



# Correlation between Interleukin-6 and Ferritin Serum in Pediatric Sepsis Patients

Ida Ayu Agung Wijayanti\*, I Wayan Gustawan, I Putu Gede Karyana, I Gusti Lanang Sidiartha, Eka Gunawijaya, Dewi Sutriani Mahalini, AANKP Widnyana

Department of Child Health, Faculty of Medicine, Udayana University, Sanglah Hospital, Bali, Indonesia

## Abstract

**Edited by:** Ksenija Bogoeva-Kostovska

**Citation:** Wijayanti IAA, Gustawan IW, Karyana IPG, Sidiartha IGL, Gunawijaya E, Mahalini DS, Widnyana AANKP. Correlation between Interleukin-6 and Ferritin Serum in Pediatric Sepsis Patients. Open Access Maced J Med Sci. 2022 Feb 13; 10(B):1298-1301. https://doi.org/10.3889/oamjms.2022.8872

**Keywords:** Children; Sepsis; Interleukin-6; Ferritin

\***Correspondence:** Ida Ayu Agung Wijayanti, Department of Child Health, Faculty of Medicine Udayana University/Sanglah Hospital, Bali, Indonesia. E-mail: dayuagungwijayanti@gmail.com

**Received:** 12-Mar-2021

**Revised:** 02-Feb-2022

**Accepted:** 03-Feb-2022

**Copyright:** © 2022 Ida Ayu Agung Wijayanti,

I. Wayan Gustawan, I. Putu Gede Karyana,

I. Gusti Lanang Sidiartha, Eka Gunawijaya,

Dewi Sutriani Mahalini, AANKP Widnyana

**Funding:** This research did not receive any financial support

**Competing Interests:** The authors have declared that no competing interests exist

**Open Access:** This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

**BACKGROUND:** Sepsis is the leading cause of death in children. Sepsis is caused by dysregulation of immune system that triggers the production of pro-inflammatory cytokines, one of which is interleukin-6 (IL-6). In addition, several markers of infection also increase such as c-reactive protein (CRP) and procalcitonin (PCT), moreover in sepsis serum ferritin also increase. Serum ferritin is secreted by stimulation of pro-inflammatory cytokines such as TNF- $\alpha$ , interleukin-1 (IL-1), and IL-6 that occur in the inflammatory process.

**AIM:** The aim of the study was to prove correlation between interleukin-6 and ferritin serum in pediatric sepsis patient.

**METHODS:** This was cross-sectional study. Subjects were children aged 1 month–18 years with sepsis in pediatric intensive care unit (PICU) and intermediate ward (IW) at Sanglah General Hospital Denpasar in period of September 2020–June 2021. Statistical analysis was done by Pearson correlation test.

**RESULTS:** Total 37 subjects were analyzed in this study. The median level of Interleukin-6 was 12 pg/ml (range, 1–355 pg/ml) and the median of ferritin level was 997 (range, 180–13418 ng/mL). The correlation between interleukin-6 and serum ferritin showed moderate positive correlation ( $r = 0.54$ ) which was statistically significant ( $p = 0.001$ ). After adjusting confounding variables, namely, age, gender, nutritional status and time of sampling using partial correlation, the correlation between IL-6 and ferritin became stronger with  $r = 0.702$  and  $p = 0.00$ .

**CONCLUSION:** There was a significant positive correlation after adjusting for the confounding variables between interleukin-6 level and ferritin in pediatric sepsis patient.

## Introduction

Sepsis is defined as life-threatening condition accompanied by organ dysfunction as result of dysregulated immune response to infection [1]. Sepsis is also recognized as the leading cause of child death worldwide, with estimation 7.5 million deaths due to sepsis. In United States of America, 72,000 children were hospitalized with sepsis with mortality rate around 25% [2]. A study conducted at Sanglah General Hospital from April 2015 to April 2017 showed from 63 septic patients, most patients were <12 months old and 29 (46%) patients died [3].

Immune system dysregulation in sepsis triggers the production of pro-inflammatory cytokines such as interleukin-6 (IL-6). Interleukin-6 is a pleiotropic cytokine, which stimulates hepatocytes to produce acute phase proteins, acts as growth factor for B-cells and increase several markers of infection such as c-reactive protein (CRP), procalcitonin (PCT), and ferritin [4].

Elevated serum ferritin levels are often associated with inflammatory conditions such as sepsis and multiple organ dysfunction syndromes (MODS).

Many studies have looked for the relationship between ferritin levels and the severity of sepsis, but research on the association between interleukin-6 levels and serum ferritin in sepsis patients in Indonesia has never been performed. Interleukin-6 has been shown in many studies related with the severity of sepsis, but the high cost of the examination is an obstacle. Ferritin is one of the diagnostic markers that can also be used in sepsis patients, which is cheaper.

