



INTERLEUKIN 18 LEVELS AS A PREDICTORS OF SEVERITY IN SEPSIS PATIENTS ARE ASSOCIATED WITH SOFA SCORES AT THE ICU H. ADAM MALIK HOSPITAL MEDAN

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ABSTRACT

Background: Sepsis is still a global health problem because the mortality rate is quite high. There are many markers being evaluated to assess the severity of sepsis, including IL-18. The purpose of this study is to find out whether IL-18 levels can be used as a predictor of severity in sepsis patients associated with SOFA scores.

Methods: Design of this study was a prospective cohort. 42 patients with sepsis who were treated in ICU H. Adam Malik Medan Hospital who met the inclusion criteria were included in this study. Samples were examined for IL-18 for the first day and the third day, as well as SOFA scores for the first day and the third day.

Results and Discussion: The first day level of IL-18 had a significant relationship with the first day of SOFA score ($p < 0.05$) and the third day level of IL-18 had a significant relationship with the third day of SOFA score ($p < 0.05$).

Conclusions: IL-18 levels can be used as an alternative parameter to assess the severity in sepsis patients in addition to the SOFA Score

KEYWORDS : Sepsis, IL-18, SOFA Score

INTRODUCTION

Sepsis is a major health care problem with a significant mortality rate in the intensive care unit (ICU). One of the main contributors to this process is the inflammatory response together with the release of inflammatory cytokines. It is characterized by an excessive response of the immune system due to infection, with the release of excessive inflammatory mediators.¹

According to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock 2016, Sepsis is a state of life-threatening organ dysfunction where there is a dysregulation of the body's response to infection. Clinically it can be explained that organ dysfunction has an increased score of sequential organ failure assessment (SOFA) ≥ 2 points associated with an increased risk of death in the hospital $> 10\%$ and < 9 a risk of death of 35%.²

Research conducted in the UK in 2001 to 2010 by Mc. Pherson et al. (2013) states that 1 in 20 deaths that occur in the UK are caused by sepsis, with an prevalence of 5.5% for women and 4.8% for men. The reported number of sepsis in the United States is 750,000 annually and about 2% of deaths are related to severe sepsis.³

Organ failure is one of the causes of high mortality and morbidity rates.⁴ Because the mortality rate of sepsis patients is still high, the prediction of severity or mortality in ICU patients is very important, both clinically and administratively. Predicting the condition of patients in the ICU can help provide information related to the state of the patient's disease and can be used as a guide to determine further therapy in patients.⁵

In recent years several assessment models have been developed to describe the severity of the disease in patients who are treated in intensive care or to predict intensive care outcomes. An example is the Sepsis related Organ Failure Assessment, which became known as the Sequential Organ Failure Assessment (SOFA) and was introduced in 1994.⁶

Besides using SOFA scores in predicting the mortality of sepsis patients, it can also use biomarkers to evaluate the mortality of sepsis patients or septic shock, these biomarkers must be able to reflect the concept or inflammatory process that plays a role in the pathophysiology of sepsis.⁷

IL-18 is a cytokine that is included in the IL-1 superfamily and is produced by macrophages and other cells. IL-18 works by binding to interleukin-18 receptors, and together with IL-12 will induce cell-mediated immunity after infection with microbial products such as lipopolysaccharides (LPS).⁸ Increased IL-18 levels reflect the severity of the infection process, where the higher IL-18 levels will be followed by an increase in SOFA scores or vice versa.⁹ Several studies have shown that circulating cytokines, especially IL-6, IL-8, IL-10 and TNF- are considered as diagnostic and prognostic markers in sepsis patients.¹⁰

II.Aims

This study aims to determine IL-18 levels can be used as a predictor of the severity of sepsis patients associated with SOFA scores.

III.METHODS

The study was conducted at the Department of Clinical Pathology, Faculty of Medicine, University of North Sumatra / Haji Adam Malik Medan Hospital in collaboration with the Department of Anesthesiology and Intensive Therapy at the Faculty of Medicine, University of North Sumatra. This study was an observational study with a prospective cohort study design. The study was conducted for 3 months from April 2019 to July 2019. The research subjects were male and female patients treated at the ICU H. Adam Malik Hospital Medan who was diagnosed with sepsis.

The sample size in this study was determined at 42 samples. Inclusion criteria in this study were patients who met the criteria for sepsis according to the Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2016 treated in ICU H. Adam Malik Hospital Medan, age > 18 years and < 65 years, and agreed to join the research. The exclusion criteria are patients

with malignancy, chronic infection and immune system disorders. Every sample was examined for IL-18 on days 1 and 3. Vital signs, GCS, platelets, total bilirubin, creatinine, blood gas analysis were performed to assess SOFA scores on days 1 and 3. IL 18 examination using serum was examined using an automatic analyzer Chamwell, with the principle of a sandwich using the ELFA (Enzyme-Linked Fluorescent Assay) method.

IV. Statistic Analysis

The results of the study were analyzed statistically using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows. The description of the characteristics of the research subjects is presented in tabulated form and described. Correlation of IL-18 level and SOFA score were used by the Spearman rank test. All statistical tests with $p < 0.05$ were considered significant.

