Original article

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Correlation of pentraxin-3 and procalcitonin levels with Sequential Organ Failure Assessment (SOFA) scores in septic patients

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Abstract

***Objective*: This study aimed to determine the correlation between pentraxin-3 and procalcitonin levels with Sequential Organ Failure Assessment (SOFA) scores in septic patients.**

***Design*: This observational analysis with a cross-sectional method assessed the correlation between pentraxin-3 (PTX-3) and procalcitonin (PCT) levels and the SOFA scores of septic patients.**

***Setting*: We conducted this study in the Intensive Care Unit (ICU) of Dr. Wahidin Sudirohusodo Hospital and Medical Laboratory Center of Hasanuddin University from December 2023 to April 2024.**

***Patients and participants*: Thirty-two patients with clinical sepsis were admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital.**

***Intervention*: Blood samples were collected on day 1 and day 2 of ICU care in septic patients to measure pentraxin-3 and procalcitonin levels.**

***Measurements and results*: The Wilcoxon test showed a significant difference in pentraxin-3 levels on ICU care's first and second days (p=0.036). Similarly, there was a significant difference in procalcitonin levels on the first and second days of ICU care.**

The Spearman correlation test found a significant correlation between procalcitonin and SOFA scores (p=0.008) with a correlation value r=0.462 on the first and second days. The resulting correlation value showed a positive correlation, which meant that the higher the procalcitonin level in septic patients, the higher the SOFA scores with moderate strength (correlation value 0.4-<0.6). The correlation of pentraxin-3 with the Spearman test showed a positive correlation on the first day. In contrast, on the second day, there was no significant statistical value with the SOFA scores with a correlation value p=0.093 (p>0.05).

***Conclusion*: Pentraxin-3 and procalcitonin levels correlate with SOFA scores in septic patients admitted to the ICU.**

Key words: Pentraxin-3, procalcitonin, SOFA, sepsis.

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Introduction

Sepsis is a condition that is still a global health problem due to its difficult treatment and high mortality rate. Sepsis is most commonly caused by Gram-negative bacteria (52% of septic cases), followed by Gram-positive bacteria (37%), and fungi or other microorganisms cause the rest. Proper knowledge is required to improve the ability to diagnose and treat septic patients accurately. Knowledge of the background infection causing sepsis is crucial to properly managing the patient. Appropriate timing and proper intensive care are key in managing sepsis and septic shock patients. (1)

According to the Surviving Sepsis Campaign (SSC): International Guidelines for Management of

Severe Sepsis and Septic Shock: 2021, sepsis is a life-threatening organ dysfunction with dysregulation of the body's response to infection. It can be described that organ dysfunction has an increase in the Sequential Organ Failure Assessment (SOFA) scores >2 points or more associated with an increased risk of in-hospital mortality >10%. (2,3)

Pentraxin-3 (PTX-3) is an acute-phase protein representing the pentraxin subfamily and is expressed in various cells, such as monocytes, endothelial cells, dendritic cells, or neutrophils, during inflammatory processes. Many studies have shown that PTX-3 levels are strongly related to the severity of infection. PTX-3 production is induced by cytokines such as interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), and toll-like receptor (TLR) agonists but not by interleukin 6 (IL-6) or interferon. (4)

Procalcitonin (PCT) is a prohormone calcitonin found in the human body. Elevated blood levels of PCT are significant and can be used as a sepsis biomarker. Compared to other sepsis biomarkers, such as C-reactive protein (CRP), PCT is more sensitive, and its levels increase most rapidly after exposure to infection. (5)

Several studies have found increased PTX-3 expression due to various specific infectious agents such as Aspergillus fumigatus, Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella pneumonia, E. coli, Neisseria meningitides, and some viruses. PTX-3 shows potential significance as an early diagnostic and prognostic or as a biomarker in infectious disorders and septic patients. (4)

Hu C et al. (2018) have examined PTX-3, PCT, and lactate levels as biomarkers to assess severity or mortality in septic patients. The study was conducted on 141 patients admitted to the Intensive Care Unit (ICU) with a diagnosis of sepsis and septic shock. PTX-3, PCT, and lactate levels were examined on days 0, 3, and 7. SOFA scores were calculated as an evaluation of organ dysfunction. It was found that PTX-3, PCT, and lactate levels tended to increase in sepsis and septic shock patients and correlated with SOFA scores. (6)

Materials and methods

Setting and design

This study was conducted in the ICU of Dr. Wahidin Sudirohusodo Hospital and Hasanuddin University Medical Research Center (HUMRC) from December 2023 to April 2024. This observational analytic study used the cross-sectional method to assess the correlation between PTX-3 and PCT levels and SOFA scores of septic patients. Blood samples were collected to measure PTX-3 and PCT levels on day 1 and day 2 in septic patients. The Medical Research Ethics Committee of Hasanuddin University Makassar (972/UN4.6.4.5.3L/PP36/2023) approved all protocols employed in this study.

