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The Relationship between Pentraxin 3 and Procalcitonin with SOFA Score as a Prognostic Factor in Septic Patients Admitted to the ICU at H. Adam Malik Hospital Medan

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Abstract: ***The statistical spearman correlation test showed that the levels of pentraxin3 and procalcitonin on day 1 had no significant relationship with the SOFA score on day 1 with (P>0.05). While the levels of procalcitonin on day 3 there wash a significant relationship with the SOFA score on the third day (P=0.032) with a correlation value (r=0.374). Further studies need to be carried out and associated with other inflammatory markers and sepsis associated including CRP, IL6, NLR to assess the severity of sepsis patient.***

Keywords: Sepsis, Pentraxin3, SOFA score, Infection

1. Introduction

Sepsis is a complex condition of the body that is stimulated by infection and then triggers an excessive body immune response. In sepsis, the body's immune response initiated to fight infection can reverse causing various damage to the body. The three important signs of sepsis are excessive inflammation and coagulation and suppression of fibrinolysis. In the United States, which is also a developed country, deaths from sepsis each year reach 70, 000 people. Approximately 500, 000 new cases develop sepsis where the mortality reaches 35%. This death rate tends to rise and now ranks as the 10th cause of death in the United States.[1]

Organ failure is one of the causes of the high mortality and morbidity rates of patients in the ICU and the high costs that must be incurred. Therefore, evaluation of organ dysfunction at any time during ICU care is helpful in following the progression of the disease. There are many scoring systems to predict patient outcome in ICU such as SOFA, SAPS, APACHE, MPM and a number of other scoring systems. One scoring system that is widely used in the world is the SOFA score.[2]

Pentraxin 3 (PTX3) is an acute phase protein that represents the pentraxin subfamily and is expressed in various cells, such as monocytes, endothelial cells, dendritic cells or neutrophils during the inflammatory process. PTX 3 as a multifunctional pattern recognition molecule, has been reported to be strongly associated with the severity of infection. PTX3 and PCT were all detected in patients with sepsis long after the onset of sepsis, whereas other proinflammatory cytokines (such as interleukins and tumor necrosis factor-alpha) were short-expressed.[3]

PCT was first identified from medullary thyroid carcinoma cells. PCT is a protein consisting of 116 amino acids (AA) with a BM ± 13 kDa, encoded by the Calc-I gene located on chromosome 11 and produced in C cells of the thyroid gland as a prohormone of calcitonin. PCT is now a diagnostic tool for identifying severe bacterial infections and can be relied upon to indicate a complication secondary to systemic inflammation in the body. The amount of procalcitonin is increased in cases of sepsis.[4]

2. Methods

The research was conducted at the Department of Clinical Pathology, Faculty of Medicine, University of North Sumatra / Haji Adam Malik Hospital, Medan in collaboration with the Department of Anesthesiology and Intensive Therapy, Faculty of Medicine, University of North Sumatra. This study is an observational study with a cohort study design. The study was conducted in April 2021 – June 2021. The research subjects were male and female patients who were treated in the ICU of H. Adam Malik Hospital who was diagnosed with sepsis.

The sample size in this study was determined at 33 samples. The 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 who were treated at the ICU H. Adam Malik Hospital, Medan, aged > 18 years and < 65 years, and agree to participate in the research. The exclusion criteria were liver disease and chronic kidney disease,, receiving natrium bicarbonate drugs and patients with alcohol and drug intoxication.

Each sample was examined for Pentarxin 3 and Procalcitonin on days 1 and 3. Examination of vital signs, GCS, platelets, total bilirubin, creatinine, blood gas analysis as well as SOFA score assessment on days 1 and 3. Examination of PTX 3 and PCT using serum was examined using an automatic device analyzer with the principle of ELISA examination.

3. Statistic Analysis

Data analysis was performed 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. The correlation of PTX3 and PCT levels with patients with sepsis used the Pearson correlation test if the data were normally distributed. If the data is not normally distributed, the Spearman rank test is used. All statistical tests with p value < 0.05 were considered significant.

