by promoting bacterial phagocytosis. In addition, increased ferritin in sepsis can occur as a consequence blockade of iron release due to virulence factors induced by microorganisms in the acute phase (Sharma et al, 2018; Chiou et al, 2018; slats et al, 2016).

The ROC curve in our study had AUC value of 0.760 with the serum ferritin cut-off point for predicting mortality in sepsis patients of 975 ng/ml which a sensitivity of 87.5 %, specificity of 75 %, and p value of 0.006. Meanwhile Sharma et al study in childre with sepsis reported that elevated ferritin levels of > 1000 ng/L had a sensitivity of 58.9% and a specificity of 75.3% as a predictor of death with a relative risk of 2.38 (95% CI: 1.57-3.61) and an odds ratio of 4.36 (95% CI: 2.14 -8.88) while the AUC value was 0.68 (Sharma et al., 2018).

In conclusion, in septic patients the serum ferritin level with the cut-off point of 975 ng/ml has high sensitivity and specificity to predict mortality. Therefore serum ferritin level can be used as mortality predictor among pediatric patients with sepsis.

AUTHOR CONTRIBUTION

Agus Sucianto is the lead author who conducted the research, conducted data analysis, and wrote the manuscript. Pudjiastuti examined the background and discussion of the research. Diah Lintang Kawuryan formulated the research framework.

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This research was funded independently.

CONFLICT OF INTERESTS

There is no conflict of interest in this study.

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