Study group

Patients with clinical sepsis were admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital.

Study protocol

The inclusion criteria for this study were patients who included sepsis criteria who were admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital, with an age range of 18-65 years, patients who were examined for PCT and PTX-3 levels in the first 24 hours and the second 24 hours of ICU care, and SOFA scores criteria were calculated.

A total of 32 patients who met the inclusion criteria were included. Samples were selected sequentially and met the inclusion criteria. The study subjects explained the purpose of the study and the benefits of the study, and then the study subjects participated in the research and filled out the consent form. The patient's SOFA scores were calculated on days 1 and 2, while PTX-3 and PCT levels were also measured. Vital signs, Glasgow coma scale (GCS), platelets, total bilirubin, creatinine, blood gas analysis, and SOFA scores were assessed on days 1 and 2. PTX-3 and PCT levels were examined using an automatic device analyzer with the ELISA examination principle.

Data analysis

The collected data were analyzed and presented as mean±SD or frequency and percentage. Statistical analysis was performed using IBM SPSS Statistics version 26.0.1.1 (SPSS Inc., Chicago, IL, USA). The normality test showed that the data were not normally distributed. Data are presented in the Tables. If the data were normally distributed, the correlation of PTX-3 and PCT levels in patients with sepsis was assessed using the Pearson correlation test. Meanwhile, for the data that were not normally distributed, we used the Spearman rank test. All statistical tests with p-values <0.05 were considered significant.

Results

Homogeneity

Table 1 shows the demographic data of the subjects. All of them met the inclusion criteria. A total of 19 patients (59.4%) were male. The mean age of the study subjects was 45.13 years, with the youngest being 18 and the oldest being 65. This study included ten subjects (31.3%) with sepsis and 22 subjects (68.8%) with septic shock.

PTX-3, PCT, and SOFA scores

Table 2 shows the results of the analysis of septic parameters on the first and second days of septic patients admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital. Based on the normality test, it was found that the SOFA scores, PTX-3 levels, and PCT levels were not normally distributed on both the first and second days. The median SOFA score on the first day was 7.00, with the lowest score of 3 and the largest score of 16. On the second day, the median SOFA score was 7.00, with the lowest score of 2 and the largest score of 15. Based on the Wilcoxon test, there was no significant difference in SOFA scores on the first and second days (p=0.574). The median PTX-3 level on the first day was 2.60 ng/ml, with the lowest level of 1.43 ng/ml and the highest level of 13.39 ng/ml, while on the second day, it was 3.40 ng/ml, with the lowest level of 1.17 ng/ml and the highest level of 14.26 ng/ml. A significant difference in PTX-3 levels was obtained on the first and second days of ICU treatment (p=0.036). The median value of PCT levels on the first day was 10.25 ng/ml, with the lowest level of 2 ng/ml and the highest of 51.80 ng/ml, while on the second day, it was 13.38 ng/ml, with the lowest level of 0.14 ng/ml and the highest of 162.96 ng/ml. There was a significant difference in PCT levels on the first and second ICU treatment days (p=0.010).

Table 3 shows the blood gas and blood chemistry analysis results on the first and second days of septic patients admitted to the ICU. Based on the analysis results, the mean arterial pressure (MAP) and the ratio of arterial oxygen partial pressure (in mmHg) to fractional inspired oxygen (PaO2/FiO2) variables were found to be normally distributed, so a paired sample t-test analysis was carried out. While other variables were analyzed by Wilcoxon analysis, no statistically significant differences were found between the results of blood gas analysis and blood chemistry on the first and second days of ICU treatment.

Table 4 shows the Spearman correlation test, which found a significant correlation between PTX-3 and SOFA scores on the first day of ICU treatment (p=0.025). Similar results were also shown between PCT and SOFA scores on the first day of ICU treatment (p=0.035). The correlation value showed a positive correlation, which means that the higher the PTX-3 or PCT levels in septic patients, the higher the SOFA scores with weak strength (correlation value 0.2-<0.4).

