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Cut-Off Value of Procalcitonin in Sepsis and Septic Shock patients at Dr. Soetomo Hospital

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ABSTRACT

Sepsis is a state of life-threatening organ dysfunction caused by dysregulation of the body's response to infection, and it is marked by an increase in SOFA score ≥ 2 or qSOFA score ≥ 2. Septic shock is a subset of sepsis accompanied by severe circulatory disorders that can greatly increase mortality. Although the current gold standard diagnosis method for sepsis is bacterial culture, Procalcitonin (PCT) level can help identify sepsis severity because bacterial culture requires a relatively long time. This study aims to determine the cut-off point of PCT to detect severity in patients with sepsis and septic shock. The data taken were secondary data from the medical records of sepsis and septic shock patients in Dr. Soetomo General Hospital from 2017 to 2019. The cut-off value of PCT for sepsis and septic shock was determined using Receiver Operating Characteristic (ROC) analysis curve. Most sepsis patients were young (18-65 years) (69%) (p=0.331) and male (60%) (p=0.156). There was a significant difference in PCT levels between the septic and non-septic group (p=0.000), and there was a positive correlation between PCT and sepsis. The cut-off of procalcitonin in sepsis was 0.6 ng/mL, and the cut-off of PCT in septic shock was 10 ng/mL.

Keywords: Cut-off, procalcitonin, sepsis, septic shock

INTRODUCTION

Sepsis is a state of life-threatening organ dysfunction caused by dysregulation of the body's response to infection. Organ dysfunction is diagnosed if the increase in the Sequential Organ Failure Assessment (SOFA) score is ≥ 2. Septic shock is a subset of sepsis with severe circulatory and cellular/metabolic disorders, leading to a drastic increase in mortality.

Procalcitonin (PCT) is a hormone that will increase in the case of bacterial infections. Serial PCT measurements can be used to monitor the course of the disease. Increased or consistently high PCT values indicate continued disease activity. A decreased PCT value indicates decreased inflammatory reaction and resolution of infection. Procalcitonin can be used as a basis for stopping antibiotic therapy.[1]

In 1994 the European Society of Intensive Care Medicine issued a consensus called the Sequential (Sepsis-related) Organ Failure Assessment (SOFA) score to quantitatively describe the degree of organ dysfunction as objectively as possible. Organ dysfunction is diagnosed when the SOFA score increases ≥ 2. The SOFA score was further simplified by using qSOFA to identify septic patients outside the ICU. qSOFA does not require laboratory testing and can be performed quickly and repeatedly. The use of qSOFA is expected to help clinicians early recognize organ dysfunction and sepsis to start or improve the current therapy immediately.[2]

Septic shock is sepsis with persistent shock/ hypotension (even with fluid resuscitation). Septic shock is sepsis with arterial blood pressure <90 mmHg or 40 mmHg below the patient's normal blood pressure for at least one hour despite fluid resuscitation or a vasopressor needed to keep systolic blood pressure ≥ 90 mmHg or mean arterial pressure ≥ 65 mmHg and serum lactate levels greater than 2 mmol/L (>18 mg/dL) without hypovolemia.[3]

Most of the microorganisms that cause sepsis are Gram-negative bacteria.[4] Suwondo, who examined sepsis in the ICU at Dr. Kariadi Hospital in Semarang found that the most causative microorganisms of sepsis from blood culture were *Staphylococcus aureus* and *Staphylococcus haemolyticus*.[5]

In physiologic conditions, the transcription of the Calc-1 gene is limited to neuroendocrine cells in the

thyroid gland and lungs; therefore, the serum PCT levels in healthy individuals are very low (<0.05ng/mL). In healthy people, PCT is produced due to increased calcium, glucocorticoids, glucagon, and gastrin. In this state, the PCT is broken down into CT.[6]

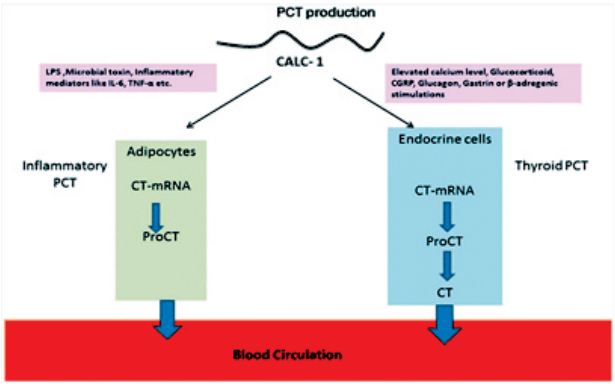

Figure 1. Induction of Calc-1 gene in calcium homeostasis and inflammation[1]