## Materials and Methods

Study was performed in Sanglah General Hospital, Bali, Indonesia, involving 37 children aged 1 month–18 years old with diagnosis sepsis in period September 2020–June 2021. After obtaining parental consent to participate in the study, subjects were examined for IL-6 and ferritin serum at the time of initial diagnosis of sepsis. Children with malignancy, HIV/AIDS, chronic liver disease, thalassemia, autoimmune disease, post-surgery, and viral infections such as dengue were excluded from this study.

This study used Shapiro–Wilk test for data normality. Data that are not normally distributed will be transformed using log 10. Data with normal distribution on both variables will be tested with Pearson correlation. Several confounding variables were controlled by analysis such as age, gender, nutritional status, and time of sampling.

These variables were analyzed using Pearson partial correlation. All statistical analyses were performed using SPSS. This study was approved by Research Ethics Commission of the Faculty of Medicine, Udayana University/Sanglah General Hospital with number 1577/UN.14.2.2.VII.14/LP/2020. This research has also received permission from the Indonesian Ministry of Health, the Direktorat General of Health Services, Sanglah General Hospital with the number LB.02.01/XIV.2.2.1/31455/2020.

## Results

The study was conducted in Pediatric Intensive Care Unit (PICU) and Intermediate Ward (IW) Sanglah General Hospital from September 2020 to June 2021. During the study period there were 51 sepsis patients and 37 met inclusion criteria as research subjects (Figure 1).

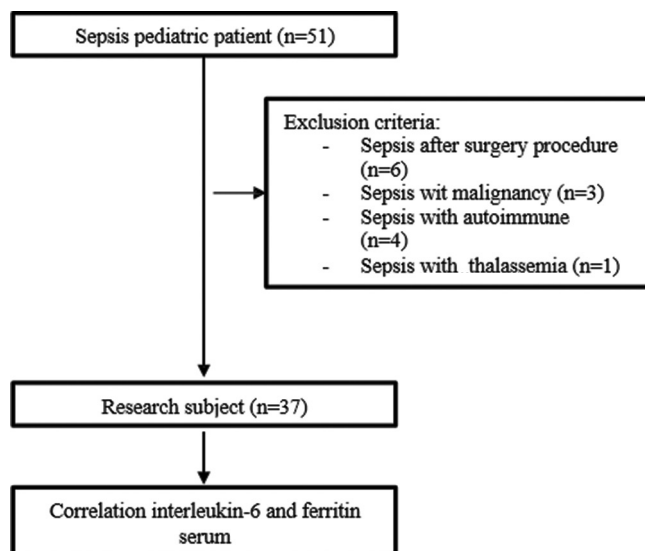


Figure 1: Flowchart of research

All subjects underwent research procedures in the form of filling out research sheets, measurement of IL-6 and ferritin serum at Prodia Clinical Laboratory Denpasar. Those subjects had median age 24 months (range 2 months–17 years). Most of the research subjects were female.

The median of interleukin-6 level was 12 pg/ml (range 1–355 pg/ml) and the median for ferritin level was 997 (range 180–13418 ng/ml). The characteristics of the research are shown in Table 1.

Table 1: Characteristic of samples

Characteristics	n = 37 subject
Gender, n (%)	
Male	16 (43.2)
Female	21 (56.8)
Age (year), median (IQR)	24 (2-204)
Nutrition status, n (%)	
Well nourished	20 (54.1)
Mild PEM	5 (13.5)
Moderate PEM	7 (18.9)
Severe PEM	0 (0)
Overweight	2 (5.4)
Obesity	3 (8.1)
Sampling time (hour), median (IQR)	6 (6–48)
Source of infection, n (%)	
Respiratory	17 (45.9)
CNS	14 (37.8)
Gastrointestinal	3 (8.1)
Genitourinary	1 (2.7)
Skin infection	1 (2.7)
Endocrine	1 (2.7)
Blood culture, n (%)	
Growth	15 (40.5)
No growth	22 (59.2)
Interleukin-6 (pg/ml), median (IQR)	12 (1-355)
Log Interleukin-6	118 ± 0.65
Serum ferritin, (ng/ml), median (IQR)	997 (180–13418)
Log ferritin	3.02 ± 0.49

The results of data analysis showed that there was a correlation between interleukin-6 and serum ferritin, which showed moderately positive correlation  $r = 0.54$  and  $p = 0.001$  (Figure 2). After performing partial correlation test, it showed that the levels of IL-6 and serum ferritin had strong positive correlation of 0.702 and statistically significant ( $p = 0.001$ ).

