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## THE RELATIONSHIP BETWEEN THE LEVEL OF INTERLEUKIN-6 AND PROCALCITONIN IN SEVERE SEPSIS PATIENTS AT THE ADAM MALIK HOSPITAL

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### ABSTRACT

Severe sepsis is defined as sepsis that is accompanied by one or more organ dysfunctions, hypotension or hypoperfusion (decreased renal function, hypoxemia, lactic acidosis, oliguria, mental status changes). Macrophages and monocytes produced Procalcitonin (PCT) in serious bacterial infections and sepsis. Interleukin-6 (IL-6) is an interleukin that acts as proinflammatory cytokines. The high IL-6 level is due to chronic inflammation and sepsis. IL-6 is found increased more rapidly in the acute phase, so it can be used to evaluate early phase infection and sepsis. The purpose of this study was to find out IL-6 and PCT levels in severe sepsis patients. This study was a cross-sectional observational study. The subjects were sepsis patients treated in Adam Malik Hospital on Jan-Mar 2016. Statistical data was analyzed using SPSS and the Spearman rank correlation, with significant p-value < 0.05. IL-6 was tested using Chem Well 9210 series. Procalcitonin examination was done by mini VIDAS BRAHMS PCT. There were 40 people observed as subjects in this study, 26 males (65%) and 14 females (35%). The average age of male was  $49.42 \pm 18.19$  years old, the youngest 18 years old, and the oldest 79 years old. The average age of females  $57.35 \pm 20.73$ , the youngest 18 years old, and the oldest 87 years old. The average of IL-6 was  $10862.12 \pm 25489.16$  and PCT was  $9666.73 \pm 10540.13$ . Spearman rank test was also used, the value of  $r = 0.176$  and  $p = 0.277$ . The conclusion is there is no significant correlation between IL-6 and PCT. There is no significant correlation between IL-6 and PCT levels in severe sepsis patients.

**Key words:** Severe sepsis, interleukin-6, procalcitonin

### INTRODUCTION

Sepsis is a clinical syndrome due to an excessive body response towards the stimulation of microorganisms and is often the leading cause of death in some hospitals in Indonesia, particularly in the Intensive Care Unit (ICU). Sepsis itself is a continuation of the Systemic Inflammatory Response Syndrome (SIRS) syndrome with known or defined infection including a positive culture of the organism.<sup>1</sup>

Where SIRS is the body's response to systemic inflammation, characterized by two or more of the following conditions: Temperature > 38° C or < 36° C; Tachycardia (HR > 90 x / min); Tachypnea (RR > 20 x / min) or PaCO<sub>2</sub> < 32 mmHg; Blood leucocytes > 12.000/ $\mu$ L or neutrophil stem > 10%.

Sepsis is a disease that contributes to more than 200,000 deaths per year in the United States. The incidence of severe sepsis and septic shock has increased over the past 20 years, and the number of cases is > 700,000 per year (3 per 1000 population).

Sepsis treatment costs in the United States reach to some 17 billion dollars each year.<sup>2</sup>

Sepsis is an inflammatory response to infection. Interactions between antigens and the immune system occur. This interaction will activate T cells, B cells and macrophages and pro-inflammatory cytokine mediators including IL-6. This condition will make the thyroid gland c cell produce PCT. Procalcitonin is also found in the production of macrophages. This interaction will cause endothelial damage and plasma leakage and eventually can cause severe sepsis and septic shock.<sup>3</sup>

PCT is a calcitonin precursor composed of 116 amino acids secreted by C cells from the thyroid gland. Under normal circumstances, PCT levels are elevated in cases of septicemia, meningitis, pneumonia and urinary tract infections. Macrophages and monocyte cells produce procalcitonin in some cases of severe bacterial infections and sepsis.<sup>7</sup>

The high levels of IL-6 are associated with chronic inflammation and sepsis. IL-6 has an essential role in

inducing the synthesis of acute phase proteins such as CRP. The increase of IL-6 was found to be faster than the increase of acute phase protein in CRP. This finding makes IL-6 an interesting molecule for evaluating the initial phase of infection, and sepsis.<sup>9</sup> Severe sepsis is sepsis accompanied by one or more signs of organ dysfunction, hypotension, or hypoperfusion. Hypoperfusion disorders include: decreased renal function, hypoxemia, lactic acidosis, oliguria, mental status changes.<sup>2,3</sup>

Blood cultures usually makes the sepsis diagnosis of patients. However, the results of the test can only be issued after 48 hours to 72 hours, so the management of sepsis is often delayed. As a result, it may aggravate the patient's condition and may even lead to death.<sup>5</sup>

The purpose of this study was to investigate the relationship between IL-6 and PCT levels in patients with severe sepsis.