In a state of bacterial sepsis, the expression of the Calc-1 gene is increased, and PCT is released by almost all body tissues, which have adipocyte cells such as the liver, lung, kidney, and intestine.[7] Procalcitonin values of >0.5 ng/mL can indicate sepsis, >2 ng/mL indicate a severe infectious process, and >10 ng/mL are often found in patients with septic shock.[8]

The combination of microbial products and proinflammatory cytokines IL-1β, TNF-α, and IL-6 led to increased PCT expression.[9] In this event, PCT is not broken down into CT (Figure 1). Interestingly, PCT induction can be attenuated by IFN-γ, which plays an essential role in the initial host defense against viruses. Consequently, serum PCT concentrations can be used to differentiate between bacterial and viral infections, where the most PCT levels of viral infection often are >0.05 ng/mL but usually <1 ng/mL.

Compared with other sepsis biomarkers such as C-Reactive Protein (CRP), PCT is more sensitive, and its levels rise the fastest after exposure to bacterial infection. Procalcitonin levels are detected rapidly within 2 hours after stimulation and reach their peak after 12 to 48 hours, whereas CRP is absent for 6 hours. Therefore, from several studies, it can be suggested that PCT markers are more sensitive than CRP markers.

The cut-off point of PCT varies depending on the clinical infection. A study by Arif showed that the PCT level of 1.60 ng/mL had a sensitivity value of 82.4%, and a specificity of 65.2%, and it was concluded that 1.60 ng/mL was the best value used as a cut-off in the study between bacterial sepsis and viral sepsis.[10]

METHODS

This study was a retrospective study. The study sample was the medical records in Dr. Soetomo Academic General Hospital from 2017 to 2019, whereas medical records of non-septic patients whose PCT data at Dr. Soetomo General Academic Hospital were used as the control. The inclusion criteria were all medical records of sepsis, septic shock, and non-sepsis patients with available PCT, bacterial culture, SOFA, or qSOFA data; and the exclusion criteria were chronic kidney failure patients, because of the high basal PCT levels due to high inflammatory cytokines. However, PCT as a biomarker of infection can still be used in patients with CRF by increasing the cut-off. If the standard cut-off for bacterial infection is 0.5 ng/mL, CRF patients are diagnosed with PCT infection at a PCT level of 0.75 ng/mL.[11]

A Receiver Operating Characteristic (ROC) analysis was constructed to determine the best cut-off value for this study. In addition, Chi-Square, Pearson, and Mann-Whitney U tests were used to determine differences and correlations between

Table 1. Sociodemographic characteristics of patients (n=73)

	Sepsis; n=23	Septic Shock; n=35	Control; n=15	P
Male; n (%)	13 (56.5%)	22 (62.8%)	12 (80%)	
Age; mean±SD	43.5±32.2	55.5±14.9	40.53±26.9	
Child (0-17 y.o); n (%)	5	1	4	
Adolescent (18-65 y.o); n (%)	15	25	8	
Middle age (66-79 y.o); n (%)	3	9	3	
Elderly (= 80 y.o); n (%)	0	0	0	
PCT (ng/mL); med	1.38	12.8	0.13	**0.037**

Table 2. Clinical diagnosis of sepsis patients (n=58)

	Sepsis; n=23	Septic Shock; n=35	Non-Sepsis; n=15	P
Comorbid disease				
Diabetes Mellitus (DM)	3	11	0	0.109
Hypertension	4	4	1	0.519
Stroke	2	3	2	0.987
Kidney illness	5	4	1	0.289
Malignancy	4	6	4	0.98
Causes of infection				
Respiratory tract infection	8	24	9	0.011
Urinary tract infection	4	8	0	0.615
Intra-abdominal infection	4	6	0	0.98
Central nervous system infection	6	2	1	0.028
Integumentary system infection	4	6	0	0.98
Other infections (musculoskeletal and reproductive systems)	4	2	0	0.153
PCT (ng/mL); med	2.88	1.38	0.13	0.22

Table 3. Risk factors for septic shock

Septic Shock Patients with OR*	OR
DM	3.056
Respiratory tract infections (pneumonia, TB, empyema, pleural effusion, bronchitis)	6.182
Digestive system involvement (diarrhea, inguinal hernia, diaphragmatic hernia, appendicitis, caecum resection	0.266
Urinary tract involvement (AKI, UTI, ACKD)	1.440
Integumentary system involvement (gangrene, skin ulcers, cellulitis, combustion)	1.440
Malignancy	0.586

*Description: ACKD: Acquired Cystic Kidney Disease; AKI: Acute Kidney Injury; UTI: Urinary Tract Infection; TB: Tuberculosis

each group. There were only 73 medical records that were used for this study due to the lack of PCT data in Dr. Soetomo General Academic Hospital and only 58 medical records of sepsis and septic shock patients, met the inclusion criteria.