V.RESULTS

This study used samples collected according to the inclusion criteria in this study as many as 39 patients treated at H. Adam Malik Hospital Medan. 18 of the total sample were male (46.2%) and the remaining 21 people (53.8%) were female. The youngest is 19 years old and the oldest is 64 years old. 3 patients were excluded from the study because the patient died in less than 48 hours of treatment at the ICU. (Table 1)

Table 1 Descriptive Data Analysis of Gender in Sepsis Patients

SEX	n	%
Male	18	46,2%
Female	21	53,8%
Total	39	100%

Table 2 Spearman Correlation Test Level IL-18 with SOFA Score day 1

Variable	IL-18 levels		
	n	r	p
SOFA score	39	0,739	0,001

*) Correlation analysis uses the Spearman correlation test because the data are not normally distributed

Table 3 Spearman Correlation Test Level IL-18 with SOFA Score day 3

Variable	IL-18 levels		
	n	r	p
SOFA score	39	0,701	0,004

*) Correlation analysis uses the Spearman correlation test because the data are not normally distributed

Spearman correlation test statistic test showed SOFA score on the first day there was a significant relationship with IL-18 on the first day ($r = 0.739$ and $p = 0.001$). While the third day SOFA score there is a significant relationship with IL-18 the third day with ($r = 0.701$) and ($p = 0.004$).

Table 4 IL-18 Correlation Test with PaO2 / FiO2, GCS, Bilirubin, Creatinine, Platelets and Mean Arterial Pressure.

Variable	IL-18 levels		
	n	r	p
PaO ₂ /FiO ₂			
Day 1	39	-0,250	0,028
Day 3	39	-0,134	0,235
GCS			
Day 1	39	0,099	0,427
Day 3	39	0,062	0,631
Bilirubin			
Day 1	39	0,177	0,120
Day 3	39	0,199	0,082

Creatinine			
Day 1	39	0,193	0,086
Day 3	39	0,243	0,030
Platelets			
Day 1	39	-0,176	0,118
Day 3	39	-0,351	0,002
Mean Arterial Pressure			
Day 1	39	-0,072	0,521
Day 3	39	-0,095	0,416

*) Spearman Correlation Test is used because the variables are not normally distributed

Correlation of the elements of SOFA scores with IL-18 first and third days were analyzed using Spearman correlation analysis. Based on the analysis it was found that the respiratory system, the kidney system and the coagulation system are important organs that have a significant correlation with the increase in IL-18.

VI.DISCUSSION

The study was conducted for 3 months from April 2019 to June 2019, on 39 patients who had gone through the process of inclusion and exclusion. The number of patients who became the study sample were 39 patients (18 male and 21 female). Of all study participants, they had a median age of 56 years. The youngest age is 19 years and the oldest is 64 years.

According to Jordan et al. 2016, showing that older age is a risk factor for sepsis. The risk of sepsis has a bimodal age distribution, with an increase in age-adjusted incidents, where the baby's risk decreases through childhood, then increases again in adulthood with an increased risk of increasing around the age of 50-60 years. Although there are some variations in the sex distribution in the prevalence of sepsis, male gender is consistently associated with a higher incidence of sepsis.¹¹

In a cohort study of sepsis, the mortality was 24.4%. Age is a free risk factor that determines the cure and death rates from this sepsis condition. In the infant-pediatric category, the younger the age, the survival rate will be smaller, in contrast to the adult category, the higher the age, the higher the mortality rate of 27.7% compared to 17.7% (LaRosa and Steven, 2010).¹² Spearman correlation test statistic test shows SOFA score on the first day there is a significant relationship with IL-18 on the first day ($r = 0.739$ and $p = 0.001$). While the third day SOFA score there is a significant relationship with IL-18 the third day with ($r = 0.701$) and ($p = 0.004$).

In contrast to the study of Michelle et al. 2016. Show that patients with IL-18 above the prescribed values have experienced a significant decrease in survival rates in all samples ($p < 0.0001$), severe sepsis ($p = 0.038$) and septic shock ($p < 0.0001$). In this study also showed an SOFA score in sepsis patients who died with an average value of 10.1 ± 0.6 , compared with an average SOFA score of a surviving sepsis patient that is 5.8 ± 0.7 .¹

Correlations of the elements of the SOFA score include Respiration (PaO₂/FiO₂), central nervous system (GCS), Coagulation (Platelets), Liver (Total Bilirubin, Kidney (Creatinine), and Cardiovascular (MAP) with IL-18 the first and third days in IL-18 analysis using Spearman's correlation analysis Based on the analysis it was found that the respiratory system, the kidney system and the coagulation system are important organs that have a significant correlation with the increase in IL-18.

These results are different from the results of research conducted by Yoon et al 2018, they found that organs that often experience organ dysfunction in sepsis patients are the

respiratory system, kidneys and the central nervous system. This is caused by microcirculation dysfunction, which is endothelial damage caused by activation of the immune system with antigens so that the release of inflammatory mediators will produce cytokines which will stimulate the activation of blood clots that will eventually trigger thrombosis in the microcirculation. Decreased lung, kidney and central nervous function can also reflect tissue hypoxia (hypoperfusion) and can be used to predict the prognosis and response to therapy.¹³

VII. CONCLUSIONS AND SUGGESTIONS

The first IL-18 day had a strong correlation with the first day's SOFA score ($r = 0.739$ and $p = 0.001$) and the third day IL-18 level had a strong relationship with the third day's SOFA score ($r = 0.701$ and $p = 0.004$) so IL-18 levels can be used as an alternative parameter to assess the severity in sepsis patients in addition to the SOFA score. Research is needed to assess the mortality of sepsis patients during ICU treatment, so IL-18 can be used as a predictor of mortality.

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