GSC Advanced Research and Reviews

eISSN: 2582-4597 CODEN (USA): GARRC2

Cross Ref DOI: 10.30574/gscarr

Journal homepage: https://gsconlinepress.com/journals/gscarr/

(RESEARCH ARTICLE)

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Relationship between serum ferritin level and outcome of septic shock in children

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GSC Advanced Research and Reviews, 2023, 17(01), 023–031

Publication history: Received on 08 August 2023; revised on 05 October 2023; accepted on 7 October 2023

Article DOI: https://doi.org/10.30574/gscarr.2023.17.1.0373

Abstract

Background Sepsis is a life-threatening organ dysfunction caused by dysregulation of the immune system against infection. Sepsis that leads to septic shock is one of the causes of morbidity and mortality in children who are treated in intensive care and inpatient rooms. Ferritin is a protein whose synthesis is increased in inflammatory and infectious conditions and can be a marker of active infection. The cut off ferritin in septic shock was not established and not absolutely clear in our patients.

Objective To determine the cut-off value of ferritin levels in patient with septic shock and the relationship between high serum ferritin levels with poor outcome (mortality) in pediatric patients with septic shock.

Methods This study used an observational-analytic design with prospective cohort study design. The research was conducted in pediatric ward, Prof. Dr. I.G.N.G. Ngoerah hospital from October 2021 to August 2022. Data analysis was done in 2 steps, first by using receiver operator characteristic curves to find the optimal cut-off point value and the second step was bivariate and multivariate analysis to determine the relationship between ferritin levels and the outcome of septic shock in children. The significance level (α) of this study was set with probability value less than 0.05.

Results This study involved 76 subjects, 49 subjects died and 27 subjects survive. The Area Under Curve of ferritin levels from ROC curve obtained was 83.7% (p=0.001, 95% CI 74.2%-93.1%). The cut off for ferritin level 660.78 ng/ml gave sensitivity 85.7% and specificity 77.8% for mortality in patients with septic shock. The value of ferritin levels ≥ 660.78 generate mortality risk 39.50 times (95% CI 8.057 – 183.422) in pediatric patients with septic shock.

Conclusion Higher ferritin levels can increase the risk of mortality in pediatric septic shock patients.

Keywords: Septic Shock; Children; Ferritin; Mortality

1. Introduction

Sepsis is one of the causes of morbidity and mortality in children treated in intensive care and inpatient rooms. Sepsis is a collection of clinical symptoms caused by dysregulation of the body's response to infection[1]. Sepsis is initiated by an infectious process. Infection can cause sepsis which is characterized by organ dysfunction due to dysregulation of immune system. Vascular endothelial damage triggers refractory hypotension, multi-organ failure that is difficult to treat and is the most common cause of mortality in septic patients[2]. At various ages, sepsis can progress to severe sepsis and septic shock. Septic shock can manifest in two main clinical features, cold shock and warm shock. In these two situations, clinical signs of shock will appear beside the cardiovascular system and neurological function is most often impaired. In general, blood pressure is maintained normally until the late phase of shock and hypotension is a

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terminal sign of shock[1]. The existence of early markers for the assessment of the outcome in sepsis patients is very necessary. This will facilitate clinical decision-making in terms of determining more aggressive diagnostic or therapeutic measures, optimizing available resources and providing appropriate counseling to patients or their families.

Global data showed mortality from sepsis in children is estimated 60% in children under 5 years of age. Morbidity and mortality rates of sepsis patients in developed and developing countries are still high. Epidemiological data show the incidence of severe sepsis in the United States in 1995 was 0.56 cases per 1000 children per year which increased to 0.89 cases per 1000 children in 2005. The incidence of severe sepsis was significantly higher in younger age groups[1,2].

