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COMPARISON OF CHOLESTEROL PLASMA CONCENTRATION AND PROCALCITONIN LEVEL AS PREDICTOR WORSENING OF SEPSIS

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ABSTRACT

ICU patients with infection and MODS, measurements of PCT, CRP and cholesterol were measured on day 1, 5 and the last day of ICU admission. PCT and cholesterol values have high sensitivity and specificity in septic patients with MODS This study aims to determine the comparison of cholesterol levels and procalcitonin levels as predictors of mortality in septic patients. The research method used is analytic observational. The study was conducted at the General Hospital of the Department of Anesthesiology and Intensive Therapy of the Faculty of Medicine, University of North Sumatra from June to August 2018. The total samples obtained were 46 sepsis patients. The diagnosis of sepsis is based on the QSOFA criteria assessed when sepsis is established (T0), at 3 days after sepsis (T1), at 5 days after sepsis. From the results obtained showed that there were 46 patients consisting of 30 people (65.3%) and 16 women (34.7%). The average age of patients in this study was 42.39 years the results of the analysis found that a significant relationship between procalcitonin and cholesterol with worsening in sepsis at sepsis was established (T0), at 3 days after sepsis (T1), at 5 days after sepsis (T2) using Pearson correlation ($p < 0.05$). From the results of the analysis using the ROC curve at T0, T1, and T2 it was found that the area under the ROC curve (AUC) with the percentage of 44.7%, 40.3% and 44.1% respectively (95% CI 26.6% - 62.8%, $p = 0.556$). In addition, it was also found that there was no correlation between the results of cholesterol levels as a predictor of worsening in septic patients ($t<4,06$). The diagnostic value of cholesterol levels does not have a good ability to predict worsening in sepsis patients ($p> 0.05$), whereas procalcitonin can be a gold standard in establishing sepsis but does not have a good relationship as a predictor of worsening in sepsis

KEYWORDS : Cholesterol, Procalcitonin, Sepsis, SOFA scores

1. INTRODUCTION

Sepsis has a gold culture standard but the results are not always positive, so we need other tests such as procalcitonin (PCT) to be used as a marker of sepsis and to know the relationship with the severity of sepsis so that the diagnosis and management of sepsis can be faster and more precise which causes a decrease in mortality.[1]

Apart from more expensive examination prices, PCT was found to be a more accurate diagnostic parameter for sepsis, and therefore daily PCT determination may be very helpful in following up critically ill patients. A systemic review and meta-analysis conducted on 30 studies showed that PCT had an average sensitivity of 0.77 (95% CI 0.72 to 0.81) and specificity of 0.79 (95% CI 0.74 to 0.84) So it can be concluded that PCT is a very useful marker for diagnosing sepsis in critically ill patients. However, it cannot be recommended as a single definitive test for the diagnosis of sepsis but must be accompanied by clinical data.[2]

Serum PCT levels are elevated in patients with bacterial infections, but are below the detection limit in healthy individuals and in patients with viral infections. This suggests that PCT levels are useful for the diagnosis of systemic bacterial infections. PCT secretion reflects the severity of inflammation. The normal reference value is around 0.15 ng / mL. PCT levels between 0.15 and 2.0 ng / mL do not exclude the diagnosis of infection, because local infection (without systemic signs) can also be a cause of increased PCT. A level of 2.0 ng / mL is highly suggestive of sepsis or severe local bacterial infection.[2] The PCT level increases with increasing of 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 3.593and septic shock of 21.703. The sepsis severity affects on the increased of PCT level in patients with sepsis.[3]

In the study conducted on ICU patients with infection and MODS, measurements of PCT, CRP and cholesterol were measured on day 1, 5 and the last day of ICU admission. PCT, CRP and cholesterol values have high sensitivity and specificity in septic patients with MODS.[4]

In recent years cholesterol reduction has been a concern in patients with sepsis and septic shock. During the infection process, significant changes in lipid metabolism and lipoprotein composition occur. In patients with infection, elevated serum levels of total cholesterol, LDL, and serum triglycerides and a decrease in serum HDL have been reported in several studies. This is due to several mechanisms, including the reduction of hydrolysis of TG, LPS and pro-inflammatory cytokines inducing the production of free fatty acids and the synthesis of TG in the liver. Such LDL receptors are a key step in the clearance of pathogenic lipids from circulating sepsis, severe sepsis and septic shock.[5]

Research conducted in Sweden found that in patients with infection and sepsis, there was a significant decrease in cholesterol levels compared to local infections.[6]. In a study conducted in Seoul, South Korea, patients with severe sepsis had low cholesterol levels, including HDL, LDL, and apolipoprotein A, accompanied by high triglyceride levels. Where LPL activity (lipoprotein lipase) decreases in the acute phase and recovery, whereas HL (hepatic lipase) decreases only in the acute phase of infection Changes in lipoprotein and lipase are associated with the severity of infection but are independent of infective agents.[7]

2. METHOD

This research is an analytic observational research conducted in the intensive care ward of RSUP.H. Adam Malik Medan. The time for the research was conducted from June to August 2018.

