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Procalcitonin as a Biomarker of Severity Degree in Sepsis Due to Pneumonia

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Abstract: Measuring PCT level can be as the examination having the role to differ the *systemic inflammatory response syndrome* (SIRS) and sepsis. This study aims to know the PCT level in accessing the sepsis degree at pneumonia patients. This study was an analytical study with cross-sectional design. There were 30 samples obtained since February 2013 until March 2014 at the Emergency Room and Inpatient Room of Internal Medicine Local Public Hospital Dr. Zainoel Abidin Banda Aceh. The sample collection was conducted with quota sampling technique. The data was analysed with Anova and followed with LDS. The data was considered to be significant if the p value is $< 0{,}05$. The study results were obtained the minimum limit value of PCT level at pneumonia of 0,091 ng/dl, sepsis of 0,686 ng/dl, severe sepsis of 3,593 ng/dl and shock sepsis of 21,703 ng/dl. The analysis results showed that the higher PCT level makes the higher disease severity.

Keywords: Procalcitonin (PCT), Sepsis Degree, Pneumonia

1. Introduction

Respiratory diseases cause of morbidity and mortality in worldwide. Pneumonia is an acute lower respiratory infection found around 15-20%. Pneumonia is an inflammation of the lung parenchyma and the distal portion of the terminal bronchioles caused by the bacterium as a common cause with a percentage of 56.4% occurred in 1979-2000 in the United States. [1, 2]

Data from the *National Prospective Multicentre Study* conducted in Germany found that 527 patients (39.1%) of the total 1348 samples with sepsis were caused by community-acquired pneumonia (CAP), hospital-acquired pneumonia of 186 patients (13.8%), ventilator-acquired pneumonia of 443 (32.9%) and unknown pneumonia of 192 patients (14.2%). Sepsis is the leading cause of death with a mortality rate of 400,000-500,000 patients each year in the United States. [1–3] It is reported that there were 10 million cases of sepsis patients for a period of 22 years at 750 hospitals in the United States. The number of patients with sepsis increased from 164 million in 1979 to 659 million in 2000, an increase of 82.7 cases per 100,000 population to 240.4 cases per 100,000 population. [2, 4]

Sepsis as a cause of death in the hospital is an important thing, so it is necessary to look for appropriate markers in assessing the sepsis degree. Lately, it has developed a new test for detecting sepsis which is procalcitonin (PCT). Many studies have been conducted to try to assess the role of PCT as a marker sepsis. [5–7] Meisner revealed that PCT concentrations increase at every degree of sepsis with a concentration of 0.05 to 0.5 ng / ml in non-septic infections, 0.5-2 ng/ml in sepsis, 2-10 ng/ml in severe sepsis, and more than 10 ng/ml in shock sepsis.[8]

The Measuring PCT level can be used as an examination with the role in the diagnosis of acute bacterial infection. Moreover, this examination can also be used to distinguish the *systemic inflammatory response syndrome* (SIRS) and sepsis, as well as play a role in monitoring the treatment outcomes. [2] The measuring PCT has a better role as an inflammation marker, compared to other markers, such as *tumour necrosis factor* α (TNF-α), interleukin 6 (IL-6), interleukin 1 (IL-1) and C-*reactive protein* (CRP) in predicting the patients' prognosis. [9]

A PCT increase in patients' serum with sepsis as a whole is greater when compared to the patients without sepsis, this is being the early research about PCT as the sepsis marker. However, there are also studies that found a failure to determine the PCT threshold level in the sepsis determination. [5, 10] Procalcitonin is a precursor peptide of calcitonin hormone (CT), which will increase in response to an inflammatory stimulus. PCT has been suggested as bacterial infection and sepsis marker which the levels are related to the disease severity. PCT levels tend to decrease rapidly after antibiotic administration in CAP patients

showing a correlation between inflammations, mainly CAP and PCT. Several studies have shown that PCT increasing level can be used for early diagnosis of sepsis and to assess the disease severity. This suggests that, PCT can be used as a sepsis marker. [2, 11, 12]

2. Method

This research is an analytical study with cross-sectional design conducted in the ER room and inpatient room of Medicine Regional Public Hospital Dr. Zainoel Abidin Banda Aceh. The research was conducted from February 2013 to March 2014.