Ferritin is an iron storage protein whose production is increased in acute phase of infection. In critical conditions caused by sepsis, the systemic inflammatory response (SIRS) will trigger pro-inflammatory cytokines such as interleukin 6, interleukin 8 and tumor necrosis factor (TNF). This pro-inflammatory cytokine triggers ferritin synthesis so that ferritin level will increase. Elevated ferritin levels may indicate inflammatory reaction due to infection in the body.[3]

Biomarkers for infection that are commonly used and associated with the degree of infection and its prognosis are procalcitonin levels and C-reactive protein levels. On the other hand, not all health centers have this examination modality, in addition the price relatively expensive for biomarker examination. Examination of serum ferritin level is more affordable than other infection biomarkers. Several studies have reported the relationship between ferritin level and the severity of sepsis, but they are still limited and have not been studied further. Researchers want to investigate further about the relationship between serum ferritin level and outcomes of pediatric septic shock patients so that the existing data are expected to be used as basic for providing management in children with septic shock.

2. Method

This prospective cohort study with inclusion criteria including all adolescence aged 1 month - 18 years old who first diagnosed septic shock in Prof. Ngoerah General Hospital Denpasar Bali and parents agreed to their children to participate in the study and signed informed consent. Exclusion criteria were alcohol abused, with metabolic disease, with haemolytic anemia, repeated transfusion in the last 1 month, hyperthyroidism and hemochromatosis. Subjects were taken consecutively and stopped once minimum subjects were reached.

Sepsis defined as life-threatening organ dysfunction caused by dysregulation of immune response to infection and is determined when the PELOD-2 score is ≥ 7. Laboratorium data supporting PELOD-2 score was performed in Prof Ngoerah hospital. Septic shock defined as sepsis with persistent cardiovascular dysfunction after initial fluid resuscitation (40 ml/kg intravascular in less than 1 hour) or blood pressure drop (hypotension) < 50^{th} percentile for age or requiring vasoactive drugs to maintain blood pressure within normal range (dopamine, dobutamine, epinephrine, or norepinephrine), or two of the following conditions: Metabolic acidosis with base deficit > 5.0 mEq/L, increased lactate 2 times normal, oligouria with urine output < 0.5 ml/kg/hour, capillary refill time > 5 seconds, difference between core temperature and peripheral temperature > 3ºC[4]. Ferritin is the level of ferritin that is known through examination of the subject's blood serum using alinity-I machine. Examination of ferritin levels was carried out on subjects when the diagnosis of septic shock was made, maximum on the 8^{th} day after being diagnosed with septic shock. Ferritin level was expressed in unit of ng/ml, and are presented as numerical measurement scale which is then categorized based on the cut-off value. Outcome is determined by observing the subject's outcome until discharged from hospital, which is categorized into alive or dead. The other variables were age, gender, nutrition status, comorbidity (epilepsy, congenital heart disease, malignancy, diabetes, chronic kidney disease, systemic lupus erythematosus, COVID-19), source of infection, bacteremia, and length of stay at hospital.

Data analysis using SPSS computer software. Data analysis includes descriptive analysis and hypothesis testing. In descriptive analysis, data with categorical scale is expressed in frequency distribution and percentage, while data with continuous scale is expressed in mean and standard deviation, but if the data is not normally distributed, the data will be expressed in median with minimum to maximum value. Data analysis was carried out in two stages. The first step is to find the cut-off point with the receiver operator curve (ROC). This was done because several previous studies provided various cut-off point values, so it could not be used as an absolute reference. The next step is to find the relationship between ferritin levels and the outcome of septic shock using bivariate analysis and followed by multivariate analysis. Pearson chi-square is used to relate 2 categorical variables based on the ferritin cut off value with the outcome of survive or death. Multivariate analysis using logistic regression was performed to control confounding variables if these variables were significantly related to the dependent variable. The level of significance (α) of this study was set at probability value less than 0.05.[5]

3. Result

This research was conducted at the General Hospital Prof. DR. I.G.N.G. Ngoerah Denpasar from October 2021 to August 2022. During the study period there were 82 children with septic shock, but 6 children were excluded so that 76 patients became the research subjects. Study settings were shown in Figure 1.