Table 5 shows the Spearman correlation test. On the second day of ICU treatment, a significant correlation was found between PCT and SOFA scores (p=0.008) with a correlation value r=0.462. The resulting correlation value shows a positive correlation, which means that the higher the PCT level in septic patients, the higher the SOFA scores with moderate strength (correlation value 0.4-<0.6). The PTX-3 correlation test with the SOFA scores on the second day was statistically insignificant (p>0.05).

Discussion

Sepsis is a life-threatening organ dysfunction caused by dysregulation of the host immune system against infection, and the SOFA score is a score to assess sepsis-related organ failure. An increase in SOFA scores is associated with worse patient outcomes. The SOFA score parameters consist of parameters to assess respiration (PaO2/FiO2), central nervous system (GCS), cardiovascular (MAP), coagulation system (platelets), liver (bilirubin), and kidney (serum creatinine). (7)

Organ failure is one of the causes of high mortality and morbidity of patients in the ICU, as well as high costs. Therefore, evaluation of organ dysfunction at any time during ICU care is helpful in following disease progression. Several scoring systems predict patient outcomes in the ICU, such as SOFA, Simplified Acute Physiology Score (SAPS), Acute Physiology And Chronic Health Evaluation (APACHE), Mortality Probability Models (MPM), and several other scoring systems. One of the world's most widely used scoring systems is SOFA scores. (8)

Adult patients of older age and male gender are 2.562 times more likely to suffer from sepsis compared to adult female patients. Older men often suffer from chronic diseases and have many comorbidities, which cause the immune system to weaken if they have an infection. Therefore, if they have sepsis, the chance of death is greater. Based on research, septic patients aged 65 years have a higher sepsis mortality rate compared to younger patients. The incidence of sepsis increased sharply in the elderly aged 65 years by 27.7%. (9)

In this study, all study subjects met the inclusion criteria. A total of 19 patients (59.4%) were male. The average age of the study subjects was 45.13 years, with the youngest being 18 and the oldest being 65. This study included ten subjects (31.3%) of septic patients and 22 subjects (68.8%) of septic shock patients. The survey conducted by Tsui et al. (2021) conducted a cohort study of 115 septic patients. The results of their research showed that the dominant age characteristics in septic patients were elderly (67 years old), with male gender dominating in septic patients. (10)

PCT is a calcitonin prohormone found in the human body. Elevated blood levels of PCT have a signifi-

cant value and can be used as a sepsis biomarker. PCT levels are categorized into values below 0.5 ng/ml (local bacterial infection), between 0.5-2 ng/ml (sepsis), between 2-10 ng/ml (severe sepsis), and values greater than 10 ng/ml (septic shock). Compared to other septic biomarkers (e.g., CRP), PCT is more sensitive, and its levels increase most rapidly after exposure to infection. PCT can differentiate infections caused by bacteria from infections caused not by bacteria. PCT is mainly induced in large amounts during bacterial infections. However, the concentration of PCT in the body is low in other types of inflammation, such as viral infections, autoimmune diseases, and the body's rejection of organ transplants. The elevated value of PCT differs between Gram-positive and Gram-negative bacteria. It is useful as a source of information when choosing the best antibiotic therapy if blood culture results are not available or the site of infection is not clearly known. This makes PCT a specific biomarker in assessing the severity of systemic bacterial infections and sepsis. (11)

PTX-3 is an acute-phase protein representing the long-arm pentraxin subfamily and is expressed in various cells, such as monocytes, endothelial cells, dendritic cells, or neutrophils during inflammatory processes. PTX-3 also acts as a multifunctional pattern recognition molecule in the immune response to infection and has been reported to be strongly associated with the severity of infection, especially in sepsis. (12)

The study found that the SOFA scores, PTX-3 levels, and PCT levels were not normally distributed on both the first and second days. The median SOFA score on the first day was 7.00, with the lowest score of 3 and the largest score of 16, while on the second day, it was 7.00, with the lowest score of 2 and the largest score of 15. Based on the Wilcoxon test, there was no significant difference in SOFA scores on the first and second days of ICU care ($p=0.574$). The median PTX-3 level on the first day was 2.60 ng/ml, with the lowest level of 1.43 ng/ml and the highest level of 13.39 ng/ml, while on the second day, it was 3.40 ng/ml, with the lowest level of 1.17 ng/ml and the highest level of 14.26 ng/ml. A significant difference in PTX-3 levels was obtained on ICU treatment's first and second days ($p=0.036$). The median value of PCT levels on the first day was 10.25 ng/ml, with the lowest level of 2 ng/ml and the highest of 51.80 ng/ml, while on the second day, it was 13.38 ng/ml, with the lowest level of 0.14 ng/ml and the highest of 162.96 ng/ml. There was a significant difference in PCT levels on the first and second ICU treatment days ($p=0.010$).

