Diagnostic Value of Serum Procalcitonin in Hospitalized Sepsis Patients

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Abstract

Introduction: Early diagnosis of sepsis is important to reduce the mortality and morbidity. A marker for diagnostic, stratifying, prognostic, and treatment evaluation of sepsis is utmost important.This study aimed to evaluate the potency of procalcitonin (PCT) as a diagnostic marker in sepsis patients.

Material and Methods: A case-control was conducted at Intensive Care Unit of Adam Malik Hospital, Medan, Indonesia.Patients diagnosed with sepsis as well as healthy individuals, matched gender and age with the sepsis patients, were included. The levels of PCT were measured by the semi-quantitative immunochromatographic method and were categorized into four: <0.5 ng/ml, ≥0.5-<2 ng/ml, ≥2 - <10 ng/ml, and ≥10 ng/ml. In addition to PCT, leukocyte count, hemoglobin level, and erythrocyte sedimentation rate (ESR) were also measured.

Results: The mean of leukocyte count was significantly higher in sepsis group than control (18.89±7.40x10^3/µl*vs.*8.33±1.30x10^3/µl, p<0.001). The mean ESR in case group was significantly higher (31.09 mm/hour) than in control group (10.45 mm/hour) with p<0.001. In contrast, the mean hemoglobin level in sepsis patients was significantly lower than in controls, 9.84±1.91 gr/dl and 14.48±1.68, respectively with p<0.001. PCT level in all healthy individuals (100%) was <0.5 ng/ml; while within the sepsis group, 2 (15.4%) had PCT level less than 0.5 ng/ml, 5 (38.5%) was >2 ng/ml, and 6 (46.1%) was >10 ng/ml. No significant difference was found on PCT level when stratified by the severity of sepsis (p=0.524). Spearman's correlation test suggested there was significant and strong association between PCT and leukocyte level (r=0.588, p=0.034).

Conclusion: Our data suggest that PCT could be a potential diagnostic marker of sepsis. Further studies are needed to understand optimal use of PCT in combination with other markers for early diagnosis of sepsis.

Keywords: *Procalcitonin, sepsis, biomarker, disease severity, diagnosis*

Introduction

Sepsis is one of the leading causes of mortality and morbidity, even with the advanced medical care available today. Around 18 million new sepsis cases reported annually with 30-50% mortality rate worldwide[1]. Bacteria are the most common cause of sepsis, although other microbes such as virus, fungi, and parasites could also cause sepsis[2]. As sepsis is associated with high mortality rate, early diagnosis and prompt therapy is crucial in its management. However, diagnosis of sepsis might be challenging because the signs and symptoms may overlap with other conditions such asburn, trauma, pancreatitis, transplant rejection, and autoimmune diseases[3].

Much effort is being placed on the study of biomarkers that able to detect sepsis at the early phase

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to decrease mortality and morbidity[4]. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are two commonly used biomarkers of sepsis; however, ESR and CRP are unable to distinguish sepsis from systemic inflammatory response syndrome (SIRS) and are more accurate as markers of inflammation rather than infection[2, 4]. Complete blood count (CBC) includes leukocyte count and hemoglobin level are also proposed as diagnostic markers of sepsis[5-8]; however, CBC alone was not a strong predictor of sepsis as it is influenced by many factors.Procalcitonin (PCT) has shown enormous potential as a biomarker of sepsis as it could identify sepsis, assess severity of the illness and guide antibiotic management[9-11].

PCT is a 116 amino-acid peptide precursor of calcitonin and is part of the inflammatory response in sepsis[4, 10]. In healthy subjects, the PCT level is very low (0.05 ng/mL)[2]. PCT level increases rapidly between 2 and 6 hours after infection, reach the peak between 12 and 48 hours, and returns to normal range (<0.05ng/mL) within very short time period[2, 10, 12]. The level of PCT is elevated during bacterial infection[10], significantly increased in patients with bacteremia[13], but low in viral infection[4].

PCT has been proposed as a reliable marker for diagnostic, stratifying, prognostic, and treatment evaluation of sepsis[10, 11, 13, 14]. However, previous studies reported that elevated PCT levels was observedin patients with autoimmune disorders[15], trauma[16], cardiac arrest[17], surgery[18], burns[19] and pancreatitis[20]. The contrasting reports leave the role of PCT as a biomarker for sepsis remains undefined. The present study aimed to assess the levels of PCT as a diagnostic biomarker of bacterial-caused sepsis in patients hospitalized at the intensive care unit.