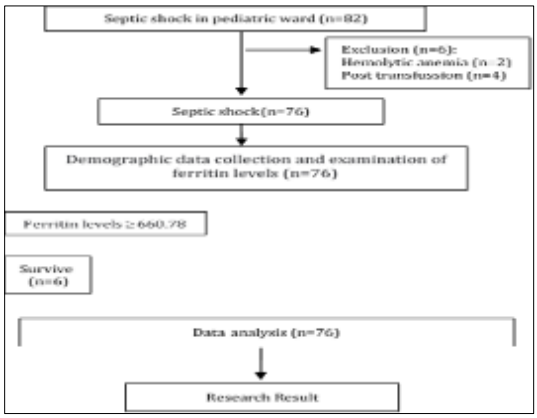

Figure 1 Study flow

A total of 76 research subjects were analyzed in this study. Characteristics of subjects with septic shock who died in this study, including 71.1% female; with 90% severe malnutrition; with the source of infection from the respiratory tract 68.9%; without comorbid 64.5%; and with negative blood culture results 66.7%. Positive blood culture result was obtained in 25% of all subjects. The microorganisms found included *Burkholderia cepacea, Eschericia colli, Klebsiella pneumonia, Acinetobacter baumanii, Staphylococcus aureus, Staphylococcus haemolyticus, Streptococcus pyogens, Pseudomonas aeruginosa, Acinetobacter iwofii, and Candida ssp*. Details of the characteristics of the research sample are shown in Table 1.

Table 1 Characteristics of subjects

Characteristics	**Died (n=49)**	**Survived (n=27)**	**Total (n=76)**
Age, n (%)			
<13 months	15 (57.7)	11 (42.3)	26 (100)
≥13 months	34 (68.0)	16 (32.0)	50 (100)
Gender, n (%)			
Male	22 (57.9)	16 (42.1)	38 (100)
Female	27 (71.1)	11 (28.9)	38 (100)
Nutritional status, n (%)			
Well nourished	24 (68.9)	11 (33.4)	35 (100)
Moderate malnutrition	10 (55.6)	8 (44.4)	18 (100)
Severe malnutrition	9 (90.0)	1 (10.0)	10 (100)
Overweight and obesity	6 (46.2)	7 (53.8)	13 (100)
Source of infection, n (%)			
Respiratory tract	31 (61.89)	14 (31.1)	45 (100)
Central nervous system	9 (69.2)	4 (30.8)	13 (100)
Gastrointestinal tract	6 (54.5)	5 (45.5)	11 (100)

	Urinary tract	3 (50.0)	3 (50.0)	6 (100)
	Skin	0 ((0)	1 (100.0)	1 (100)
Bacteremia, n (%)				
	Positive	11 (57.9)	8 (42.1)	19 (100)
	Negative	38 (66.7)	19 (33.3)	57 (100)
Comorbid, n (%)				
	Without comorbid	26 (64.5)	13 (35.5)	39 (100)
	Epilepsy	5 (38.5)	8 (61.5)	13 (100)
	Congenital heart disease	5 (83.3)	1 (16.7)	6 (100)
	Diabetes melitus	1 (25.0)	3 (75.0)	4 (100)
	Chronic kidney disease	2 (100.0)	0 (0.0)	2 (100)
	Systemic Lupus Erythematosus	2 (50.0)	2 (50.0)	4 (100)
	COVID-19	6 (100.0)	0 (0.0)	6 (100)
Length of stay, days, median (min-max)		6 (1-94)	30 (3-99)	10 (1-99)
Ferritin, ng/ml, median (min-max)		1618.32 (204.41-33511.20)	518.0 (89.63-4597.0)	1003.18 (89.63-33511.57)

To determine the relationship between serum ferritin levels and the outcome of subjects, the Mann-Whitney test (comparative hypothesis test for numerical variables which was not distributed normally) was performed because the data for value of ferritin level were not normally distributed. The statistical test showed that there was a statistically significant relationship between ferritin levels and mortality (p=0.001). Receiver Operating Characteristic (ROC) analysis was carried out to obtain the ROC curve as result of the trade-off between the sensitivity and specificity of various cut points of ferritin levels on the outcome variable (death) of the research subjects (Figure 2). The ROC procedure will get the Area Under Curve (AUC) value.

