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Research Article

Correlation between Interleukin-6 with D-dimer and C-reactive protein Levels in Patients with Confirmed COVID-19 Severe Criteria

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ABSTRACT

Background: In Coronavirus Disease 2019 (COVID-19) severe criteria, cytokine storm conditions are often found, and there will be an increase in Interleukin-6 as a cytokine and CRP as an acute phase protein induced by IL-6. In COVID-19 patients with severe criteria, coagulation disorders can also be found, characterized by an increase in the D-dimer value. **Purpose**: To determine the correlation between IL-6, D-dimer, and CRP levels in patients with confirmed COVID-19 severe criteria at Bunda Margonda General Hospital in 2021. **Methods**: This research was an analytical observation study with a cross-sectional approach, using secondary data from medical records of patients with confirmed COVID-19 severe criteria at Bunda Margonda General Hospital in 2021. **Results**: The number of patients with confirmed COVID-19 severe criteria was primarily male (59%), aged 46-55 years (33%), with degree of severity with severe criteria in 100 patients, increased IL-6 (91%), increased D-dimer levels (90%), increased CRP levels (95%). There was a correlation between increased IL-6 with D-dimer levels (p-value 0,005) and a correlation between increased IL-6 with CRP levels (p-value of 0,000). A simultaneous and significant relationship was found between IL-6, D-dimer, and CRP levels in severe COVID-19 criteria. COVID-19 patients with severe criteria were more commonly found in males in the 46-55-year age group with increased IL-6, D-dimer, and CRP values. **Conclusion**: There was a correlation between increased IL-6 and D-dimer and CRP levels in COVID-19 patients with severe criteria at Bunda Margonda General Hospital in 2021.

Keywords: COVID-19 severe criteria, c-reactive protein, d-dimer, interleukin-6

INTRODUCTION

Extraordinary conditions regarding the outbreak of new pneumonia cases caused the *World Health Organization* (WHO) to officially announce a new name for this pneumonia outbreak, *Coronavirus Disease 2019* (COVID-19) (1). *Coronavirus Diseases 2019* (COVID-19) is an infectious disease caused by *Severe Acute Respiratory Syndrome Coronavirus-2* (SARS-CoV-2). Based on WHO, the spread of COVID-19 cases around the world on 30 September 2022 recorded 614,385,693 positive confirmed cases of COVID-19 and 6,522,600 deaths (2). The main source of transmission for the spread of SARS-CoV-2 is human-to-human transmission.

Coronavirus Disease 2019 begins with an incubation period of around 3-14 days (1). The emergence of clinical manifestations in COVID-19 patients has a wide range, asymptomatic patients, mild, moderate, and severe symptoms. Most patients infected with SARS-CoV-2 show common symptoms, particularly symptoms of the respiratory system including fever, shortness of breath, sneezing, and coughing (3). In terms of detecting COVID-19, laboratory tests will be carried out with the *Nucleic Acid Amplification Test* (NAAT) / *Rapid Diagnostic Test Antigen* (RDT-Ag). After the patient has been diagnosed with COVID-19, laboratory tests will be carried out to identify patients who require hospitalization (4). The tests needed are to measure the concentration of creatinine, urea, sodium, *C-Reactive Protein* (CRP), *D-dimer*, *interleukin-6* (IL-6), potassium, bilirubin, serum glucose, *alanine aminotransferase* (ALT), *aspartate aminotransferase* (AST), and complete blood count (4).

According to research conducted by Liu et al, the research intended to examine the role of IL-6 in COVID-19 severe criteria, the study found that baseline IL-6 values were associated with the occurrence of COVID-19 with severe symptoms. Increased IL-6 values are also associated with poor chest CT scan images and a significant decrease in IL-6 levels was found in post-convalescent patients from COVID-19 (5). *D-dimer* is a product that is measured based on the analysis of blood samples and comes from the process of blood clotting and breakdown. Several studies have shown a correlation between increased *D-dimer* and increased severity of COVID-19 (6). A study conducted in Wuhei, China, found an increase in *D-dimer* levels at the time of admission to the hospital of more than 1 µg/mL and was associated with the incidence of death in the hospital in 191 COVID-19 patients (7).

When a cytokine storm occurs in COVID-19 patients with severe criteria, an increase in *C-Reactive Protein* (CRP) levels will be found (6). Based on research by Chen in China, the research was conducted to determine the role of CRP levels in determining the severity of COVID-19 infection, it was found that in cases of pneumonia due to COVID-19 that were severe and required a long hospitalization, high plasma CRP levels were found. So that plasma CRP levels are positively correlated with severity of pneumonia cases due to COVID-19 (8). The purpose of this study was to determine the relationship between IL-6 and *D-dimer* and CRP levels in patients who had confirmed COVID-19 with severe criteria at Bunda Margonda General Hospital in 2021.