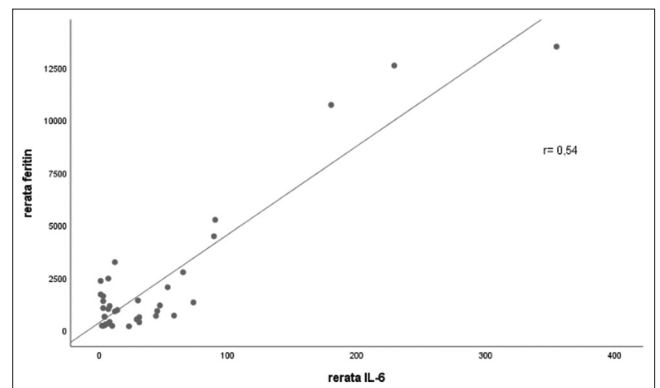


Figure 2: Scatter plot of correlation between interleukin-6 and serum ferritin

## Discussion

Thirty-seven subjects with sepsis were included in this study. Based on the characteristic data, majority were female 21 subjects. Based on the characteristic data, majority were female (21 subjects), ratio between female and male was 1.3:1. In this study, it was found that most of the subjects were well nourish (54.1%), mild protein energy malnutrition (13.5%), moderate protein energy malnutrition (18.9%), overweight (5.4%), and obesity (8.1%). Nutritional status is often associated with susceptibility to infection; in addition to malnourished, other nutritional deficiency often occur in children such

as iron deficiency. Iron deficiency can cause deficiency conditions that affect immune system so that children are susceptible to infection [5].

On the other hand, obese children with acute or chronic inflammation have high increment secretion of pro-inflammatory mediators by adipose tissue [6]. The most common sources of infection that caused sepsis in this study was respiratory infections, as many as 17 (45.9%) subjects and 14 (37.8%) subjects with source of infection from the central nervous system with the most common diagnoses being meningitis and encephalitis. Pneumonia was the most common diagnosis. This finding is similar to a previous study with 42.5% incidence of pneumonia [7].

In this study, 15 (40.5%) subjects had bacterial growth in two-sided blood cultures with *Pseudomonas aeruginosa* bacteria in three subjects, *Staphylococcus coagulase negative* in five subjects, *Burkholderia cepacia* in two subjects, and the rest were *Staphylococcus haemolyticus*, *Kocuria kristinae*, *Acinetobacter baumannii*, and *Pseudomonas oryzihabitans*. This finding is similar to previous research, which 42.6% of subjects had positive culture [8]. This rarity of positive blood cultures could be caused by aggressive empiric outpatient infection treatment or early administration of antibiotic therapy before cultures are taken in patients. The median ferritin and IL-6 in subject with positive blood cultures were high 1151 ng/ml (204–13418) and 21.5 pg/ml (3–355) than the median ferritin and IL-6 in negative cultures, which were 997 ng/ml (180–10629) and 8.36 pg/ml (1–180). Most of the subjects with positive blood cultures had severe sepsis that can affect level of ferritin and IL-6.

Interleukin-6 (IL-6) is a pleiotropic cytokine (stimulates hepatocytes to produce acute phase proteins and also acts as a growth factor for B cells). Interleukin-6 modulates several functions, such as proliferation, cell differentiation and apoptosis. Interleukin-6 is synthesized by local inflammation that distributed to the liver through bloodstream followed by rapid induction of various acute-phase proteins. Interleukin-6 is secreted by monocytes and macrophages in response to bacteremia. In this study, the median level of IL-6 was 12 pg/ml (range, 1–355 pg/ml).

This finding is different from previous studies which the median value of IL-6 was higher, namely high 63.21 pg/ml (0.86–409 pg/ml) in the sepsis group and 213.10 pg/ml (10.85–396.70) in the septic shock group [9]. In this study, the average blood sampling was 6 h. This difference can be caused by down regulation phenomenon (decrease of cytokines even though the infection is still continuing). The rapid kinetics of IL-6 is the cause of lower levels of IL-6 in this study. Interleukin-6 will increase in the first 2 h at the onset of sepsis and starts to decrease 6 and 12 h later [10]. In this study, the average blood sampling was 6 h.

Ferritin is a protein that plays important role in the process of iron metabolism. Iron is stored in the form of ferritin and hemosiderin which is found in spleen, liver, and bone marrow. Serum ferritin is secreted by stimulation of pro-inflammatory cytokines that occur in inflammatory process. Elevated serum ferritin levels is often associated with inflammatory conditions such as sepsis and multiorgan dysfunction syndrome (MODS). In this study, the median ferritin level was 997 (180–13418) ng/ml, in contrast to previous studies where the median ferritin level was lower, 303 (21–2210) ng/ml. In this study, blood samples were taken immediately after the diagnosis of sepsis, so it is possible that ferritin yet reached their peak [11].