Inclusion criteria in this study were patients aged over 19 years, patients who met the criteria of sepsis, patients or families of patients willing to participate in the study. Exclusion criteria in this study were patients with a history of dyslipidemia, menopausal women, patients with a history of liver disease, a history of steroid

administration, immunocompromised patients, malignancies, and patients taking TPN less than 12 hours.

Fourty-six patients who met the inclusion and exclusive criteria were diagnosed through the QSOFA criteria. PCT and Cholesterol examination was done at the beginning of admission (T0), on the third day (T1) and on the fifth day (T2). Assessment of patient outcomes was carried out using SOFA scores to assess patients recovering, shock, and dying on days 3, 4 and 5. After data was collected, data analysis was carried out.

Patients were taken with 3 cc of blood with Ethylenediamin etetraacetic Acid (EDTA) anticoagulant for complete blood tests. The second part is 3 cc of blood without anticoagulants and the serum is taken for PCT examination.

Procalcitonin examination was carried out using Enzymed Link Fluorescent Assay (ELFA) examination method, provided that as a sample in the form of serum or plasma (Li Heparin), the reference value was <0.05 ng / ml, reagent / tool: Elecsys BRAHMS PCT / VIDAS. (Meisner, 2002).

3. RESULTS

TABLE 1. Sample Characteristics

Sample Characteristics	Amount	Percentage
Age		
19-38 years	10	21,7%
39-58 years	19	41,3%
>58 years	17	37%
Gender		
Male	30	65,3%
Female	16	34,7

Based on the results obtained and analyzed, there was a significant relationship between cholesterol and worsening in sepsis at 3 days after sepsis was established (T1) (p <0.05) using Pearson correlation.

Based on the results obtained and analyzed, there was no significant relationship between cholesterol and procalcitonin with worsening in sepsis at 5 days after sepsis was established (T2) (p> 0.05) using Pearson correlation. Cholesterol values compared to sofa scores were statistically significant in assessing sepsis worsening (p <0.05).

From the analysis using the ROC curve at T0 it was found that the area under the ROC curve (AUC) was 44.7% (95% CI 26.6% - 62.8%, p = 0.556). The results of this analysis can be seen based on the table and the ROC curve attached to table 6 and figure 1. From the analysis using the ROC curve at T1 it was found that the area under the ROC curve (AUC) was 40.3% (95% CI 23.2% - 57.4%, p = 0.284). The results of this analysis can be seen based on the table and the ROC curve attached to table 7 and figure 2. From the analysis using the ROC curve on T2 it was found that the area under the ROC curve (AUC) was 44.1% (95% CI 27% - 61.1%, p = 0.087). The results of this analysis can be seen based on the table and the ROC curve attached to Tables 8 and Figure 3.

The statistical test results by using *One way anova* test with CI 95% and α = 0,05, it is obtained that p *value* at TDS is p<0,001, the heart frequency is p<0,001 and the mental status is 0,001 so that Ho is rejected meaning that TDS, 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 2 Correlation of Sepsis severity degree and common variable

Severity Degree	Sepsis	Severe Sepsis	Shock sepsis	p Value
TDS*	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	0,001
Apatis	0	8	6	
Somnolen	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
Trombosite	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 trombosite is p=0,285 so that hypotheses is declined meaning that trombosite has no correlation with sepsis severity degree.

3.1 PCT Level to the Sepsis degree at Pneumonia Patients

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	<0,001
Severe Sepsis	8	4,24	7,95	
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
Trombosite	0,117	-0,292
Output urine	<0,001*	-0,646
TDS	<0,001*	-0,698
Heart Frequency	<0,001*	0,697
Breath Frequency	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, TDS, heart frequency, breath frequency and mental status have the significant correlation to the sepsis severity degree. While, the variables of leukocyte, trombosite 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, TDS, 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.[-2,1517]

4.1 Correlation of sepsis severity degree and study variables

Based on Table 2, it shows that the sepsis severity degree has a correlation to common variables, namely TDS, 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*.[22]

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.[8,23]

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.[8,24]

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 calcitonine (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.[25]

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.[26] 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 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.[27]

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.[28] 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.[29]

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 2007 recommendation, 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 3.593and septic shock of 21.703. The sepsis severity affects on the increased of PCT level in patients with sepsis due to pneumonia.

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