METHODS

This research was an analytical observational study. The approach used in this study is the type of cross sectional approach. This research was conducted using secondary data obtained from the medical records of patients who had confirmed COVID-19 with severe criteria at Bunda Margonda General Hospital in 2021. Sampling was carried out by purposive sampling by designating Bunda Margonda General Hospital as the sampling location which was one of the referral hospitals for COVID-19 in Depok. Researchers used the Lemeshow formula with an unknown number of samples. Based on calculations using this formula, the required research sample size is 96 samples. In this study, the sample size to be taken is 100 samples.

Patients with complete medical records aged more than or equal to 18 years who have confirmed COVID-19 severe criteria in 2021. For the exclusion criteria was patients with increased levels of *D-dimer* caused by pregnancy, cancer, post-surgery. Data analysis in this

study was carried out using univariate, bivariate, and multivariate analysis. The tests used in the bivariate analysis are Chi Square Test and Fisher's Exact Test as an alternative if Chi Square Test conditions are not fulfilled. For multivariate analysis, this study uses multiple correlation tests. This test was used in many variables that were suspected of having relationship with each other. This study has received an ethics assessment from Health Research Ethics Commission Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta, number 288/PE/KE /FKK-UMJ/XI/2022.

RESULTS

Based on the data obtained from the medical record of COVID-19 patients with severe criteria at Bunda Margonda General Hospital in 2021, the following results were obtained.

Table 1. Description of Patients Who Have Confirmed COVID-19 Severe Criteria at Bunda Margonda General Hospital in 2021

Variable	Total	Percentage (%)
Age (Year)		
26-35 years	3	3.0
36-45 years	12	12.0
46-55 years	33	33.0
56-65 years	30	30.0
>65 years	22	22.0
Sex		
Male	59	59.0
Female	41	41.0
Degree of Severity		
Severe	100	100
Interleukin-6		
Normal ≤ 7 pg/mL	9	9.0
High > 7 pg/mL	91	91.0
D-dimer		
Normal < 0,5 ug/mL	10	10.0
High ≥ 0,5 ug/mL	90	90.0
C-Reactive Protein		
Normal < 5 mg/L	5	5.0
High ≥ 5 mg/L	95	95.0

Based on age distribution, it was found that patients with confirmed COVID-19 severe criteria at Bunda Margonda General Hospital in 2021 showed that the most patients were in the 46-55 year age group with 33 patients (33%). Based on gender distribution, it was found that males experienced a higher prevalence than females, with 59 male patients (59%) and 41 female patients (41%). Based on the degree of severity, it was found that patients with severe criteria had a presentation of 100 patients (100%).

Based on table 1, it was found that patients with high Interleukin-6 (IL-6) values were found in 91 patients (91%), there were 90 patients (90%) who had increased *D-dimer* values,

and it was found that there was an increase in *C-Reactive Protein* (CRP) values in 95 patients (95%).

Table 2. Correlation Interleukin-6 (IL-6) value with *D-dimer* value and IL-6 values with CRP in Patients with Confirmed COVID-19 Severe Criteria at Bunda Margonda General Hospital in 2021

Interleukin-6 (IL-6)	***D-dimer* values**		***P-value***
	Normal	**High**	
Normal ≤ 7 pg/mL	4	5	0.005
High > 7 pg/mL	6	85	
Interleukin-6 (IL-6)	***C-Reactive Protein* values**		***P-value***
	Normal	**High**	
Normal ≤ 7 pg/mL	4	5	0.000
High > 7 pg/mL	1	90	

Based on table 2, the results of the analysis of the relationship between Interleukin-6 and *D-dimer* levels in patients with confirmed COVID-19 severe criteria obtained a p-value of 0.005 and the value between IL-6 and CRP levels in patients with confirmed COVID-19 severe criteria, a p-value of 0.000 was obtained from the analysis <0.05, so there was a significant relationship between IL-6 value and *D-dimer* levels and the IL-6 with CRP values in patients with confirmed COVID-19 severe criteria at Bunda Margonda General Hospital in 2021.

Table 3. Multiple Correlation Test for the correlation between IL-6 values and D-dimer and CRP levels in Patients with Confirmed COVID-19 Severe Criteria at Bunda Margonda General Hospital in 2021

Interleukin-6 (IL-6)	***D-dimer* values**		**CRP values**		***p-value****
	Normal	**High**	**Normal**	**High**	
Normal ≤7 pg/mL	4	5	4	5	0.000
High >7 pg/mL	6	85	1	90	

*Significant F Change

In table 3, a multiple correlation test was carried out, the correlation test results were obtained with a significant F value of 0,000 from the analysis results <0,05, so with this IL-6 has a simultaneous and significant relationship to *D-dimer* and CRP levels in patients with COVID-19 severe criteria.