Safari et al. (2016) reported that baseline, highest, and mean SOFA scores were associated with mortality and could be used to assess the extent of organ dysfunction on first admission to the ICU. They also stated that SOFA scores >11 had a mortality rate of >90%, and a decrease in these scores within 48 hours was associated with a 6% decrease in mortality if these scores did not change or tend to increase. The mortality rate increased by 37% if the initial score was 2-7 and 60% if the initial score was 8-11. (13)

The results of blood gas and blood chemistry analysis on the first and second days of septic patients admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital showed that the variables of MAP and PaO2/FiO2 were usually distributed. So, a paired sample t-test was conducted, while other variables were analyzed using Wilcoxon analysis. Based on the study, there was no statistically significant difference in the blood gas analysis results and blood chemistry on the first and second days.

Our results showed decreased PTX-3 levels from day 1 to day 2. The Wilcoxon test showed a significant difference in the mean levels of PTX-3 between the first and second days ($p<0.001$), likewise a decrease in PTX-3 levels from day 1 to day 2. The Wilcoxon test showed a significant difference in the mean levels of PCT between the first and second days ($p=0.001$). Research conducted by Masruri et al. (2023) showed a significant difference in the mean levels of PTX-3 between the first and third days ($p<0.001$) in septic patients admitted to the ICU. The Wilcoxon test showed a significant difference in the mean levels of PCT between day 1 and day 3 ($p=0.001$) in ICU-treated septic patients. (14)

This study found a significant correlation between PTX-3 and SOFA scores on the first day of ICU care. Similar results were also shown in PCT levels with SOFA scores on the first day of ICU care in the ICU of Dr. Wahidin Sudirohusodo Hospital ($p<0.05$). The correlation value showed a positive correlation, which meant that the higher the PTX-3 or PCT levels in septic patients, the higher the SOFA scores with weak strength (correlation value 0.2-<0.4). A study by Yang Y et al. (2016) stated that if septic patients in the ICU got SOFA scores of 0-1, then organ dysfunction/mortality was almost nonexistent. If the SOFA scores were >2, the mortality rate was 10%; SOFA scores <9 meant the mortality rate was 33%, and if the SOFA scores were >10, the mortality rate was >95%. (9)

The decrease in PTX-3 and PCT levels from day 1 to day 2 indicated clinical improvement in septic patients treated in the ICU. Therefore, patient improvement was seen clinically and from the decrease in PTX-3 and PCT during 24 hours of ICU

care, because these two markers were highly correlated with the degree of inflammation and bacteremia in septic patients. So, a decrease in these two markers illustrated a good prognosis. (6)

PTX-3, an acute-phase protein, has emerged as a promising sepsis biomarker in recent years. PTX-3 is a prototypical member of the long-arm pentraxin subfamily and a key component of innate and humoral immunity. PTX-3 is expressed in several tissues, particularly dendritic cells and macrophages, in response to proinflammatory stimuli. In addition, PTX-3 is stored in neutrophil granules and localized in the neutrophil extracellular trap. Once released, PTX-3 acts by recognizing microbes, activating complement, and facilitating pathogen recognition by phagocytes, thereby promoting pathogen clearance, tuning the inflammatory response, and promoting tissue remodeling. Thus, increasing PTX-3 is consistent with the severity of inflammation and pathogenesis in sepsis and has been elevated since sepsis was first established. (15)

The increase of PTX-3 early in sepsis is closely related to the risk factor of 28-day mortality. In healthy subjects, plasma PTX-3 levels are very low (<2 ng/ml) but can increase rapidly under inflammatory and infectious conditions. Its levels increase in critical illness with a gradient from systemic inflammatory response syndrome (SIRS) to sepsis and septic shock. Thus, PTX-3 has been proposed as a prognostic marker for sepsis. In a systematic review and meta-analysis, PTX-3 significantly predicted disease severity and mortality in sepsis. (15)