In this study, there was a moderate positive correlation which means the two variables had linear correlation, the increase of interleukin-6 levels was the same direction as the increase of serum ferritin with  $r = 0.54$  and  $p = 0.001$ . The Scatter plot curve (Figure 2) showed wide distribution range of IL-6 and ferritin, due to subjects with high levels of IL-6 and ferritin experienced severe sepsis with death outcome. Sampling time also has effect, blood samples were taken approximately 12 h after the onset of sepsis, when level of ferritin was at their peak and IL-6 remained high due to severe and unresolved sepsis. After partial correlation with confounding variables, namely; age, gender, nutritional status and time of sampling, the correlation coefficient of IL-6 and serum ferritin increased into  $r = 0.70$  and  $p = 0.001$ . This value indicates that age, gender, nutritional status, and time of sampling affect the correlation between IL-6 and serum ferritin.

The limitation of the study is Interleukin-6 and ferritin levels have different peak times, the first 2 h and the first 12 h after infection. In this study, samples of both examinations were taken simultaneously so that the sampling time may not precisely simultaneously at the time of peak levels of IL-6 and ferritin in the blood.

## Conclusion

This study showed strong positive correlation between interleukin-6 and serum ferritin in pediatric sepsis patients.

## References

1. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al.* The third international consensus definitions for sepsis and septic shock (Sepsis-3). *J Am Med Assoc.* 2016;315(8):801-10. <https://doi.org/10.1001/jama.2016.0289> PMID:26903338

2. Weiss SL, Fitzgerald JC, Pappachan J, Wheeler D, Jaramillo-Bustamante JC, Salloo A, et al. Global epidemiology of pediatric severe sepsis: The sepsis prevalence, outcomes, and therapies study. *Am J Respir Crit Care Med*. 2015;191(10):1147-57. <https://doi.org/10.1164/rccm.201412-2323oc> PMID:25734408
3. Agustini NM, Wati DK, Suparyatha IB, Hartawan INB, Utama IMGDL, Budayanti NNS. The relationship between bacterial types and antibiotic resistance with the clinical outcomes of sepsis patients in pediatric Intensive Care Unit at Sanglah Hospital Denpasar, Bali-Indonesia. *Indones J Biomed Sci*. 2018;12(1):13-8. <https://doi.org/10.15562/ijbs.v12i1.144>
4. Sharma J, Sharma R. Serum ferritin: A prognostic marker in patients with sepsis in pediatric age group: A prospective cohort study. *Int J Med Health Res*. 2018;4(3):86-9.
5. Lestari ED, Siregar R, Nugroho HW. The relationship between ferritin levels and morbidity in children with malnutrition. *Sari Pediatr*. 2012;3(6):397-400.
6. Ridha NR, Daud D. The relationship between hepcidin levels with iron status in inflammation due to obesity. *Sari Pediatr*. 2014;16(3):161-6. <https://doi.org/10.14238/sp16.3.2014.161-6>
7. Yulianto S, Runtuwuwu AL, Pateda V, Mandei JM, Lolombulan JH. Correlation between interleukin-6 and septic shock. *Paediatr Indones*. 2012;52(6):352-5. <https://doi.org/10.14238/pi52.6.2012.352-5>
8. Panday A, Lammers EM, Alam M, Nanayakkar PW. An overview of positive cultures and clinical outcomes in septic patients: A sub analysis of the Prehospital Antibiotics Against Sepsis (PHANTASi) trial. *Crit Care*. 2019;23(1):182. <https://doi.org/10.1186/s13054-019-2431-8> PMID:31113475
9. Fioretto JR, Martin JG, Kurokawa CS, Carpi MF, Bonatto RC, Ricchetti SM et al. Interleukin-6 and procalcitonin in children with sepsis and septic shock. *Cytokine*. 2008;48(2):160-4. <https://doi.org/10.1016/j.cyto.2008.05.005> PMID:18565757
10. Nainggolan SC, Aman AK, Hanafie A. The relationship between the level of interleukin-6 and procalcitonin severe sepsis patient at the Adam Malik hospital. *Indones J Clin Pathol Med Lab*. 2018;25(1):38-41. <https://doi.org/10.24293/ijcpml.v25i1.1488>
11. Garcia PC, Longhi F, Branco RG, Piva JP, Lacks D, Tasker RC. Ferritin levels in children with severe sepsis and septic shock. *Acta Paediatr*. 2007;96(12):1829-31. <https://doi.org/10.1111/j.1651-2227.2007.00564.x> PMID:18001337