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Relationship between Procalcitonin Levels (PCT) and Disease Severity in Hospitalized Patients Confirmed Positive for COVID-19

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Abstract
Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease attacks the respiratory tract and spreads rapidly almost throughout the world, hence, WHO has declared COVID-19 as a global pandemic. The presence of inflammation and bacterial co-infection in COVID-19 hospitalized patients can increase procalcitonin (PCT) levels as a biomarker of inflammation. Elevated PCT levels are also associated with disease severity. The objective of this study is to determine the relationship between PCT levels and disease severity in hospitalized patients who are confirmed positive for COVID-19. This research method is analytic observational with cross sectional design. The sample is in the form of medical record data for 180 COVID-19 patients who are hospitalized at Bhayangkara Tk. I Raden Said Sukanto Hospital, Jakarta for the period July-December 2020. The relationship between PCT levels and disease severity was statistically analyzed using the Chi Square test. The results of this study were 109 (60.6%) men and 71 (39.4%) women with the highest age group being 46-59 years. The average PCT level was 10.38 ng/mL with the lowest level of 0.01 ng/mL and the highest level of 282.00 ng/mL. PCT levels <0.5 ng/mL were discovered in 111 patients (61.7%) and PCT levels 0.5 ng/mL in 69 patients (38.3%). The severity of disease in mild-moderate illness was 87 patients (48.4%), severe was 35 patients (19.4%), and critical was 58 patients (32.2%). The Chi Square test showed that there was a relationship between PCT levels and disease severity in COVID-19 patients ($p = 0.000$). The higher the PCT level, the higher the severity of the disease, thus, PCT can be used as an indicator to see the severity of the disease.

Keywords: COVID-19, Procalcitonin (PCT), Disease Severity.

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1. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) is an infectious disease caused by the recently discovered Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (WHO, 2020). Common signs and symptoms of COVID-19 infection include symptoms of acute respiratory distress such as fever, cough and shortness of breath. The average incubation period for COVID-19 ranges from 5-6 days with the longest incubation period being 14 days. In severe cases of COVID-19, it can cause pneumonia, acute respiratory syndrome, kidney failure, and even death (Kementerian Kesehatan Republik Indonesia, 2020). This disease was first discovered in Wuhan City, China at the end of December 2019 and was declared a pandemic by WHO on March 11, 2020 (WHO, 2020).

The increase in cases took place quite quickly and spread to various countries in a short time. WHO reported 149,216,984 positive confirmed cases of COVID-19 with 870,419 new cases and 3,144,028 deaths to April 28, 2021. COVID-19 has infected 223 countries in the world, of which Asia ranks third in the number of confirmed COVID-19 patients after America and Europe (WHO, 2021). In Indonesia, the first two cases of patients who were confirmed positive for COVID-19 were reported on March 2, 2020 (Kementerian Kesehatan Republik Indonesia, 2020). Data from the Task Force for Handling COVID-19 on April 28, 2021, shows that the number of confirmed positive cases of COVID-19 in Indonesia is 1,657,035 with 5,241 new cases. Of the confirmed cases, there were 100,502 active cases or 6.1%, recovered 1,511,417 or 91.2% and 45,116 or 2.7% died (Satuan Tugas COVID-19, 2021).

Laboratory tests for the diagnosis of COVID-19 could be conducted by examining viral cultures, nucleic acid amplification tests (NAAT)/molecular detection and serology (Li et al., 2020; WHO, 2020). The gold standard of testing for positive confirmation of COVID-19 is molecular. Molecular examination of SARS-CoV-2 nucleic acid employed real time reverse transcriptase polymerase chain reaction (rRT-PCR) (WHO, 2020).

Other supporting laboratory tests play a crucial role in the detection of COVID-19. Identification of appropriate laboratory biomarkers can classify patients based on the risk of severity so that they can guarantee appropriate treatment (Ponti et al., 2020). Laboratory biomarkers have the potential for diagnosis and prognosis, prediction of complications and monitoring of treatment response (Tomo et al, 2020). The biomarkers examined consisted of hematological, coagulation, biochemical and inflammatory biomarkers (Ponti et al., 2020). These various laboratory biomarkers may increase in COVID-19 patients during this outbreak (Elshazli et al., 2020).