4. Result

This study was followed by 33 people with sepsis who were treated in the ICU room at Haji Adam Malik Hospital, Medan. All research subjects have met the inclusion criteria. There were 19 male patients with sepsis (57.6%). The mean age of the research subjects was 50.3 years with the youngest being 18 years old and the oldest being 65 years old. The most ethnic subjects were Batak with 21 people (63.6%) followed by Javanese subjects with 7 people (21.2%). Based on the diagnosis, it is divided into a diagnosis that requires surgery and a diagnosis that does not require surgery, the results of the diagnosis show that most of the research subjects are patients who do not require surgery, amounting to 25 people (75.8%). While patients with a diagnosis requiring surgery amounted to 8 people (24.2%)

Table 1: Demographic Characteristics of Research Subjects

Demographic Characteristics	n = 33
Sex, n (%)	
Male	19 (57, 6)
Female	14 (42, 4)
Age, Years	
Mean (SD)	50, 3 (15, 74)
Median (Min – Max)	57 (18 – 65)
Ethnic, n (%)	
Batak	21 (63, 6)
Jawa	7 (21, 2)
Karo	3 (9, 1)
Melayu	2 (6, 1)
Diagnosis, n (%)	
Burst Fracture cu frankle A	1 (3)
Lung cancer + Sepsis	3 (9, 1)
CHF + Pneumonia + Sepsis	2 (6, 1)
Colitis + sepsis	1 (3)
Combutio gr. II-III 90% + sepsis	1 (3)
Diffuse axonal injury gr. I + sepsis	1 (3)
DM tipe II + sepsis	2 (6, 1)
Fraktur Compressed c4 + sepsis	1 (3)
Pneumonia + sepsis	1 (3)
surgical wound infection + sepsis	1 (3)
Pneumonia + sepsis	1 (3)
COPD + sepsis	1 (3)
Pneumonia + sepsis	2 (6, 1)
SLE + sepsis	1 (3)
Spondilitis TB + sepsis	1 (3)
Stroke + sepsis	5 (15, 2)
Subaracnoid Hemorrhagik + sepsis	3 (9, 1)
GBS + sepsis	1 (3)
syok sepsis	2 (6, 1)
TBC + Sepsis	1 (3)
Urosepsis	1 (3)

Table 2 shows the mean and standard deviation (SD) of the results of the SOFA, pentraxin 3 and procalcitonin scores on the measurement on the first and third day of treatment in the ICU H. Adam Malik Hospital Medan. The mean SOFA score on the first day of treatment was 4.82 (SD = 2.11) while on the third day the mean SOFA score decreased with a mean value of 4.27 (SD = 3.19). However, using the Wilcoxon test, it did not show a significant difference in the mean SOFA score between the first and third day SOFA scores (p = 0.083).

Table 2: SOFA Score Results, Pentraxin 3 and Procalcitonin

	Day I	Day III	p*
SOFA, mean (SD)	4, 82 (2, 11)	4, 27 (3, 19)	0, 083
Pentraxin 3, mean (SD), ng/mL	2, 73 (0, 32)	1, 76 (0, 71)	<0, 001
Procalcitonin, mean (SD), ng/mL	16, 2 (16, 87)	12, 65 (18, 38)	0, 001

*Wilcoxon

The mean of pentraxin 3 on the first day of treatment was 2.73 ng/mL (SD = 0.32 ng/mL) while on the third day the mean of pentraxin 3 decreased with a mean value of 1.76 ng/mL (SD = 0.71 ng/mL). Using the Wilcoxon test showed a significant difference in the mean levels of pentraxin 3 between the first day and the third day (p < 0.001).