The inclusion criteria in this study were the pneumonia patients with sepsis with the age group above 18 years with sepsis, Hb≥8 g/dl and the patient's family is willing to fill the informed consent (the patient is unconscious) or patient fills out the informed consent (the patient is conscious). The exclusion criteria in this study were pancreatitis, thyroid carcinoma, severe trauma, lung carcinoma and meningitis.

Thirty patients based on the inclusion and exclusive criteria were diagnosed according to the guidelines for the diagnosis and pneumonia treatment in Indonesia. The steps being taken to diagnose the pneumonia are patient complained of fever; cough with sputum or purulent mucous, sometimes also with blood; shortness of breath and chest pain; the patients then conducted the physical examination. On the inspection, it could be seen that the sick part leaving for the breathing time, on fremitus palpation, it can harden at the faint percussion; at the auscultation, there are sounds of broncho vesicular breath to the bronchial with crackles; the patients conducted the upheld diagnosis of pneumonia based on history and physical examination. The diagnosis without x-ray chest is supported by several studies. [13, 14]

The patients conduct the blood sampling as much as 3 cc of blood with anticoagulant Ethylene Diamine Tetra acetic Acid (EDTA) is for a complete blood examination. The second part is as much as 3 cc of blood without anticoagulant and taken the serum for PCT examination.

The Measuring PCT examination is conducted with the examination method of *Enzyme Link Fluorescent Assay* (ELFA) by the terms as the following, the samples are serum or plasma (Li Heparin), the reference value: <0,05 ng/ml, reagent/tool: Elecsys BRAHMS PCT /VIDAS. The PCT value is classified into 5 categories, namely normal (< 0,05 ng/ml), non-sepsis infection (0,05 ng/ml - 0,5 ng/ml), sepsis (0,5 ng/ml - 2 ng/ml), severe sepsis (2 - 10 ng/ml) and shock sepsis (> 10 ng/ml). [8]

3. Results

The sample characteristics are seen at table 1.
The statistical test results by using *One way anova* test

with CI 95% and α = 0,05, it is obtained that p *value* at systolic blood pressure (SBP) is p<0,001, the heart frequency is p<0,001 and the mental status is 0,001 so that hypotheses is rejected meaning that SBP, heart frequency and mental status have the correlation with the sepsis severity degree. While, p *value* at the breath frequency of p=0,059 and the temperature of p=0,883 so that hypotheses is declined meaning that the breath frequency and temperature do not have correlation to the sepsis severity degree (table 2).

Table 1. *The Study Sample Characteristics.*

Sample Characteristics	Description
Gender	
Men	17 (56,7)
Women	13 (43,3)
Age	58,30 ±12,45
Awareness	
Compos mentis	12 (40,0)
Apathies	14 (46,7)
Somnolence	2 (6,7)
Stupor	2 (6,7)
Sepsis Severity	
Sepsis	12 (40,0)
Severe Sepsis	8 (26,7)
Shock sepsis	10 (33,3)
Systolic Blood Pressure (SBP) mmHg	106,67 ±24,54
Heart Frequency	106 (90-122)
Breath Frequency	28 (25-40)
Temperature	38 (36,4-39,2)
Haemoglobin	10,1 (8,5-13,5)
Leucocyte	14063,33±4408,96
Thrombocyte	158000 (65000-660000)
Serum	1,75 (0,57-7,3)
Urine	125 (50-800)
Procalcitonin (ng/ml)	24,56 (0,45-192,69)