Inflammatory biomarkers function in determining inflammatory reactions that occur in the body. Inflammatory biomarkers that are frequently used in COVID-19 patients are C-reactive protein (CRP), interleukin 6 (IL-6) and procalcitonin (PCT) (Ponti et al., 2020). The inflammatory response triggered by SARS-CoV-2 can make the body overreact by producing many cytokines, resulting in the phenomenon of a cytokine storm. The effect of this hyperinflammatory reaction is an increase in levels of PCT, CRP and IL-6 examinations (Cecconi et al., 2020; Ji et al., 2020).

PCT levels are also increased in COVID-19 patients who are co-infected with bacteria (Schuetz, 2020). Many patients die with suspected bacterial coinfection (Dolci et al., 2020; Xu et al., 2020). Bacterial coinfection can occur in COVID-19 patients because SARS-CoV-2 that enters the body will cause lung tissue damage, thereby weakening the immune response. As a result, bacteria are easier to infect the lungs which can cause bacterial lung pneumonia (Schuetz, 2020). Research by Dolci et al., (2020) in cases of COVID-19 presented bacterial coinfection of 39.8% during hospitalization.

In addition to PCT, inflammatory biomarkers such as CRP were also increased (Gregoriano et al., 2020; Huang et al., 2020). However, the specificity of PCT is higher than that of CRP in bacterial infections (Cleland & Eranki, 2020). Lippi & Plebani, (2020) stated that PCT is produced as part of the systemic inflammatory response to bacterial infection but remains low in viral infection. It provides another advantage of PCT examination to differentiate pneumonia due to virus or bacteria. PCT is also considered to be more accurate in assessing response to antibiotic therapy and determining prognosis in severe bacterial infections than CRP (Das, 2020; Gregoriano et al., 2020).

Procalcitonin (PCT) is produced as a result of the stimulus response to bacterial products. PCT levels are lower than 0.1 ng/mL in healthy individuals. Elevated levels of 0.5 ng/mL indicate severe inflammation and a bacterial infection is occurring in the body (Meisner, 2014). Measurement of PCT at the time a COVID-19 patient is admitted to the hospital can be used to assess the risk of bacterial infection and progression to severe bacterial sepsis and septic shock (Das, 2020). Increased PCT in COVID-19 patients is associated with prognosis of disease severity (Hu et al., 2020; Liu et al., 2020).

The severity of COVID-19 is determined according to the criteria and clinical manifestations based on the pneumonia present in the patient (Kementerian Kesehatan Republik Indonesia, 2020). The severity of illness in COVID-19 patients includes asymptomatic, mild, moderate, severe and critical illness. Around 80% of cases of COVID-19 are mild or moderate, 13.8% are seriously ill, and 6.1% of patients are critical (Susilo et al., 2020). Patients who are asymptomatic and who show mild symptoms generally only undergo self-isolation at home. Patients with symptoms of moderate to critical illness should be referred for hospitalization (Levani et al., 2020).

Increased PCT is associated with disease severity in hospitalized patients (Chen et al., 2020; Li et al., 2020; Liu et al., 2020). The average PCT level in patients with severe illness is 4 times higher than moderately ill, while critically ill increases 8 times that of moderate illness (Lippi, & Plebani, 2020). Increased PCT tends to be found in patients admitted to the intensive care unit (ICU) with severe/critical symptoms (Luo et al., 2020; Wang et al., 2020). The trend of increasing PCT associated with the severity of COVID-19 disease needs to be investigated in Indonesia because there is not much data available during the current pandemic. On this basis, researchers are interested in examining the relationship between PCT levels and disease severity at Bhayangkara Tk. I Raden Said Sukanto Hospital, which is one of the referral hospitals for COVID-19 patients in East Jakarta.

2.   RESEARCH METHOD

The trend of increasing PCT associated with the severity of COVID-19 disease needs to be investigated in Indonesia because there is not much data available during the current pandemic. On this basis, researchers are interested in examining the relationship between PCT levels and disease severity at Bhayangkara Raden Said Sukanto Tk. I Hospital, which is one of the referral hospitals for COVID-19 patients in East Jakarta.