Table 3 shows the results of the analysis of blood gases and blood chemistry on the first and third days of sepsis patients who were treated in the ICU room of Haji Adam Malik Hospital, Medan

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Table 3: Laboratory Examination Results Blood Gas Analysis and Blood Chemistry

	Day I	Day III	p*
PaO_2, mean (SD), mmHg	161, 31 (40, 82)	175, 25 (31, 06)	0, 441
FiO_2, mean (SD), %	40, 61 (7, 04)	39, 42 (6, 96)	0, 282
PaO_2/FiO_2, mean (SD)	413, 27 (132, 31)	467, 15 (100, 24)	0, 150
GCS, mean (SD)	11, 03 (2, 42)	11, 12 (2, 43)	0, 707
Platelet, mean (SD), ribu/µL	234, 76 (109, 76)	233, 58 (126, 95)	0, 903
Bilirubin Total, mean (SD), mg/dl	1, 34 (0, 83)	1, 23 (0, 8)	0, 030
Creatinin, mean (SD), mg/dl	2, 08 (1, 78)	2, 24 (2, 12)	0, 670
MAP, mean (SD), mmHg	93, 43 (48, 23)	114, 28 (63, 71)	0, 001

*Friedman

There were no significant differences in the values of PaO2, FiO2, PaO2/FiO2, GCS, platelet levels and creatinine between the first and third day of examination in the ICU room at Haji Adam Malik Hospital Medan (p>0.05). However, for the parameters of total bilirubin and MAP values, there was a significant difference (p<0.05).

Table 4: The relationship between Pentraxin 3 and Procalcitonin on SOFA scores in Sepsis Patients on the First Day of Treatment

	SOFA score	
	P	R
Pentraxin 3	0, 688	0, 073
Procalcitonin	0, 070	0, 320

Using the Spearman correlation test showed that there was no significant correlation between pentraxin 3 and procalcitonin with SOFA scores on the first day of treatment in the ICU Haji Adam Malik Hospital (p>0.05).

Table 5: Relationship of Pentraxin 3 and Procalcitonin to SOFA scores in Sepsis Patients on Day Three of Treatment

	SOFA score	
	P	R
Pentraxin 3	0, 911	0, 020
Procalcitonin	0, 032	0, 374

Using the Spearman correlation test showed that, for the third day of treatment, a significant correlation was found between procalcitonin and SOFA score (p = 0.032) with a correlation value of r = 0.374. The resulting correlation value indicates that a positive correlation was found, which means that the higher the pentraxin level in the septic patient, the higher the SOFA score with weak strength (correlation value > 0.2 to 0.4).

5. Discussion

This study was followed by 33 people with sepsis who were treated in the ICU room at Haji Adam Malik Hospital, Medan. There were 19 male patients with sepsis (57.6%). The mean age of the research subjects was 50.3 years with the youngest being 18 years old and the oldest being 65 years old. Based on the diagnosis, it showed that most of the patients with sepsis who did not require surgery amounted to 5 people (75.8%), followed by sepsis patients who needed surgery which amounted to 8 people (24.2%).

In line with the study conducted by Tsui et al, 2021. They conducted a cohort study of 115 septic patients. The results of their study showed that the predominant age characteristic of septic patients was elderly, 67 years with male sex predominating in sepsis patients. However, their study showed that based on diagnosis and comorbidity, cases were dominated by pulmonary infections, kidney infections, cerebrovascular disorders and malignancy.[5]

Sepsis is a medical emergency that must be treated immediately. Sepsis can be triggered by an infection in any part of the body, but the most common areas of infection that cause sepsis are the lungs, urinary tract, abdomen, and pelvis. Sepsis is usually caused by a bacterial infection (though sepsis can be viral, or more often, fungal). There are several risk factors that are considered to play a role in the incidence of sepsis: age, gender, race, comorbid disease, genetics, corticosteroid therapy, chemotherapy, and obesity.[5]