Table 2. *Correlation of Sepsis severity degree and common variable.*

Severity Degree	Sepsis	Severe Sepsis	Shock sepsis	p Value
SBP*	115 (100-150)	125(100-150)	80 (60-90)	<0,001
Heart frequency*	98 (90-122)	103(98-110)	120 (110-122)	<0,001
Breath frequency	27(25-34)	30(26-40)	30 (26-38)	0,059
Temperature	37,98±0,82	38,09 (0,86)	37,88(0,95)	0,883
Mental Status*				
Compos mentis	12	0	0	
Apathies	0	8	6	0,001
Somnolence	0	0	2	
Stupor	0	0	2	

Note: *Superscript* (*) shows the significant different (P<0, 05)

Table 3. *Correlation of sepsis severity degree and inflammation variable.*

Severity degree	Sepsis	Severe Sepsis	Shock sepsis	p Value
PCT*	0,85 (0,62-1,21)	5,66 (4,24-7,95)	35,09 (20,95-70,48)	<0,001
Leukocyte	13(4,2-22,1)	14,5 (12-23,4)	16,1(2-19)	0,307

Note: *Superscript* (*) shows the significant different (P<0, 05)

Based on Table 3, it shows that the statistical test result by using *One way anova* test at CI 95% and α=0,05, it is obtained the p *value* at PCT p<0,001 so that hypotheses is accepted meaning that PCT has the correlation with the sepsis severity degree. While p *value* at leukocyte of p=0,307 so that hypotheses is declined meaning that leucocyte does not have correlation with the sepsis severity.

The study results of correlation of sepsis severity degree and organ dysfunction variable can be seen at table 4 below.

Table 4. *Correlation of sepsis severity and organ dysfunction variable.*

Severity degree	Sepsis	Severe Sepsis	Shock sepsis	p Value
Creatinine serum*	0,95(0,57-1,7)	2,1(1,8-2,5)	1,8 (0,8-7,3)	<0,001
Thrombocyte	215 (106-455)	140 (106-420)	145(65-660)	0,285
Output Urine*	320(100-800)	100(50-280)	100(50-200)	0,001

Note: *Superscript* (*) shows the significant different (P<0, 05)

Based on Table 4, it shows that the statistical test result by using *One way anova* test at CI 95% and α=0,05, it is obtained the p *value* with creatinine serum p<0,001 and *output* urine p=0,001 so that hypotheses is accepted meaning that creatinine serum and *output* urine have the correlation with the sepsis severity degree. While p *value* at thrombocyte is p=0,285 so that hypotheses is declined meaning that thrombocyte has no correlation with sepsis severity degree.

The study result of PCT level comparison between the groups can be seen in Table 5 below.

Table 5. *Comparison of PCT level between groups.*

Groups	n	PCT Median
Sepsis	12	0,85[a]
Severe Sepsis	8	5,66[b]
Shock Sepsis	10	35,09[c]

Note: *Superscript* of different letter shows the significant different (P<0, 05)

Based on table 5, it shows that the study results of PCT level comparison in each sepsis degree can be seen by the PCT level at the groups of sepsis of 0,85 ng/ml, severe sepsis of 5,66 ng/ml and shock sepsis of 35,09 ng/ml. This shows that the increase of PCT median at the disease severity degree.

The test results of *one way anova* of PCT level between groups can be seen in table 6 below.

Table 6. *Test of One Way Anova of PCT level between Groups.*

| Group | n | IK 95% | | p Value |
		Min	Max	
Sepsis	12	0,62	1,21	
Severe Sepsis	8	4,24	7,95	<0,001
Shock Sepsis	10	20,95	70,48	

Note: *Superscript* of different letter shows the significant different (P<0, 05)

Based on table 6, it shows that PCT value at the sepsis group is 0,62-1,21 ng/ml, severe sepsis is 4,24-7,95 ng/ml and shock sepsis is 20,95-70,48 ng/ml. The higher the PCT level so the higher the disease severity level. This shows that the hypothesis in this study is accepted. The PCT level threshold increases along with the disease severity.