3. RESULTS AND DISCUSSION

Table 1. Characteristics of Inpatients Confirmed Positive for COVID-19 Based on Gender and Age at Bhayangkara Tk. I Raden Said Sukanto Hospital Period July–December 2020.

Characteristics	Frequency	%
Gender		
Male	109	60,6
Female	71	39,4
Total	180	100
Age (year)		
19-30	21	11,7
31-45	28	15,5
46-59	79	43,9
≥60	52	28,9
Total	180	100

Table 1 shows that hospitalized COVID-19 patients tend to be more male (60.6%) than female (39.4%). Similar results were discovered in previous studies which displayed a predominance of male patients (Cecconi et al., 2020; Chen et al., 2020; Minuljo et al., 2020). This difference in distribution is thought to be related to the higher prevalence of active smokers in men. In smokers, hypertension, and diabetes mellitus, it is suspected that there is an increase in ACE2 receptor expression which makes it easier for SARS-CoV-2 to infect the human body (Cai, 2020; Fang et al., 2020). Another reason could be that men have lower CD4 cells than women, resulting in less production of antibody-forming B cells. The X chromosome also contributes to the production of antivirals such as type 1 interferon. Males only have 1 X Chromosome, so that the antiviral produced is not as much as women to fight SARS-CoV-2 infection (Peckham et al., 2020).

The age characteristics in table 1 show that the majority of COVID-19 disease suffered by patients aged >46 - 59 years as much as 43.9% and age >60 years 28.9%. Meanwhile, the analysis of data from the Indonesian COVID-19 Task Force as of April 25, 2021, for patients being treated/isolated, it is known that the age group of 31-45 years (28.29%) is the highest followed by those aged 19-30 (25.6%) and age 46 - 59 years (14.8%). These data show differences in the age group of the majority with this study. The number of patients aged >45 years in this study is suspected because COVID-19 is more at risk of infecting older people with chronic comorbidities due to decreased immune function (Chen et al., 2020). However, the limitation of this study was that there were no data on patient co-morbidities.

Table 2. Descriptive Data on PCT Levels in Inpatients Confirmed Positive for COVID-19 at Bhayangkara Tk. I Raden Said Sukanto Hospital Period July - December 2020

Variable	Mean	Min	Max
PCT (ng/mL)	10,38	0,01	282,00

Table 2 shows the mean (mean) level of PCT is 10.38 ng/mL with a minimum level of 0.01 ng/mL and a maximum level of 282.00 ng/mL. This mean result is in the condition of severe sepsis/septic shock. Normal PCT levels in healthy people<0.5 ng/mL. Procalcitonin is one of the inflammatory biomarkers besides CRP and interleukin that is often examined in COVID-19 patients (Ponti et al., 2020). PCT is produced from various parenchymal cells in the lung, liver and fat as well as leukocytes in response to endotoxins and proinflammatory cytokines (Meisner, 2014; Ponti et al., 2020). The role of PCT can be used as a prognostic or diagnostic disease. According to Schuetz, (2020), PCT biomarkers in COVID-19 patients can be used to assess the risk of bacterial infection,

differentiate bacterial and viral pneumonia and progression of disease severity. The presence of bacterial coinfection can lead to systemic infection and sepsis in COVID-19 patients. The diagnosis of sepsis in patients with elevated PCT can be confirmed by blood and sputum cultures to determine the type of infecting bacteria (Schuetz, 2020).

The production and release of PCT from extrathyroidal sources into the circulation is enormous during bacterial infection, which is actively maintained by increased concentrations of interleukin (IL)-1β, tumor necrosis factor (TNF)-α and IL-6. However, the synthesis of this biomarker is inhibited by interferon (INF)-γ, which concentration increases during viral infection. Therefore, it causes PCT levels to remain normal (<0.5 ng/mL) in some patients with SARS-CoV-2 infection without bacterial co-infection. Based on the PCT levels, viral and bacterial pneumonia infections in COVID-19 patients can be distinguished (Lippi & Plebani, 2020). Meanwhile, Shah (2020) stated that the use of PCT in COVID-19 can also be used as a marker of disease severity due to dysregulation of cytokine production. As an inflammatory marker, PCT will increase with the severity of COVID-19 disease so that PCT can be used as a severity prognostic (Ji et al., 2020).