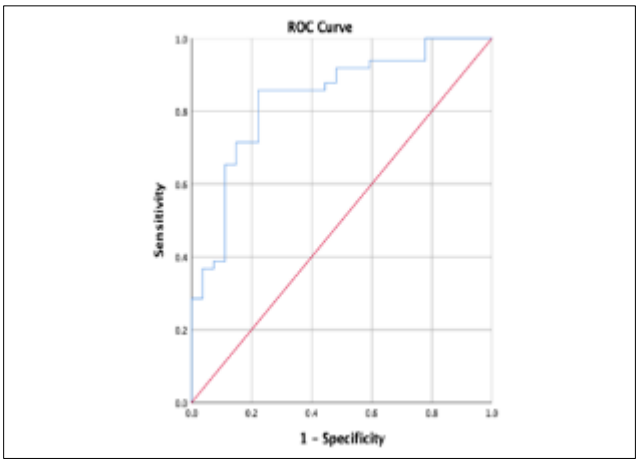

Figure 2 ROC curve

The value of the under curved area (AUC) can be used to obtain visually and numerically the predictive value (AUC) of diagnostic tests in general. AUC value that is below 60% is the worst values and value close to 100% is the best values. The AUC value of ferritin content from the ROC curve obtained an area of 83.7% (p=0.001, 95% CI 74.2%-93.1%), indicating a good AUC. The cut-off ferritin level of 660.78 ng/ml gave sensitivity 85.7% and specifity 77.8% for mortality in patients with septic shock.

Bivariate analysis using the chi-square test was performed to determine the relationship of ferritin levels with mortality in children with septic shock. The magnitude of the Odds Ratio (OR) with 95% confidence interval can be seen in Table 2. Multivariate analysis with logistic regression was carried out after analysis for interaction variables was done and analysis with confounder (gender, age, severe malnutrition, bacteremia, and source of infection from respiratory tract). Multivariate analysis found that ferritin levels ≥ 660.78 ng/ml was statistically significant for mortality in patients with septic shock, with OR 39.501 (95% CI 8.507 – 183.442). Patients with septic shock who have ferritin levels ≥ 660.78 have 91.92% probability of dying. The results of the analysis are shown in Table 3.

Table 2 Bivariate analysis

Parameter	**Died (n=49)**	**Survived (n=27)**	**OR (95% CI)**	**p-value**
Cut off ferritin, n (%)			21.0 (6.27-70.40)	0.001
≥660.78	42 (87.5)	6 (12.5)		
<660.78	7 (25.0)	21 (75.0)		

Table 3 Multivariate analysis

	Variables	**Coefficient**	**Wald**	**p-value**	**OR**	**95% CI**	
Step 1	Ferritin ≥660.78	3.926	20.766	0.000	50.705	Minimal	Maximal
	Gender	0.273	0.128	0.721	1.313	9.369	274.403
	Age < 13 months	-1.032	1.705	0.192	0.356	0.295	5.855
	Severe malnutrition	2.414	2.562	11.174	11.174	0.076	1.677
	Bacteremia	-1.209	2.170	0.298	0.298	0.582	214.609
	Source of infection (respiratory tract)	0.349	0.239	1.418	1.418	0.060	1.491
	Constant	-1.364	2.680	0.256	0.256	0.350	5.752
Step 2	Ferritin ≥660.78	3.840	22.030	0.000	46.513	9.359	214.609
	Age < 13 months	-1.048	1.783	0.182	0.351	0.075	1.632
	Severe malnutrition	2.508	2.824	0.093	12.276	0.659	228.673
	Bacteremia	-1.233	2.251	0.134	0.292	0.058	1.459
	Source of infection (respiratory tract)	0.354		0.620	1.425	0.352	5.772
	Constant	-1.171	0.246	0.062	0.363		
Step 3	Ferritin ≥660.78	3.842	22.143	0.000	46.640	9.412	231.109
	Age < 13 months	-0.987	1.629	0.202	0.372	0.082	1.697
	Severe malnutrition	2.651	3.302	0.069	14.166	0.812	247.186
	Bacteremia	-1.196	2.141	0.143	0.302	0.061	1.501
	Constant	-1.013	3.632	0.069	0310		
Step 4	Ferritin ≥660.78	3.676	22.021	0.000	39.501	8.507	183.422
	Severe malnutrition	2.611	3.659	0.056	13.619	0.938	197.790
	Bacteremia	-1.503	3.484	0.062	0.223	0.046	1.078
	Constant	-1.244	6.012	0.014	0.288		