The correlation test results of spearman variable to the sepsis severity degree can be seen at Table 7 below.

Table 7. *Correlation test of spearman variable to the sepsis severity degree.*

Variable	p Value	r value
Procalcitonin	<0,001*	0,939
Leukocyte	0,127	0,285
creatinine	0,003*	0,520
Thrombocyte	0,117	-0,292
Output urine	<0,001*	-0,646
SBP	<0,001*	-0,698
FJ	<0,001*	0,697
FN	0,033*	0,390
Temperature	0,762	-0,058
Mental status$	<0,001*	0,915

Note: *Superscript* of different letter shows the significant different (P<0, 05)

Based on table 7, it shows that the variables of PCT, creatinine, output urine, SBP, heart frequency, breath frequency and mental status have the significant correlation to the sepsis severity degree. While, the variables of leukocyte, thrombocyte and temperature do not have the significant effect.

4. Discussion

This research is conducted to know the PCT level in assessing the sepsis degree at the pneumonia patients. Based on Table 1, it shows that the common variables evaluated in this study are awareness, SBP, heart frequency, breath frequency and temperature, as well as the inflammation variables are leukocyte and PCT having the parameter mean value above normal. This is based on *The American College of Chest Physician* (ACCP) *and The Society for Critical Care Medicine (SCCM) Consensus Conference on Standardized* that the parameter of common variable and inflammation variables can be used to upheld the sepsis. [2, 15–17]

Based on table 2, it shows that the sepsis severity degree has a correlation to common variables, namely SBP, breath frequency and mental status. Table 3 shows that the sepsis severity has a correlation to the inflammatory variable, namely PCT. Table 4 shows that the sepsis severity has a correlation with the variable of organ dysfunction namely creatinine serum and urine output. It is based on the *Surviving Sepsis Campaign* 2012, which makes the common variables, the inflammation variable and dysfunction organ variable as the indicator in determining the severity sepsis. [18]

Based on table 5, it shows that the increasing of PCT level is followed by the disease severity. This is consistent to the research by Brunkhorst et al. conducted in Germany with 185

patients, which it is obtained that 17 patients with SIRS, 61 patients with sepsis, 68 patients with severe sepsis and 39 patients with septic shock, that there PCT concentration increases by the increasing sepsis severity. This study obtains PCT level in sepsis of 0.53 ± 2.89 ng/ml, severe sepsis of 6.91 ± 3.87 ng/ml and septic shock 12.89 ± 4.39 ng/ml.[19] Another study conducted by Harbarth et al. in Geneva with 78 patients obtained 18 patients with SIRS, 14 patients with sepsis, 21 patients with severe sepsis and 25 patients with septic shock also obtained the same results. This study obtained the median of PCT concentration in sepsis of 3.5 ng/ml, 6.2 ng severe sepsis / septic shock of 21.3 ng/ml. [20]

Based on table 6 that the PCT value in sepsis group is from 0.62 to 1.21 ng/ml, severe sepsis is from 4.24 to 7.95 ng / ml and septic shock is from 20.95 to 70.48 ng / ml. The PCT value is based on the research conducted by Meisner, that out of 7 studies on 145 samples, there were 22 patients with no sepsis, 96 patients with sepsis, 19 patients with severe sepsis, and 8 patients with septic shock, there is a PCT increase in any sepsis severity degree. The highest PCT level is in patients with septic shock. The greater the sepsis degree, the more severe the PCT increase in the blood. Meisner revealed that PCT concentration increases at every sepsis degree with a concentration of 0.05 to 0.5 ng/ml in non-septic infections, 0.5-2 ng/ml in the sepsis, 2-10 ng/ml in severe sepsis and over 10 ng/ml in shock sepsis.[8] Dorizzi et al. also reported that the median of PCT concentration increases in every sepsis degree severity. The study was conducted in Italy with 103 patients and obtained 32 patients with SIRS, 24 patients with sepsis, 15 patients with severe sepsis and 12 patients with septic shock, and obtained the median of PCT concentration in SIRS of 0.41 ng/ml, sepsis of 1.98 ng/ml, severe sepsis of 4.4 ng/ml and septic shock of 5.44 ng/ml. [21] The PCT concentration change increased appropriate with the sepsis severity which was also reported by Bourboulis et al. doing research in Greece with 1156 patients that there was PCT concentration change of 1.25 ng/ml to 12.37 ng/ml in the sepsis becoming septic shock and 1.78 ng/ml to 28.56 ng/ml in septic shock becoming the *organ failure*. [5]