Adult patients with old age and male gender are 2, 562 times more likely to suffer from sepsis compared to adult female patients. Because older men often suffer from chronic diseases and have many comorbidities, this causes a weakened immune system if they have an infection and if they have sepsis the chances of dying are greater. Based on the study, septic patients aged 65 years had a higher sepsis mortality rate compared to younger patients. The incidence of sepsis increased sharply in the elderly aged 65 years with 27.7%.[6]

Septic patients of geriatric age also died earlier on hospitalization; about 26% died in the first week of hospitalization. Different at a young age can provide a better inflammatory response than old age. In addition, women are more likely to survive sepsis because they have female sex steroids that produce immunoprotective substances, besides that women have two X chromosomes; This is what makes women immunological protection better against infection.[6]

The results of our study showed a decrease in SOFA scores from day 1 to day 3. However, using the Wilcoxon test did not show a significant difference in the mean SOFA score between the first and third day SOFA scores (p = 0.083). This is because almost all septic patients admitted to the ICU on the first day with SOFA scores > 5, after intensive treatment, within 48 hours of ICU care there was a decrease in SOFA scores < 5.

Sepsis is a life-threatening condition of organ dysfunction caused by dysregulation of the host's immune system against infection and the Sequential Organ Failure Assessment (SOFA) score is a scoring to assess sepsis-related organ failure. An increase in the SOFA score was associated with a worse patient outcome. SOFA score parameters consist of parameters to assess respiration (PaO2/FiO2), central nervous system (Glasgow coma Scale [GCS]), cardiovascular (Mean arterial pressure [MAP]), coagulation system (platelet), liver (bilirubin), and renal (serum creatinine).[7]

A study conducted by Yang Y et al, 2016 states that if a septic patient in the ICU gets a SOFA score of 0-1, then organ dysfunction/mortality is almost non-existent, but if SOFA score > 2 then mortality is 10%, SOFA score <9 means mortality is 33. % and if SOFA score >10 then mortality >95%.[8]

Our results showed a decrease in PTX3 levels from day 1 to day three. Using the Wilcoxon test showed a significant difference in the mean levels of pentraxin 3 between the first day and the third day (p < 0.001). Likewise, our results showed a decrease in PTX3 levels from day 1 to day 3. Using the Wilcoxon test showed a significant difference in the mean levels of procalcitonin between the first and third days (p = 0.001).

The decrease in PTX3 and PCT levels on Day 1 to Day 3 indicates a process of clinical improvement in sepsis patients treated in the ICU, one of these clinical improvements is management and monitoring of sepsis according to the standards applied to septic patients treated in the ICU, so that patient improvement not only seen clinically but also seen from a decrease in PTX 3 and PCT during 48 hours of treatment, because these two markers are highly correlated with the degree of inflammation and bacteremia in septic patients. So that the decrease in these two markers describes a good prognosis.

Study conducted by Hu et al, 2018. They conducted a study of 114 septic patients admitted to the ICU, then they performed PTX3 examinations, PCT and calculated SOFA scores on days 0.3, 7. The results of their study showed that sepsis patients who died generally had elevated PTX3 levels

(>100 ng/ml) and PCT levels of 38.7 and SOFA scores >10.9

Pentraxin 3 (PTX3) is an acute phase protein that represents the long-arm pentraxin subfamily and is expressed in various cells, such as monocytes, endothelial cells, dendritic cells or neutrophils during the inflammatory process. PTX3 also plays a role as a multifunctional pattern recognition molecule in the immune response to infection, it has been reported to be strongly associated with the severity of infection, especially in sepsis.[10]

Procalcitonin is a calcitonin prohormone found in the human body. In sepsis, an increase in procalcitonin levels in the blood has a significant value that can be used as a biomarker of sepsis. Procalcitonin levels were 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 more than 10 ng /mL (septic shock). In addition, PTX3 and PCT can all be detected in patients with sepsis long after the onset of sepsis, so these markers have good prognostic value for mortality.[11]

In our study, researchers conducted laboratory tests regarding SOFA score parameters. The results of our study showed that there were no significant differences in the values of PaO2, FiO2, PaO2/FiO2, GCS, platelet levels and creatinine between the first and third day of examination in the ICU room at Haji Adam Malik Hospital Medan (p> 0.05). However, for the parameters of total bilirubin and MAP values, there was a significant difference (p<0.05).