Using the Spearman correlation test, on the second day of ICU treatment, a significant correlation was found between PCT and SOFA scores ($p=0.008$) with a correlation value $r=0.462$. The resulting correlation value showed a positive correlation, which meant that the higher the PCT level in septic patients, the higher the SOFA scores with moderate strength (correlation value 0.4-<0.6). There was no statistical value in the PTX-3 correlation test with the SOFA scores on the second day ($p>0.05$). The study by Hu et al. (2018) showed that PTX-3, along with other biomarkers such as PCT, is highly relevant to the severity of patients with sepsis and septic shock and can predict sepsis outcomes and may be a potential biomarker of disease stratification in sepsis. (6)

In addition to using SOFA scores in predicting mortality in septic patients, biomarkers can also be used to predict prognosis and evaluate mortality in sepsis or septic shock patients; these biomarkers must be able to reflect the concept or inflammatory process that plays a role in the pathophysiology of sepsis. Sensitive and specific tests, such as CRP and albumin, are needed quickly in sepsis without waiting for blood culture results so that they can provide fast and appropriate therapy to reduce mortality and morbidity in patients. (16)

Schmidt et al. (2019) conducted a prospective analysis using PCT, CRP, albumin, and blood culture as early markers of sepsis diagnosis or predictors of outcome. They found a significant association between PCT, CRP, and albumin levels in patients with sepsis and septic shock ($p<0.005$). (17)

Further research is needed to use PTX-3 as a prognostic marker and predictor of mortality in septic patients admitted to the ICU.

Conclusions

PTX-3 and PCT levels correlate with SOFA scores in septic patients admitted to the ICU.

Conflict of interest statement

No potential conflicts of interest relevant to this article have been reported.

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Table 1. Demographic data

Variables	Results
Gender, n (%) - Men - Women	 19 (59.4%) 13 (40.6%)
Age (years), mean±standard deviation	45.13±14.81
Age (years), median (min-max)	48 (18-65)
Diagnosis, n (%) - Sepsis - Septic shock	 10 (31.3%) 22 (68.8%)

Table 2. SOFA scores, PTX-3, and PCT

Variable	Day 1	Day 2	p-value
SOFA, median (min-max)	7.00 (3-16)	7.00 (2-15)	0.574
PTX-3 (ng/ml), median (min-max)	2.60 (1.43-13.39)	3.40 (1.17-14.26)	0.036
PCT (ng/ml), median (min-max)	10.25 (2-51.80)	13.38 (0.14-162.96)	0.010

Legend: SOFA=Sequential Organ Failure Assessment; PTX-3=pentraxin-3; PCT=procalcitonin.
Data were tested using the Wilcoxon signed-rank test.

Table 3. Blood gas analysis and blood chemistry test results

Variables	Day 1	Day 2	p-value
PaO2 (mmHg), median (min-max)	197.2 (70.3-246)	186.5 (84-301.9)	0.78
FiO2 (%), median (min-max)	60 (40-100)	60 (40-100)	0.061
PaO2/FiO2, median (min-max)	260.6 (87.9-436)	315.8 (84-530)	0.069*
GCS, median (min-max)	8 (0-14)	9.5 (3-15)	0.224
Platelets ($x10^3/\mu l$), median (min-max)	164.5 (19-549)	166 (7-618)	0.192
Total bilirubin (mg/dl), median (min-max)	0.94 (0.03-5.58)	0.9 (0.06-11.59)	0.701
Creatinine (mg/dl), median (min-max)	0.77 (0.43-13.08)	0.83 (0.44-11.18)	0.91
MAP (mmHg), median (min-max)	79 (67-95)	78 (65-91)	0.125*

Legend: PaO2=arterial oxygen partial pressure; FiO2=fractional inspired oxygen; GCS=Glassgow coma scale; MAP=mean arterial pressure.
Data were tested using the Wilcoxon signed-rank test, except * (data were tested using paired sample t-test).

Table 4. Correlation of PTX-3 and PCT with SOFA scores in septic patients on day 1 of ICU care

	SOFA scores	
	p-value	r
PTX-3	0.025	0.395
PCT	0.035	0.375

Legend: PTX-3=pentraxin-3; PCT=procalcitonin; SOFA=Sequential Organ Failure Assessment. Data were tested using the Spearman correlation test.

Table 5. Correlation of PTX-3 and PCT with SOFA scores in septic patients on day 2 of ICU care

	SOFA scores	
	p-value	r
PTX-3	0.093	0.302
PCT	0.008	0.462

Legend: PTX-3=pentraxin-3; PCT=procalcitonin; SOFA=Sequential Organ Failure Assessment. Data were tested using the Spearman correlation test.

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