According to the research results conducted by Meisner that procalcitonin can be increased 2-3 hours after induction and can be increased up to several hundred of ng/ml with very stable molecule condition *in vitro* or *in vivo*. The PCT induction results in the in vivo experiment showed that in animal sepsis within 24 hours, PCT increased relatively high and IL-1β, TNF-α increased twice. [8, 22]

This is consistent to the theory that the PCT mRNA is expressed on human peripheral blood mononuclear cells and various proinflammatory cytokines and LPS have stimulating effects. Approximately one-third of human lymphocytes and monocytes unstimulated PCT protein which can be explained in immunology, this condition is triggered by bacterial LPS, but monocytes from patients with septic shock showed the increased basal values and the increase of PCT level stimulated by LPS. [8, 23]

Based on Table 7 shows that the sepsis severity affects on the increase of PCT level in patients with sepsis due to pneumonia. This is consistent to the research Elkhashab et al. 2014 conducted at the Hospital of the University of Alexandria which obtained that the level of PCT increased in septic patients with pneumonia, with p = 0.002. The study concluded that the PCT is as a specific biomarker and prognosis indicator in patients with pneumonia at the hospital. PCT is a precursor peptide hormone calcitonin (CT), which will increase in response to an inflammatory stimulus. Procalcitonin has been suggested as a bacterial infection marker and sepsis which the level was related to the disease severity. [24]

According to research by Balci et al. conducted in Turkey that PCT level is a powerful diagnostic parameter in determining the sepsis severity. This study shows that there is significant differences between PCT level and sepsis severity with p<0,005. [25] Castelli et al., Demonstrated in a study conducted in Italy that PCT concentrations can determine the sepsis severity with each concentration of 1.58 ng/ml in sepsis, 0.38 ng/ml of SIRS and 0.14 ng/ml in non-SIRS. This study results concluded that there were significant differences between PCT concentration and the sepsis severity by Mann Whitney test obtained p <0,05. [26]

Jeong et al. in 2012 explained that PCT concentrations was higher in septic patients than in non-sepsis patients with ratio concentration ratio of 3.2 ng/ml compared to 0.4 ng/ml. [27] Similar results were also obtained by Dorrizi et al. 2006 that the PCT concentration in sepsis patients is higher than in non-sepsis treated in the ICU and inpatient with each PCT concentration ratio of 3.18 ng/mL and 0.45 ng/ml. [21] The PCT levels will increases by the infection severity, so the PCT is considered as the initial inflammatory of sepsis marker. The precision and accuracy of measuring PCT examination can be conducted to detect sepsis early and predict the sepsis severity. [28]

This study has limitations that this study design was cross sectional study in which the researchers conducted a study on the variable only once. Many other factors were not examined related to the increased of PCT levels. The pneumonia diagnosis in this study was based on history and physical examination. The research sample was not performed the X-ray chest examination to make a diagnosis, based on the IDSA/ATS recommendation, [29] that the patients with x-ray chest confirmed pneumonia. The diagnosis without a x-ray chest is supported by several studies.

5. Conclusion

The higher levels of PCT increases the disease severity with a minimum threshold value of PCT levels in pneumonia of 0.091 ng/ml, sepsis of 0.686 ng/ml, severe sepsis of 3.593 ng/ml and septic shock of 21.703 ng/ml. The sepsis severity affects on the increased of PCT level in patients with sepsis due to pneumonia.

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