**METHODS**

This study was an observational, cross-sectional study conducted in Department of Clinical Pathology, Faculty of Medicine USU/Adam Malik Hospital Medan in cooperation with the Department of Anesthesiology & Intensive Therapy, Faculty of Medicine USU/Adam Malik Hospital Medan. The subjects of this study were patients with severe sepsis treated at Medan-Adam Malik Hospital in January-March 2016 that met inclusion and exclusion criteria. All severe sepsis of the patients treated in the intensive care unit.

The statistical analysis used SPSS and the correlation test used Spearman Rank Test, with significant p-value <0.05. IL-6 was examined using CHEM WELL 9210 series based on Enzyme-Linked Immunosorbent Assay (ELISA) method. PCT examination used patient serum samples and examined by mini VIDAS BRAHMS, with sandwich principle using ELFA (Enzyme-Linked Fluorescent Assay) method.

Statistical analysis was performed using SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) software for Windows. The Kolmogorov-Smirnov normality test was used to test whether the research data was normal distribution or not, and the data obtained were not normally distributed, so Spearman's correlation test was used. The statistical analysis used p-value <0.05 as the meaning limit.

**RESULTS AND DISCUSSION**

Forty patients with severe sepsis who got

treatment at Adam Malik Hospital Medan from January 2016-March 2016 and met the inclusion criteria were included in this observation. Anamnesis, physical and laboratory examination were collected from the patients. Explanations and informed consent as study subjects were then given to the families and patients.

The number of subjects included in this study was 40 people, with 26 males (65%) and 14 females (35%). The average age in the male group was 49.42 ± 18.19, with the youngest age was 18 years old, and the oldest was 79 years old. While the average age in the female group was 57.35 ± 20.73, with the youngest age was 18 years old, and the oldest was 87 years old. The characteristics of research subjects can be seen in Table 1.

**Table 1.** Characteristic data based on gender and age

Gender	n (%)	Age average ± SD (year)
Male	26 (65.00)	49.42 ± 18.19
Female	14 (35.00)	57.35 ± 20.73

The average IL-6 of the subjects in this study was 10862.12 ± 25489.16, and the average PCT was 9666.73 ± 10540.13.

**Table 2.** The characteristics data based on laboratory results of IL-6 and PCT

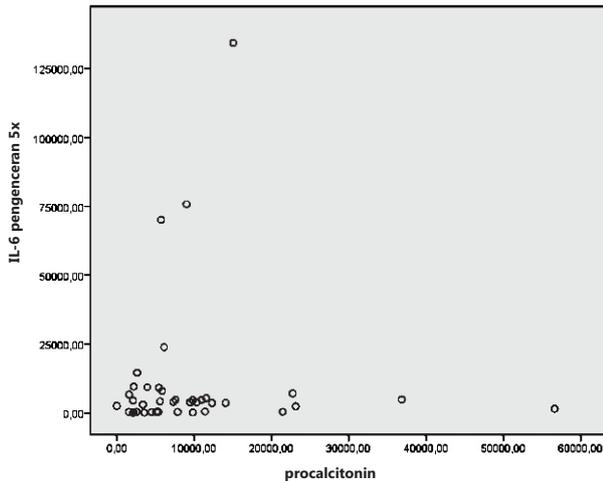
Variable	(Average ± SD)
Interleukin-6	10862.12 ± 25489.16pg/mL
PCT	9666.73 ± 10540.13 pg/mL

In this study, Spearman's correlation test was used to test the relationship between IL-6 with PCT. From the analysis, r = 0.176 and p = 0.277, so it could be concluded that there was no significant relationship between IL-6 and PCT.