4. Discussion

Seventy-six subjects with septic shock were included in this study. Based on characteristic data, it was found that children aged < 13 months experienced more deaths (57.7%) than those who lived. Wati et al found that the highest proportion of the age group with sepsis was under 2 years of age (57.1%)[6]. Siddique et al. reported that the highest mortality rate in children treated in the Pediatric Intensive Care Unit was under 1 year of age.[7] Shashikala et al. and Ramnarayan et al. reported higher mortality rate at younger ages than older ages. At young age, most of the host's immune system is immature. The younger the age, the lower the level of maturity of the immune system so that the ability to eradicate pathogens is also getting weaker. In addition, children under 1 year of age are potentially exposed to infection and malnutrition due to lack of breastfeeding and maternal care [8,9]. This study gave different results, which mortality from septic shock at the age of 13 months was 68%, higher than the age < 13 months, but not significantly different (p = 0.37). This could be because the proportion of age < 13 years was only 1/3 of the total subjects.

Based on characteristic data, male and female gender have the same proportion, as many as 38 (50%) subjects. In the group of subjects who died there were 27 female subjects (77.1%), not significantly different from male subjects (p = 0.234). This study is in line with research conducted by Ghuman et al. in California who obtained similar results. The study found that there was no difference in mortality due to sepsis in prepubertal male and female subjects (p = 0.81), but at the age of puberty, mortality rate in male was higher (p = 0.03). This is often associated with hormonal factors, that is testosterone. At the age of prepuberty testosterone levels are very low, inversely proportional to the age of puberty. Testosterone is generally an immunosuppressant. In addition to hormonal differences, X-chromosome-related genetic differences between the sexes may be a factor, although they do not play large role, given the similar mortality in prepubertal children[10].

Nutritional status in more subjects died than those who survived, which is 9 out of 10 subjects were with severe malnutrition (90%). This study is in accordance with the study by Villegas et al. that found more malnourished children (49.1%) in the group of patients with sepsis died than those who survived (35.5%). Recent surveys reported the incidence of malnutrition which includes moderate and severe malnutrition in hospitalized patients at pediatric intensive care unit ranging from 10%-24%, with high incidence of infection and mortality [11,12]. This study is also in accordance with the study by Schaible et al (6 severe malnutrition of 11 dead subjects vs 3 severe malnutrition of 21 living subjects). Malnutrition, especially severe malnutrition, can increase the host's susceptibility to disease, especially in children and cause secondary immunodeficiency. In addition, chronic infection itself can cause malnutrition, due to increased of metabolism [13]. Complications of malnutrition in children with sepsis can affect the entire system, such as decreased immune response, atrophy and facilitates translocation of gastrointestinal bacteria due to increased intestinal barrier permeability. In the end, children will experience longer wound healing period, other infections or reinfection and increased mortality [14].

This study found that the most common source of infection comes from the respiratory tract. These results are in line with the results of research from Weiss et al. who reported that the most sources of infection in patients with sepsis and septic shock came from the respiratory tract, that was pneumonia [15]. This is because the germs that cause pneumonia are very easy to enter the body through inhalation or aspiration into the lobes of the lungs. In addition, pneumonia can occur before entering the hospital, when receiving medical treatment and during the treatment process [16].