Table 3. Frequency Distribution of PCT Levels and Disease Severity Levels in Hospitalized Patients with Confirmed COVID-19 at Bhayangkara Tk. I Raden Said Sukanto Hospital Period July–December 2020.

Variable	**Frequency**	**%**
PCT level (ng/mL)		
- <0,5	111	61,7
- ≥0,5	69	38,3
Total	180	100
Disease Severity		
- Low-Medium	87	48,4
- Severe	35	19,4
- Critical	58	32,2
Total	180	100

Table 3 shows PCT levels and disease severity in COVID-19 patients. PCT levels <0.5 ng/mL were highest in mild and moderate pain. PCT levels 0.5 ng/mL were not found in mild illness, but tended to be severe and critically ill. Study by Luo et al. (2020) and Chen et al. (2020) is in accordance with this study, the highest PCT levels <0.5 ng/mL were discovered in mild/moderate illness and the highest PCT levels 0.5 ng/mL in severe/critical illness. Higher PCT levels in severe and critical cases indicate systemic inflammation that exacerbates the clinical manifestations of COVID-19 patients (Chen et al., 2020).

The severity of the disease in this study included mild, moderate, severe and critical illness. The severity of COVID-19 disease is based on clinical manifestations ranging from asymptomatic, mild symptoms, pneumonia, severe pneumonia, ARDS, sepsis to septic shock (Susilo et al., 2020). Table 3 displays that mild to moderate pain was dominant in this study with 87 patients (48.4%). This study is similar to previous studies which found more moderately ill hospitalized patients than critically ill patients (Liu et al., 2020). Understanding the disease course of COVID-19 is very helpful in distinguishing whether the disease phase is still the result of a viral pathogen or an uncontrolled inflammatory phase that causes the condition to worsen. Furthermore, the severity of the disease is useful for administering therapy, knowing the response to therapy and the clinical outcome of the patient (Soeroto et al., 2020).

Table 4. Cross Table of Disease Severity Levels and PCT Levels in Inpatients Confirmed Positive for COVID-19 at Bhayangkara Tk. I Raden Said Sukanto Hospital Jakarta Period July - December 2020

Checkup result		Disease Severity						p-value
		Mild-Moderate		Severe		Critical		
		n	%	n	%	n	%	
PCT Level (ng/mL)	<0,5	83	46,2	15	8,3	13	7,2	0,000
	≥0,5	4	2,2	20	11,1	45	25	
Total		87	48,4	35	19,4	58	32,2	

Table 4 shows that the results of the cross-table analysis between PCT levels and disease severity obtained PCT levels <0.5 ng/mL with mild to moderate pain group as many as 83 patients (46.2%), severe illness 15 patients (8.3%) and critically ill 13 patients (7.2%). PCT levels 0.5 ng/mL were found in the mild-to-moderate group of 4 patients (2.2%), seriously ill in 20 patients (11.1%) and critically ill in 45 patients (25%). The results of the Chi Square test of PCT levels with disease severity in hospitalized patients with confirmed COVID-19 obtained p value = 0.000 (p <0.05) which indicates that there is a statistically significant relationship between PCT levels and disease severity. It informs that the higher the PCT level, the higher the severity of the disease. The results obtained in this study are the same as the research conducted (Chen et al., 2020; Li et al., 2020; Luo et al., 2020; Wang et al., 2020). Meta-analysis research results by Ahmed et al. (2021) also stated that 85% of cases found showed an association between PCT levels and disease severity.

The limitation of this study is that data on culture examination as a support for bacterial coinfection could not be included in this study due to the limitations of culture examination at the hospital at that time. Thus, the recommendation of this study is to include completeness of bacterial culture data in COVID-19 patients.

4. CONCLUSION

The results of the data analysis of this study found a relationship between PCT levels and the severity of disease in inpatients who were confirmed positive for COVID-19. The higher the PCT level, the higher the severity of the disease. PCT can be used as an indicator to observe the severity of the disease during this pandemic. Bacterial coinfection in COVID-19 patients has not been proven to be the cause of the severity in this study, the increase in PCT with increasing disease severity may be due to a cytokine storm.

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