In Figure 1, it can be seen that there was no straight line pattern formed from the available plot distribution. This result showed that there was no relationship between Interleukin-6 and PCT

In the previous study, it was stated that PCT and IL-6 showed that PCT was a better parameter than IL-6 to state sepsis and PCT was the best parameter compared to other settings.<sup>10</sup>

In another study it was also found that between PCT and IL-6 there was no significant difference in severe sepsis and PCT was used as a diagnostic marker in a severe sepsis condition without differentiating patients with or without bacterial infection. IL-6 was either used as prognostic value



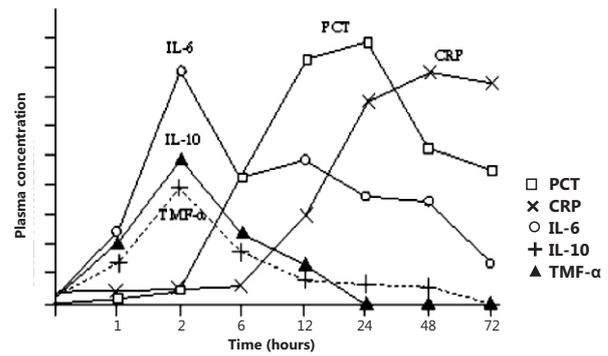
**Figure 1.** The correlation between Interleukin-6 with PCT, PCT in units: pg/mL, Interleukin-6 in units: pg/mL

and monitoring the effectiveness of antibiotic therapy in severe sepsis circumstances.<sup>11</sup>

In this study, after examination of PCT and Interleukin-6 levels in the samples of severe sepsis patients by predefined inclusion criteria, a statistical analysis was performed using SPSS, the researchers examined the relationship between PCT and IL-6 using Spearman's correlation test,  $r = 0.176$  and  $p\text{-value} = 0.277$ . It was concluded that there was no significant relationship between PCT and IL-6.<sup>6,12</sup>

In this study, it can be seen that the levels of IL-6 and PCT were increasing and there was also no increment in the samples of severe sepsis patients. This fact was due to the uniformity of sampling time in severe sepsis. As a result, the data was not homogeneous and became non-specific. As we had noted, previous research suggests that IL-6 will increase in the first 2 hours of severe sepsis and will decrease in 6 hours period of severe sepsis. While PCT was known to increase in the first 6 hours of sepsis, the previous 6 hours was not very high and would decrease at 12 hours of severe sepsis.<sup>13</sup>

The diagnosis of sepsis is often difficult to enforce in a short time because the results of germ culture which is the gold standard for diagnosis can be obtained after a few days. It is known that several laboratory tests can be used to determine the presence of inflammatory processes, including leukocyte count, tumor necrosis factor alpha, and interleukin 6. However, the examination is not too specific. Therefore it is difficult to distinguish quickly between Systemic Inflammatory Response Syndrome (SIRS) and sepsis in patients in intensive care because they have to wait for the results of blood cultures for several days, while patients must receive appropriate treatment immediately. Positive



**Figure 2.** The comparison of time and procalcitonin density compared with some other sepsis markers<sup>12</sup>

culture results can also be due to some contamination factors, and negative blood cultures cannot eliminate sepsis.<sup>14,15</sup>

In this study, it was found that IL-6 and PCT levels did not have a significant difference in severe sepsis. This biomarker is not specific to infections caused by bacteria. The IL-6 can be induced in the postoperative state, autoimmune disease, reaction transplantation, and viral infection. Immunosuppression can decrease IL-6 response. IL-6 concentration in diagnosing sepsis is still below PCT. Other studies have shown that IL-6 is not an ideal biomarker for diagnosing sepsis into severe sepsis or shock septic. The peak of IL-6 was independently associated with the increased mortality.<sup>1,4,7</sup>

## CONCLUSIONS AND SUGGESTIONS

The conclusion is there is no significant correlation between IL-6 and PCT. There is no significant correlation between IL-6 and PCT levels in severe sepsis patients.

Based on the results of this study, it can be suggested to conduct further research to see the value of IL-6 and PCT levels in infectious patients with severe sepsis.

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