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Relationship Between Procalcitonin Serum Level and Septic Patient Mortality in Dr. Saiful Anwar General Hospital, Malang

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ABSTRACT

Background: Procalcitonin is more frequently analyzed for sepsis diagnosis. Procalcitonin shows a tendency to increase as sepsis worsens. However, published studies investigating the correlation between procalcitonin and mortality in an adult patient with sepsis in Indonesia were lacking. This research aims to know the relationship between procalcitonin and mortality in sepsis.

Methods: A prospective cohort study was conducted in Dr. Saiful Anwar Public General Hospital, Malang, Indonesia from March to November 2018. During the study period, patients diagnosed with sepsis according to JAMA Sepsis-3 were tested for procalcitonin using Cobas e411 ECLIA method. The demographic and mortality data were acquired from the patients' medical record. The statistical analysis was done with SPSS v.23, $\alpha = 0.05$.

Results: From a total of 69 subjects, 43 did not survive (62.32%). The procalcitonin serum level is significantly higher in the non-survivors than the survivors (37.77 ng/mL vs. 3.07 ng/mL, p=0.016). The Spearman's rank correlation test showed r=0.293 (p=0.015). Using a cutoff point of 2 ng/mL, the relative risk is 2.77 (0.950-8.078).

Conclusion: There is a statistically significant weak relationship between procalcitonin and mortality, in which patients with procalcitonin equal or more than 2 ng/mL were 2.77 times more likely not to survive sepsis.

Keywords: Procalcitonin, sepsis, sepsis survival, prognosis, adult

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INTRODUCTION

In response to proinflammatory stimulation, procalcitonin is produced by vaious cell types and organs. It has an advantageous specificity for bacterial causes of suspected infection among other proinflammatory markers.[1] Because when localized, infections rarely increase the concentration of circulating procalcitonin, The marker does well in indicating the presence of systemic inflammatory reactions.[2] Because high concentration of procalcitonin more indicates bacterial infection, several studies had explored the potential of procalcitonin in predicting the outcome of patient and in developing a antibiotic treatment guided by procalcitonin.[1,3–6] Procalcitonin shows a tendency to increase as sepsis worsens.[3] More vigilant monitoring and rigorous measures can be taken when a septic patient is predicted to have poorer outcome. The ideal predictive biomarker should be able to predict the outcome early enough so to provide physicians ample of time to prevent further deterioration of multiple organ systems.[3]

Considering the potential benefit in predicting the patient outcome using procalcitonin—which tests are readily available in Indonesian public regional hospitals—some studies conducted in Indonesia in exploring the role of procalcitonin had been published.[7,8] However, published studies investigating the correlation between procalcitonin and mortality in an adult patient with sepsis in Indonesia were still rare. Therefore, we aim to explore the relationship between procalcitonin and mortality in sepsis.

METHODS

This was a prospective cohort study conducted in Dr. Saiful Anwar General Hospital, Malang, Indonesia. The inclusion criteria for this study were: (1) adult patients of sixteen years or older who were admitted to our hospital and diagnosed with sepsis according to Sepsis-3 criteria by the attending physician, (2) the patients had at least 1 procalcitonin determination around the time of diagnosis, ordered by any of the patients' attending physicians.

We excluded: (1) patients who went home against the attending physician's recommendation, (2) the patients with SOFA score less than 2, which assessment were based on platelet count, serum creatinine concentration and Glasgow Coma Scale (GCS) within 24-hour after the procalcitonin was checked. We also excluded patients with indetermined GCS due to lack of supporting data, and

patients whose attending physician did not order for platelet count and serum creatinine within 24 hour after the procalcitonin was determined.

The subjects' procalcitonin serum levels were collected from the laboratory information system (LIS). In our hospital, procalcitonin measurement was done with the Cobas e411 automated immunology analyzer. The method of procalcitonin detection is electrochemiluminescence Immunassay (ECLIA). In addition, we also collected the subjects' platelet count and serum creatinine data from the LIS. The platelet count was done using automated hematology analyzer Sysmex XN-1000/B3. The serum creatinine was measured with Cobas 6000 or Cobas c501 chemistry analyzer. We implement a once-daily quality control for procalcitonin using the manufacturer precicontrol before any test was performed. Westgard's rules were applied to monitor whether the reference controls were in range or out of control. The latter indicates calibration or other corrective laboratory actions.