RESULT AND DISCUSSIONS

Data were collected after the issuance of the ethical clearance letter from the Ethical Committee with number 1585/KEPK/X/2019. There were 73 patients involved in this study. The patients were divided into two groups: the sepsis patient group of 58 people and the control group of 15 people. Most sepsis patients in this study belonged to the youth age category (18-65 years) and male gender. The PCT test results of the sepsis group were significantly higher than those in the control group (p=0.037) (Table 1).

This research found that the most common comorbid disease of sepsis patients was DM. Clinical manifestations in septic patients at Dr. Soetomo General Academic Hospital involved manifestations of multiple organs dominated by patients with focal infections of the respiratory system (32/58=55.17%) and followed by focal infections of the urinary tract (12/58=20.69%). There was a significant difference in the number of septic shock patients with respiratory tract infection and the number of sepsis patients with respiratory tract infection (p=0.011) (Table 2). Sepsis patients have different risk factors for developing septic shock that depends on the comorbidities and the underlying diseases (Table 3).

Based on the culture results in this study, bacteria were only identified in 26% (15/58) of patients. Contrastingly, 74% of patients were diagnosed with sepsis based on clinical criteria because there was a possibility that bacterial culture was not able to be performed in these patients because of the high mortality of sepsis. Therefore, the culture results of some patients were not released because the patient had died.

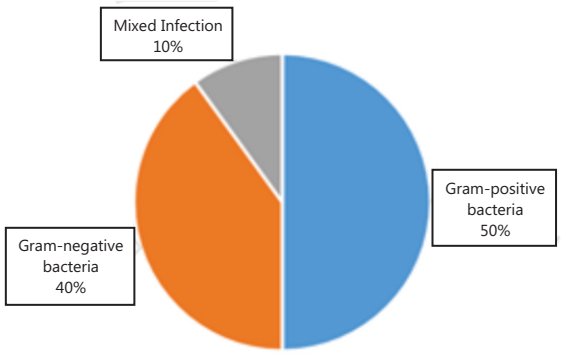

Figure 2. Pie chart of culture results

This research found that the mean PCT for the non-sepsis, sepsis, and septic shock group was 14.16 ng/mL, 27.8 ng/mL, and 37.28 ng/mL, respectively. The PCT levels in sepsis patients were significantly higher than non-sepsis patients ($p < 0.001$). Moreover, there was a significant positive relationship between PCT levels and sepsis ($p<0.001$; $r(21)=0.632$) and a significant positive relationship between PCT levels and septic shock ($p<0.001$; $r(33)=0.672$) (Figure 2).

Sepsis patients in this study have dominated the aged of 18-65 years and male. These findings were following the results of a study by Nasir, which suggested that females were less likely to suffer from sepsis and had a lower risk of death than males.[12]

This study found that patients with respiratory tract infections who experienced sepsis were 6 times more likely to develop septic shock than patients who did not have respiratory tract infections. This finding was consistent with a general elucidation of Community-Acquired Pneumonia (CAP) (48% of hospitalized patients), which showed that 4.5% of patients had septic shock.[13,14] Pneumonia can cause severe complications, such as Acute Respiratory Distress Syndrome (ARDS), which requires a ventilator. Mechanical ventilation can cause lung injury, surfactant dysfunction, and microvascular damage, resulting in decreased function of the alveolar-capillary membrane, leading to pulmonary edema and bacterial infection or sepsis.

Table 3 also showed that septic patients with DM were three times more likely to develop septic shock than septic patients without DM. Diabetes mellitus patients with uncontrolled blood glucose were 4.4 times more likely to experience septic shock because of defects in cell-mediated immunity and worse phagocytosis function.[15] Gunawan also stated that diabetes patients with low blood glucose control experience more severe sepsis and septic shock.[16]

The odds ratio of 1.440 showed that septic patients with urinary tract involvement were 1.4 times more likely to develop septic shock. Tambo stated that acute pyelonephritis with obstructive uropathy is more likely to develop into urosepsis. Guliciuc stated that urosepsis accounts for 20-30% of all sepsis patients.[17] Local factors, such as stones, obstructive uropathy, congenital uropathy, and neurogenic bladder disorders also impact the severity of urosepsis. Urinary tract obstruction patients with acute pyelonephritis bacteremia are also more likely to develop septic shock.[18,19]