DISCUSSION

In a study conducted at Bunda Margonda General Hospital, it was shown that patients with confirmed COVID-19, the most severe criteria were in the 46-55 year age group, specifically 33 patients (33%). Based on research on the relationship between age and mortality, it shows that the age group >50 years infected with COVID-19 has a higher risk of death compared to the age group <50 years (9,10). Elderly patients have a tendency to be infected along with decreased natural immunity (11).

Based on gender category, the most common were male patients, namely 59 patients (59%). Based on a meta-analysis study, it was found that men are 28% more at risk of infection

compared to women (12). In the male sex, it is known that they have a higher expression of *Angiotensin I Converting Enzyme 2* (ACE2), causing men to be more at risk of being infected with SARS-CoV-2 (13,14). Based on the category regarding the degree of severity in patients, confirmed COVID-19 was found in patients with severe criteria. Based on available data, severe COVID-19 occurs mainly in elderly patients or patients with comorbid disease such as hypertension, diabetes, or immunocompromised conditions. The main factor for the emergence of severe COVID-19 symptoms is the occurrence of an immune pathogenic process or cytokine storm (15).

Interleukin-6 values in patients with confirmed COVID-19 with severe criteria at Bunda Margonda General Hospital were found to increase by 91 patients (91%). Based on research conducted in China, it was found that changes in elevated IL-6 levels were associated with aggravation that occurred in patients with severe criteria for COVID-19 and resulted in a prolonged hospital stay in Covid-19 patients (16,17). For *D-dimer* values in patients with confirmed COVID-19, the criteria for severe COVID-19 at Bunda Margonda General Hospital were found to be increased in 90 patients (90%). Elevated *D-dimer* levels were reported to be a predictive factor for a worse prognosis. *D-dimer* in COVID-19 patients has a relationship with abnormal immune mechanisms, disease severity, and increased mortality (18). For *C-Reactive Protein* levels in patients with confirmed COVID-19 criteria for severe at Bunda Margonda General Hospital, it was found that there was an increase in as many as 95 patients (95%). Based on research by Chen in China, it shows that higher plasma CRP levels indicated more severe pneumonia due to COVID-19 and these plasma CRP levels are positively correlated with the severity of pneumonia due to COVID-19 (8).

Based on this study, it was found that there was a tendency for a significant relationship between IL-6 values and *D-dimer* levels in patients with confirmed COVID-19 severe criteria. In COVID-19 with severe symptoms, fatal complications can be found in the form of immune thrombosis due to hyperinflammation and a cytokine storm where one of the pro inflammatory cytokines that play a role is IL-6 (19). Hypercoagulable conditions are conditions that are often found in COVID-19 infection (20). Hyper coagulation results from a hyper inflammatory response in the form of coagulation and excessive platelet activation. Hypercoagulation is characterized by increased levels of *D-dimer* which is a marker of coagulation and thrombus formation (6).

In this study, it was also found that there was a trend of increasing Interleukin-6 (IL-6) values with *C-Reactive Protein* (CRP) levels in patients with confirmed COVID-19 severe criteria. In conditions of a cytokine storm, one of the excess pro inflammatory cytokines produced is IL-6. An increase in the amount of IL-6 will increase CRP levels in the blood because it is one of the acute phase reactants so that it will increase rapidly after an inflammatory process occurs, cell, and tissue damage (8).

In a study conducted at Bunda Margonda General Hospital, IL-6 values were obtained with levels of *D-dimer* and *C-Reactive Protein* (CRP) in patients with confirmed COVID-19 severe criteria at Bunda Margonda General Hospital, having a correlation test result with a significant value F of 0,000 from the results of the analysis <0,05 therefore the IL-6 values has a simultaneous and significant relationship with *D-dimer* and *C-Reactive Protein* (CRP) levels in patients with confirmed COVID-19 severe criteria.

CONCLUSION

This study found a simultaneous and significant relationship between IL-6 values with *D-dimer* and *C-Reactive Protein* (CRP) levels in patients with confirmed COVID-19 severe criteria at Bunda Margonda General Hospital in 2021.

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CONFLICT OF INTEREST

The researcher has no conflict of interest, and has no affiliation or connection with any entity or organization that may raise biased questions in the discussion and conclusion of the manuscript.

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