The subjects' clinical data such as GCS and the outcome of blood culture, demographic data such as age on admission, sex, and also the outcome whether the subject survived the sepsis or not were acquired from the medical record. The data were tabulated in Microsoft Excel 2010 for Windows.

The minimum sample was 62 for correlation analysis between mortality and procalcitonin concentration with α=0.05 with two-tailed test, β=0.8, and a minimum correlation of 0.35 is considered significant.[9] Shapiro-Wilk test was conducted for numerical data to assess the data distribution. Descriptive data were presented as mean and standard deviation (SD) when normally distributed, or as median and interquartile range (IQR) when not normally distributed. Categorical data were presented as counts and percentage within each category. Bivariate analysis was conducted to compare the difference of the variables between the survivors and the non-survivors. A concentration of procalcitonin more than or equal to 2 ng/mL was considered as high, and less than 2 ng/mL was considered as low. The cutoff point was chosen based on another study.[10] Consequently, p-value less than 0.05 was considered statistically significant. The statistical analysis was done with SPSS software (version 23.0, IBM company, SPSS Inc.).

RESULTS

A total of 151 patients were enrolled from March to November 2018. There were 39 patients left the hospital against the attending physician's recommendation. As many 30 patients were excluded because of indetermined GCS on arrival due to sedation, aphasia, or other causes. There were another 13 patients who were excluded due to missing platelet count and creatinine serum data. The main analysis eventually included 69 patients.

The subjects had a median age of 58 and 42% were female gender. Among the 69 subjects, there were a total of 43 deaths (63%). The most common comorbidities among the survivors was hypertension (27%), while among the non-survivors was cerebrovascular accident (19%). The lung is the most frequent source of infection, comprises more than 40% among the survivors and the non-survivors. The details of the subject characteristics are shown in Table 1.

There is no significant difference in the proportion of sex (p=0.8) or age (p=0.3) between the survivors and to the non-survivors (Table 1). In contrast, there is a significant difference in the concentration of procalcitonin between the 2 groups (p=0.016). The procalcitonin serum level is significantly higher in the non-survivors than the survivors (37.77 ng/mL vs. 3.07 ng/mL, p=0.016).

Table 2 shows the distribustion of subjects classified based on the survival and the concentration of serum procalcitonin. Using the cutoff point of 2 ng/mL, the Spearman's rank correlation test showed r=0.293 (p=0.015). Using the cutoff, the relative risk is 2.77 (0.950-8.078).

DISCUSSION

Our subjects had a median age of 58 years old. It confirms other studies which argued that in adult, sepsis is more frequent in older age.[11] The proportion of male subjects were more than female (58% vs. 42%). The most common comorbidities among the survivors were hypertension (27%), congestive heart failure (19%), and malignancy (19%), while among the non-survivors were cerebrovascular accident (19%), hypertension (14%), and diabetes (14%). The most frequent source of infection is the lung which comprises more than 40% among both groups, the survivors and the non-survivors. The composition of the sex and age between the survivors are comparable to the non-survivors so that the effect of the variables can be disregarded.

Early knowledge and the establishment of antibiotic to control infection, and tight monitoring remain the important measures to diminish the morbidity and mortality in sepsis.[12] Unfortunately, cultures as one of many microbiologic modalities cannot profide a timely needed information.[13] Thus, sepsis biomarkers may improve a physician's ability to recognize septic patient risk to engage early and appropriate intervention. Procalcitonin has shown a great association with increased risk and graveness of bacterial infection.[14] In our study, the concentration of serum procalcitonin in the

Table 1 The characteristics of the sepsis survivors compared to the non-sorvivors