Laboratory measurements related to this SOFA score parameter are to analyze the occurrence of organ dysfunction in sepsis patients as well as a predictor of outcome. The results of our study showed that the total bilirubin parameters showed a significant difference (p<0.05). In line with a study conducted by Brain et al 2017 which stated that suppression of hepatocellular function in early sepsis was associated with decreased hepatic perfusion, with an increase in the proinflammatory cytokine TNF alpha. Liver failure is a complication that usually occurs after renal and pulmonary dysfunction in septic patients. The pathophysiology of liver injury in sepsis is complex and not fully understood. Infection or shock, systemic inflammatory response, persistent failure of microvascular circulation, or even side effects of the given treatment may be the main causes of liver failure in septic patients.[12]

The results of our study also showed that the MAP parameter showed a significant difference (p<0.05). In line with the results of the 2017 study, Brain et al also reported that patients with SOFA scores with cardiovascular dysfunction had a 14.7 times risk of death compared to those without cardiovascular dysfunction which was only 7.6 times. This is caused by microcirculation dysfunction, namely the displacement of blood flow (shunting) from areas of microcirculation dysfunction to areas of good microcirculation, resulting in a pO2 gap between arterial and venous microcirculation. When oxygen delivery is not sufficient, compensation occurs by increasing oxygen extraction and when this compensatory mechanism is exhausted, tissue hypoxia occurs.[12]

Using the Spearman correlation test showed that there was no significant correlation between pentraxin 3 and procalcitonin with SOFA scores on the first day of treatment in the ICU Haji Adam Malik Hospital (p>0.05). Meanwhile, for the third day of treatment, a significant correlation was found between procalcitonin and SOFA score (p = 0.032) with a correlation value of 0.374.

In line with the study conducted by Hu et al, 2018. They conducted a study of 114 septic patients. Then the patients with sepsis were examined for PTX3 and PCT and at the same time, to assess organ dysfunction, SOFA and APACHE II scores were calculated. The results of their study showed a significant relationship between PTX and PCT with SOFA and APACHE II scores (p<0.001). This means that non-surviving sepsis patients have increased PTX3 and PCT levels and SOFA and APACHE II scores.[13]

Sepsis and septic shock are medical emergencies, so prompt identification and appropriate management in the early hours after onset will improve treatment outcomes, especially among high-risk patients. Thus, there is a need for biomarkers that allow early stratification and recognition of septic patients who are at high risk of death. The two most studied and used biomarkers in patients with sepsis are pentraxin 3, C-reactive protein (CRP) and procalcitonin (PCT), a prehormone. Nevertheless they have limited ability to differentiate sepsis from other inflammatory conditions or to predict outcome.[13]

In recent years, pentraxin 3 (PTX3), an acute phase protein, has emerged as a promising biomarker of sepsis. PTX3 is a prototypical member of the long-arm pentraxin subfamily and a key component of innate and humoral immunity. PTX3 is expressed in a number of tissues, particularly dendritic cells and macrophages, in response to proinflammatory stimuli. In addition, PTX3 is deposited in neutrophil granules and localizes in neutrophil extracellular traps. Once released, PTX3 acts by recognizing microbes, activating complement and facilitating pathogen recognition by phagocytes, thereby promoting pathogen clearance, tuning inflammatory responses and promoting tissue remodeling, thus increasing PTX3 is consistent with the severity of inflammation and pathogenesis in sepsis and has been elevated since early onset. sepsis is enforced.[14]