Materials and Methods

Study design and patients

Sepsis patients hospitalized at the Intensive Care Unit ofAdam Malik Hospital, Medan, Indonesiawere included. Sepsis patients were diagnosed based on the criteria from the American College of Chest Physicians (ACCP) [21]and the Society for Critical Care Medicine (SCCM) Consensus Conference on Standardized Definitions of Sepsis[22]. As control group, healthy population whose gender and age were similar to the sepsis patients were also recruited. According to the severity, the patientswere categorized into sepsis, severe sepsis, and septic shock based on ACCP[21] and SCCM Consensus Conference on Standardized Definitions of Sepsis[22]. Sepsis patients with hemoglobin <5g/dl, pancreatitis, thyroid carcinoma, or sepsis due to fungal infection were excluded from the study, given that PCT elevations might be found in these conditions. In addition, this study also evaluated the level of leukocyte, hemoglobin, and ESR.

Study procedure

Peripheralblood sample was taken within 24 h after the patientswere diagnosed with sepsis or septic shockfor the measurement of PCT, leukocyte, and hemoglobin levels, and ESR. The levels of PCT were measured by the semi-quantitative immunochromatographic method using a diagnostic kit (BRAHMS Diagnostic GmbHImmunoassay, Henningsdorf, Germany). The result was interpreted by comparing the color scale after 30 minutes of incubation. Color density is in accordance with PCT concentration in the sample and was categorized into four categories: 1st category: PCT <0.5 ng/ml; 2ndcategory: 0.5 ng/ml ≤ PCT <2 ng/ml; 3rd category: 2 ng/ml ≤ PCT <10 ng/ml; and 4th category: PCT ≥10 ng/ml.

Complete blood examination was conducted using a Cell Dyne® 3700 and peripheral blood morphology was identified from blood film with Giemsa staining. ESR examination was carried out using Westergren method.

Data Analysis

A chi-square test was employed to assess the difference of PCT concentration based on severity of sepsis. Independent student t-test was used to compared the leukocyte level between sepsis and control group,while Anova was used to assess the association between leukocyte level and ESR,and severity of sepsis. Spearman's correlation test was used to assess the correlation between leukocyte and PCT as well as ESR and PCT in sepsis group.

Results

In the present study, 13 sepsis patients were enrolled and nine healthy individuals whose gender and age were

similar with cases were included as the control group. Out of total sepsis patients, 8 (61.5%) were male while 4 (44.4%) from control group were male**(Table 1)**. The gender was not significantly different between two groups (p>0.05).

The means of leukocyte level was significantly higher in sepsis group than control (18.89±7.40x10^3/µl*vs*.8.33±1.30 x10^3/µl, p<0.001) (**Table 1**). The mean ESR in case group (31.09 mm/h) was significantly higher than in control group (10.45 mm/h), p<0.001. In contrast, mean hemoglobin level in sepsis patients was significantly lower than in control group, 9.84±1.91 gr/dl and 14.48±1.68, respectively, p<0.001. PCT level in all controls was <0.5 ng/ml, while in case group was >0.5 ng/ml. Within the sepsis group, 2 (15.4%) had PCT level >0.5 ng/ml, 5 (38.5%) had PCT level >2 ng/ml, and 6 (46.1%) had PCT level >10 ng/ml (**Table 1**).

Table 1. Characteristics of sepsis cases and control group

Variables	Control (n=9)	Case (n=13)	p-value
Gender (n, %)			0.428
Male	4 (44.4%)	8 (61.5%)	
Female	5 (55.6%)	5 (38.5%)	
Leukocyte (x103/µl), (mean ± SD)	8.33±1.30	18.89±7.40	<0.001
ESR (mm/hour), (mean)	10.45	31.09	<0.001
Hemoglobin (gr/dl), (mean ± SD)	14.48±1.68	9.84 ± 1.91	<0.001
PCT (ng/ml), (n, %)			NA
> 10	0 (0.0%)	6 (46.2%)	
> 2	0 (0.0%)	5 (38.5%)	
> 0.5	0 (0.0%)	2 (15.4%)	
< 0.5	9 (100%)	0 (0.0%)	

When stratified by the severity of sepsis, no significant difference was found on PCT level (p=0.524) (**Table 2**).

Table 2. PCT level and severity of sepsis

PCT (ng/ml)	Sepsis		Severe sepsis		Septic shock		p value
	n	%	n	%	n	%	
>10	2	15.4	1	7.7	3	23.1	0.524
>2	3	23.1	1	7.7	1	7.7	
>0.5	2	15.4	0	0.0	0	0.0	
Total	7	53.8	2	15.4	4	30.8	

Spearman's correlation test was conducted to evaluate the correlation of PCT-leukocyte and PCT-ESR in sepsis patients. There was significant and strong association between PCT and leukocyte level (r=0.588 and p=0.034). No significant association was found between PCT level and ESR in sepsis patients (r=0.323, p=0.281).