Bacteremia confirmed by positive blood cultures was obtained from 25% of subjects with septic shock and 22.4% of subjects with positive blood cultures died. Research by Hazwani et al. in Saudi Arabia found positive blood cultures in 14.3% of pediatric sepsis cases admitted to the intensive care unit. Most of the subjects with negative blood culture results [17]. Research by Pablo et al in Columbia found positive blood cultures in 33.2% of pediatric subjects with sepsis who were admitted to the PICU [18]. Several factors affect the results of blood cultures, including pre-analytic, analytic and post-analytic factors. This can lead to false negative results, so the diagnosis of sepsis is not based on positive blood culture results [19].

Subjects with comorbidities in this study as many as 62.2% experienced death, more than those who survived. Research by Rech et al. found that comorbidities can worsen the prognosis of septic shock patients admitted to the PICU. In that study it was said that patients with comorbidities had 3.4-fold risk of death compared to those without comorbidities (OR = 3.4; 95% CI 1.3 – 8.4) [20]. This is similar to the research conducted by Ruth et al. who found that patients with comorbidities had risk of death 1.4 times in severe sepsis (OR = 1.49; 95% CI 1.35 – 1.64) [21]. The most common comorbid type in this study was epilepsy, but most of the subjects with epilepsy survived. Subjects with comorbid COVID-19, chronic kidney disease and congenital heart disease mostly died (100%; 100%; 83.3%). COVID-19 infection is an infection caused by the SARS-CoV 2 virus which has become pandemic since early 2020. The death rate is higher

in COVID-19 infections with severe and critical symptoms. Acute respiratory distress syndrome and septic shock accompanying COVID-19 infection are the two most common causes of death [6]. In chronic kidney disease, there is reduced production of IL-2 which reduces the proliferation and differentiation of T cells into effector T-cells. In addition, dendritic cell dysfunction and various costimulatory molecules were also found so that the response to antigens was reduced, thereby reducing the immune response which further increased the risk of death from severe infections [22]. Patients with congenital heart disease had higher mortality rate (17.7 times higher) than those without congenital heart disease. Patients with more complex disorders with heart failure have lower survival rate, but adequate management increases the life expectancy of patients with congenital heart disease[23].

Length of stay in this study in the group who died with median 6 days ranging from 1-94 days, shorter than the length of stay of living subjects. This shorter length of stay can be caused by the condition of the subject with septic shock, which is the final stage of the course of sepsis with high mortality rate so that most of them die in short time. In this study most of the subjects died less than 15 days of treatment and there were only 6 subjects out of 49 subjects (12.2%) with length of stay >15 days. Length of stay is influenced by age, comorbidities, hypermetabolism, organ failure, and nutritional deficiencies Length of stay is an important predictor factor in influencing the outcome of critically ill patients treated at PICU [24].

The mortality rate in this study was 64.4%. Research conducted by Weiss et al. in 26 developed and developing countries, the prevalence of severe sepsis was 8.2% with mortality rate 25%, and there was no difference in mortality between developing and developed countries. The incidence of sepsis in some referral hospitals ranges from 15–37.2%, while death occurs in 37-80% of cases [15]. Priyatiningsih et al. reported that 19.3% of 502 pediatric patients treated at the pediatric intensive care unit (PICU) of Cipto Mangunkusumo Hospital had sepsis with mortality rate of 54%[25]. At Dr. Sardjito Yogyakarta, the average number of cases in the last three years is around 275 per year (25.8%) and the mortality rate is 72.9%[26]. Research in Bali (RSUP Prof. Dr. I.G.N.G Ngoerah) in 2018 found the mortality rate of patients with septic shock was 47.1%[6].This high mortality rate can be due to the fact that the research site is the main referral center of the regional hospital so that most of the patients who come are already in terminal condition.