This study found that sepsis patients with integumentary system involvement were 1.4 times

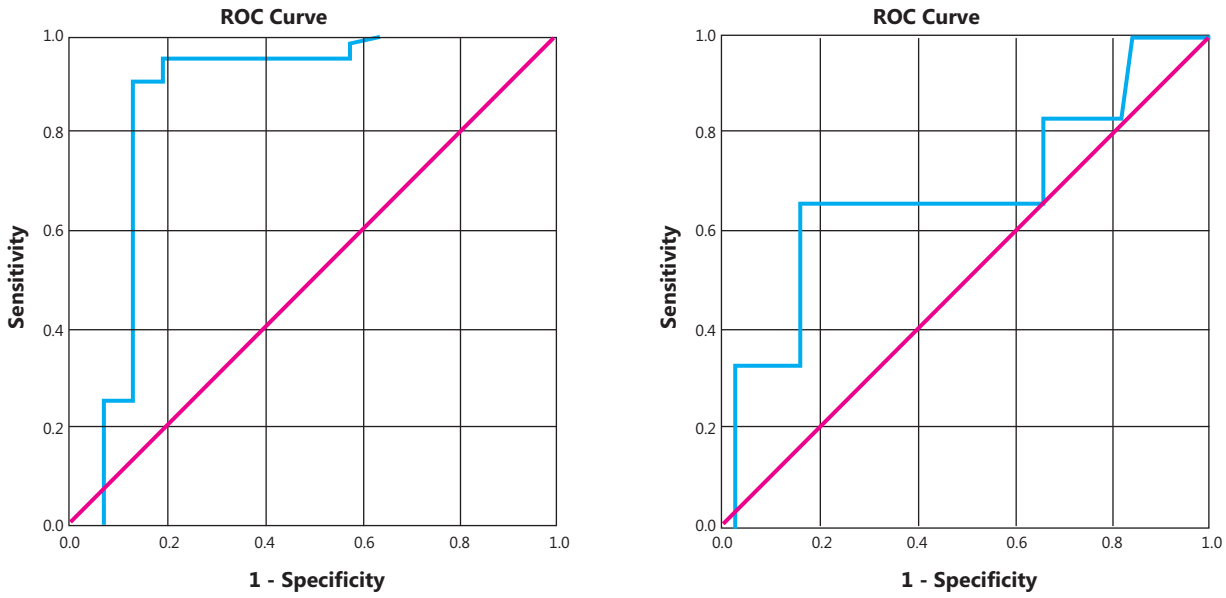

Figure 3. A: Sepsis ROC analysis; B: Septic shock ROC analysis

more likely to develop septic shock than sepsis patients who did not have integumentary system involvement. This occurrence may have happened because contamination of dead skin is a suitable medium for bacteria growth, thus facilitating infection. This infection is difficult to treat because the capillaries do not reach the area. Greenhalgh stated that sepsis could occur several times in patients with massive burns, and the patient was never free from the risk of acquiring sepsis until the burns are healed.[20] According to Fuss, 25 to 85% of those who die from burns are caused by sepsis.[21]

Reciever operating characteristic analysis (Figure 3A) showed the cut-off of PCT for the diagnosis of sepsis was 0.6 ng/mL (sensitivity=90.7%, specificity=87.5%, AUC=0.867). This result was similar to a study by Taylor, which obtained a PCT cut-off of 0.5 ng/mL, and the study by Fleuren, which found that PCT was useful for a sepsis screening test with a cut-off value >0.85 ng/mL.[22,23]

This study also found that the PCT cut-off in septic shock was 10.07 ng/mL (sensitivity=66.7%, specificity=81.6%, AUC=0.691) (Figure 3B). This finding was consistent with a study by Sharma, which reported an initial PCT value of 10.65ng/mL for septic shock.[24] It was similar to the study of Andriolo and Liu, which concluded that PCT of > 10 ng/mL indicates septic shock.[25,26]

CONCLUSIONS AND SUGGESTIONS

There was a significant difference between PCT levels for the non-sepsis, sepsis, and septic shock groups. There was a significant difference in PCT levels between the septic and non-septic group. The cut-off of PCT in sepsis was 0.6 ng/mL. The cut-off of PCT in septic shock was 10 ng/mL. More research regarding this topic with more samples and different variables is still needed to provide a better outcome.

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