Discussion

The present study evaluated the potency of PCT as marker to diagnosis the sepsis by comparing its level between sepsis patients and healthy individuals. This study found that the means of leukocyte level was significantly higher in sepsis patients than heathy individuals. The number of leukocyte increases in response to acute infection, trauma, or inflammation, and dramatically increases in sepsis, made leukocyte the most commonly used parameter to investigate the infection[5]. However, a previous study reported that patients with sepsis might present with either leukocytosis or leukopenia, made leukocyte count alone less reliable as a marker of sepsis[6]. Therefore, leukocyte count has to be carefully interpreted in the context of the clinical situation and used together with other markers such as PCT for a correct diagnosis.

This study also found the mean ESR in sepsis group was significantly higher than in non-sepsis group. This study was different from a previous study that found no significant difference in serum CRP, ESR, and leukocyte between sepsis patients and non-sepsis patients although elevated PCR was observed in sepsis patients[23]. However, our finding support a previous study that found higher level of average ESR along with PCT, CRP, and leukocyte in septic patients[24]. A previous study also showed that the use of ESR in conjunction with PCT and ESRincreased the predictive value of PCT in the diagnosis of bacteremia and sepsis[25].

Our study indicated that mean hemoglobin level in sepsis patients was significantly lower than in healthy individuals. Anemia is a common problem observed in patients with sepsis, due to several underlying mechanisms such as decreased erythrocyte production induced by systemic inflammatory response, pre-existing chronic anemia, and increased erythrocyte destruction due to hemolysis and bleeding[7, 8].

Our study found PCT level in sepsis groupwas higher than in control groups. The level of PCTincrease rapidly within 6 hours after bacterial infection and reach its peak within 48 hours[2, 10, 12].The actual mechanism of increased PCT production in patients with bacterial infection-associated sepsis is not known, but it is assumed that bacterial lipopolysaccharides and sepsis-released cytokines modulate the liver and peripheral blood mononuclear cells to produce PCT[2]. The finding of the present study supportsthe previous studies that suggested elevated PCT as a diagnostic marker of sepsis[9-11, 13]. A study showed that PCT is the most reliable diagnostic marker for sepsis, with the sensitivity and specificity of 89% and 94% respectively[13].

This study found no different of PCT level based on severity of sepsis. This is different from previous studies that suggested the elevated PCT level was significantly associated with the severity of sepsis[10, 26-29]. A previous study showed that PCT is the most reliable diagnostic marker for sepsis, with the sensitivity and specificity of 89% and 94% respectively[13]. PCT demonstrated better diagnostic value than CRP as it had significantly higher specificity (90% *vs.* 56%) and could clearly distinguish viral and bacterial sepsis[10, 24]. A statistically significant association between elevated PCT level and the severity of sepsis as determined the development of septic shock was also reported in previous studies[10, 26-28], making it useful for predicting the severity of sepsis. A previous study showed that PCT levels were higher in non-survivors of sepsis than in survivors[10], and elevated PCT levels was strongly associated with all-cause mortality in sepsis patients[14], shown its potential as a prognostic biomarker. Compared to CRP, PCT levels increase more rapidly and returns to normal range faster, which make it a better biomarker for evaluating treatment response in sepsis patients[11]. In addition, the levels of PCT are not affected by the administration of anti-inflammatory therapy such as glucocorticoids, demonstrating its superior diagnostic accuracy when compared to other sepsis biomarkers[4].

Interestingly, our data found that a significant association between PCT and leukocyte level. A previous study reported a significant correlation between PCT and leukocytein sepsis patients aged more than 70 years, but not in younger patients[30]. PCT when combine with leukocyte showed better diagnostic and prognostic

power as a sepsis biomarker[23, 30].

This study, however, is subject to some limitations. First, this study measured only the initial PCT value, and did not measure serial values. Given that PCT levels change by time, a change in PCT value as opposed to a single value may be stronger as a predictor of sepsis. Second, the relatively small sample made the results of this study could not be generalized. A study with bigger sample size is warranted to better elucidate the potential of PCT as a marker of sepsis. Despite of the limitations, this study has elaborated the role of PCT as a diagnostic marker of sepsis.

Conclusion

Elevated PCT level was found in sepsis patients, suggesting its potential as a diagnostic biomarker of sepsis. In conjunction with PCT level, this study also found that leukocytosis, longer ESR, and anemia prevalentamonghospitalized patients with sepsis. A combination of biomarkers might be more useful in early diagnosis of sepsis; however, further investigation is warrant.

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