In this study, the AUC value of ferritin levels on mortality in septic shock patients was 83.7% (p=0.001, 95% CI 74.2%-93.1%). The cut-off ferritin level of 660.78 ng/ml gave a sensitivity of 85.7% and a specificity of 77.8% for mortality in patients with septic shock. This study is in line with several studies that assessed the relationship between ferritin levels and mortality in pediatric sepsis patients. Research by Sarkar et al. in India involving 176 subjects with severe sepsis and septic shock obtained a cut-off ferritin level of 2375 ng/ml has a sensitivity of 96.7% and specificity of 88% in predicting mortality in patients with severe sepsis and septic shock with an AUC of 97% (95% CI 95.2 – 99.6)[27]. Research by Sharma et al. in New Delhi with 149 septic patient subjects showed cut off ferritin level of 1100 ng/ml providing a sensitivity of 58.9% with a specificity of 75.3% in predicting mortality in patients with sepsis and septic shock with an Area Under Curve of 68.5%[28]. Research conducted by Garcia et al. in Brazil involving 36 research subjects found ferritin levels > 500 ng/ml had sensitivity of 64% and specificity of 80% predicting mortality in patients with septic shock and severe sepsis with an AUC of 73%[3].

The results of the study obtained different cut offs due to the different number of samples in each study. These studies support that high levels of ferritin increase the risk of death in patients with sepsis and septic shock. In Indonesia, there are no studies yet that look for cut-off values for ferritin levels in pediatric patients with septic shock.

Bivariate analysis using the chi-square test in this study found that in addition to ferritin levels 660.78 ng/mL associated with mortality of septic shock. The results of multivariate analysis showed that ferritin levels 660.78 ng/mL had a risk of death 39.50 times with 95% CI 8.507 to 183.422 with a probability of death of 91.92%. Confidence intervals that are wide enough can be caused by small number of samples or very heterogenous data. In this study, the number of research subjects was calculated and met the minimum number of subjects, so this wide confidence interval could be caused by very heterogenous ferritin levels on subject who died.

The results of this study are in line with the results of a prospective cohort study conducted by Garcia et al. who had ferritin levels ≥ 500 ng/ml had a 3.2 times risk of death (95% CI 1.3 – 7.9; p = 0.01) in patients with severe sepsis and septic shock[3]. Another study conducted by Sharma et al. found that ferritin levels ≥ 1100 ng/ml were associated with 2.3 times risk of death (95% CI 1.571 – 3.614; p < 0.0001)[28]. Another study by Sarkar et al. showed that ferritin levels ≥ 2375 ng/ml in children with severe sepsis and septic shock were significantly associated with mortality (p < 0.0001)[27]. In 2021 Kulkarni et al. in his study found patients with severe sepsis with serum ferritin levels ≥300 ng/ml compared with patients with serum ferritin levels < 300 ng/ml had a significant difference in the outcome in the form of death (p = 0.001)[29]. The results of this study prove that higher ferritin levels increase the risk of death as poor outcome in patients with severe sepsis and septic shock. Under conditions of inflammation and infection, IL-6 stimulates

the synthesis of ferritin and hepcidin. Increased serum hepcidin can cause an increase in iron in enterocytes and macrophages which can further increase ferritin synthesis. Serum ferritin begins to increase on days 1-2 after an inflammatory reaction or infection and reaches its peak on day 8. Ferritin can increase moderately, from 500 g/L to 700 g/L and can be even higher in infectious conditions, even reaching 10,000 g/L in septic shock conditions[30].

The limitation of this study is that the types of comorbid diseases were not analyzed one by one, due to minimum number of subjects for each comorbid was not counted and in the end only subject classification was carried out based on the presence or absence of comorbidities that affected ferritin levels and the outcome of patients with septic shock. Several types of comorbidities that can also affect ferritin levels are not excluded because it is quite difficult to find subjects with pure septic shock without comorbidities.

5. Conclusion

This study found that higher ferritin level increases the risk of death in pediatric patients with septic shock**.**

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from participant included in the study.

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