Safari et al, 2016 reported that initial, highest SOFA score and mean SOFA score were associated with mortality and could be used to assess the degree of organ dysfunction at first admission to the ICU. Safari et al 2016 also stated that a SOFA score > 11 had a mortality rate of > 90% and a decrease in this score within 48 hours was associated with a 6% decrease in mortality and if this score did not change or tended to increase, the mortality rate increased by 37% in the initial score.2-7 and 60% if the initial score is 8-11.[15]

Elevated PTX3 early in the course of sepsis was closely associated with risk factors for 28-day morality. In healthy subjects, plasma PTX3 levels are very low (<2 ng/mL), but can rise rapidly under inflammatory and infectious conditions. Levels are elevated in critical illness with a gradient from systemic inflammatory response syndrome (SIRS) to sepsis and septic shock. Thus, PTX3 has been

proposed as a prognostic marker for sepsis. In a systematic review and meta-analysis, PTX3 significantly predicts disease severity and mortality in sepsis.[16]

The study by Hu et al, 2021 showed that PTX3, together with other biomarkers such as PCT is highly relevant to the severity of patients with sepsis and septic shock and can predict sepsis outcome and may be a potential biomarker of disease stratification in sepsis.[17]

Procalcitonin is a calcitonin prohormone found in the human body. In sepsis, an increase in procalcitonin levels in the blood has a significant value that can be used as a biomarker of sepsis. Procalcitonin levels were 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 more than 10 ng /mL (septic shock). When compared with other septic biomarkers (eg CRP), procalcitonin is more sensitive and its levels rise the fastest after exposure to infection.[18]

PCT can be used to differentiate an infection caused by bacteria from an infection that is not caused by bacteria. PCT is mainly induced in large quantities during bacterial infection, but PCT concentrations in the body are low in other types of inflammation, such as viral infections, autoimmune diseases, and the body's rejection of organ transplants.[18]

The value of the increase in procalcitonin was different between gram-positive and gram-negative bacteria. The procalcitonin value is useful as a source of information in selecting the best antibiotic therapy, when blood culture results are not readily available or the site of infection is not clearly known. This makes procalcitonin a specific biomarker in assessing the severity of systemic bacterial infection and sepsis.[18]

In addition to using the SOFA score in predicting mortality in septic patients, it can also use biomarkers to predict prognosis and evaluate mortality in patients with sepsis or septic shock, these biomarkers must be able to reflect the concept or inflammatory process that plays a role in the pathophysiology of sepsis. Sensitive and specific investigations are needed in sepsis quickly without waiting for blood culture results so that it can provide rapid and appropriate therapy to reduce mortality and morbidity in patients, such as C-Reactive Protein (CRP), and albumin.[19]

In line with research conducted by Schmidt et al 2019. Procalcitonin, C-Reactive Protein, Albumin, and Blood Cultures as Early Markers of Sepsis Diagnosis or Predictors of Outcome: A Prospective Analysis. They found that there was a significant relationship between PCT, CRP and albumin levels in patients with sepsis and septic shock ($p<0.005$). (10.7 (4.9–16.2) 16.3 (7.2–21.7), 40 (52) 8 (16.5), 2.8 (2.4–3.3) 2.4 (1.9–2.8)). sepsis and septic shock. ($p<0.001$). (3 (1–5) 7 (3–10)).[19]

6. Conclusion

Using the Wilcoxon test showed a significant difference in the mean levels of pentraxin 3 between the first day and the third day ($p < 0.001$) in septic patients admitted to the ICU. Using the Wilcoxon test showed a significant difference in the mean levels of procalcitonin between the first day and the third day ($p = 0.001$). in septic patients admitted to the ICU. Using the Spearman correlation test showed that there was no significant correlation between pentraxin 3 and procalcitonin with SOFA scores on the first day of treatment in the ICU Haji Adam Malik Hospital ($p>0.05$). Meanwhile, for the third day of treatment, a significant correlation was found between procalcitonin and SOFA score ($p = 0.032$) with a correlation value of 0.374. From the results of our study, procalcitonin levels can be used as a substitute for the SOFA score as a prognostic value in sepsis patients admitted to the ICU.

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