	Survivors		Nonsurvivors		
	n=26		n=43		
Variables	f (%)		f (%)		p-value
Sex					
male	14	(53.8%)	26	(60.5%)	0.8*
female	12	(46.2%)	17	(39.5%)	
Age in year (median, IQR)	57	(43.5-63)	58	(50-65)	0.30†
Comorbidities					
Hypertension	7	(27%)	6	(14%)	
Congestive Heart Failure	5	(19%)	4	(9%)	
Coronary Artery disease	2	(8%)	4	(9%)	
Cerebrovascular accident	3	(12%)	7	(16%)	
Chronic obstructive lung disease	2	(8%)	4	(9%)	
Diabetes	4	(15%)	6	(14%)	
Renal disease	3	(12%)	3	(7%)	
Autoimmune disease	1	(4%)	1	(2%)	
Malignancy	5	(19%)	4	(9%)	
Source of sepsis					
Lung	11	(42%)	21	(49%)	
Abdomen	0	(0%)	4	(9%)	
Wound/soft tissue/skin infection	3	(12%)	2	(5%)	
Catheter-based infection	2	(8%)	0	(0%)	
Central nervous system	1	(4%)	1	(2%)	
Unknown	9	(35%)	15	(35%)	
Positive blood culture	2	(7.69%)	6	(13.95%)	
Procalcitonin in ng/mL (median, IQR)	3.07	(0.37-18.20)	8.06	(2.32-48.16)	0.02†

IQR = interquartile range; *Fisher-exact test; †Mann-Whitney-U test

Table 2 The number of subjects with high procalcitonin in the survivor and the non-survivor groups

Procalcitonin	Non-survivor	Survivor
≥2 ng/mL	34	15
<2 ng/mL	9	11
Total	**43**	**26**

non-survivors were significantly higher than the survivors (37.77 ng/mL vs. 3.07 ng/mL, p=0.016). It is proposed that high concentration of serum procalcitonin was predictive for septic patient survival. The result is consistent with several other studies.[4,12,14–16] However, some studies investigating serial procalcitonin showed a stronger significant correlation between sepsis mortality and less decrease in procalcitonin during the patient's hospitalization.[12,17] If procalcitonin is going to be used to guide antibiotic therapy, a control over factors which may influence survival is needed. Factors such as the adequacy of antibiotic, use of diagnostic and monitoring tests, supporting nutrition and infection control, comorbidities, may influence septic patient survival.[18]

Our study utilized a cutoff of 2 ng/mL for procalcitonin. Although the result is statistically significant (p=0.015), procalcitonin only shows a weak association with patient mortality (r=0.293). A study conducted by Self et al., from which we based the cutoff point, showed a strong correlation between procalcitonin and mortality in community acquired pneumonia.[10] Other studies investigating

the relationship between procalcitonin and mortality in sepsis used different cutoff, such as 5 ng/mL, 6 ng/mL, or others.[4,15,16] The relative risk shows that patients diagnosed with sepsis whom procalcitonin cencentration more than or equal to 2 ng/mL have a mortality risk of 2.77 times higher than those with sepsis but with lower concentration of serum procalcitonin. Our study support several other studies in pediatric and adult patients.[4,14,15]

CONCLUSION AND SUGGESTION

There is a statistically significant weak relationship between procalcitonin and mortality, in which patients with procalcitonin equal or more than 2 ng/mL were 2.77 times more likely not to survive sepsis. In order to support the use of procalcitonin as a tool to guide antibiotic therapy, future studies need to address factors which may influence septic patient survival.

CONFLICT OF INTEREST & FUNDING DISCLOSURE

This study was funded by Universitas Brawijaya Faculty of Medicine research grant so that the authors have no conflict of interest related to the material in the manuscript.

ETHICS CONSIDERATION

The study has been approved by the Ethics Committee of Faculty of Medicine Universitas Brawijaya, Malang, in conjunction with Dr. Saiful Anwar General Hospital, the teaching hospital (Ethical Clearance letter no. 400/105/K.3/302/2018).

AUTHORS CONTRIBUTION

Agustin Iskandar and Deasy Ayuningtyas Tandio designed, collected and analyzed the data, and composed the manuscript. Yeni Prihastuti designed the study and collected the data.

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