



D-dimer levels as biomarker in COVID-19 Patients prognosis with Severe-Critical Degrees

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Abstract

Introduction: The SARS-CoV-2 virus pandemic has become a scourge since 2020. Research abroad states that D-dimer values are prognostic factors for COVID-19 patients, although there is no agreement on the best cut-off point for specificity and sensitivity. Therefore, it is necessary to evaluate the role of this laboratory result in estimating the prognosis of COVID-19 patients in Indonesia.

Method: This quantitative retrospective study data in the form of proportions were collected for 12 months from the hospital medical records. Overall survival was assessed by the Kaplan-Meier curve. The cut-off determination for the D-dimer variable was conducted using the Receiver Operating Curve (ROC) followed by the calculation of the Youden index. Then the hazard ratio was determined by cox regression with a p-value of <0.05 which was considered significant. Statistical analysis with SPSS software version 26 and Medcalc Statistical Software. Determine the strength of the research using PS Power and Sample Size Calculation software version 3.1.2.

Result: D-dimer levels in the surviving patients are lower than in patients who died. However, the level of D-dimer did not show a significant correlation with the survival of COVID-19 patients statistically ($p > 0.05$).

Conclusion: The D-dimer value could be a predictor of the severity of COVID-19. However, the D-dimer could not use as a single parameter of the prognostic outcome of COVID-19. The clinician should fully become aware of the other laboratory test results that have predictor values for sepsis condition.

Keywords: COVID-19, d-dimer, prognostic factor

1. Introduction

COVID-19 caused by the SARS-CoV-2 virus is a scourge for the whole world. The first appeared in the form of a pneumonia cluster on December 31, 2019, in Wuhan, China. Then January 13, 2020, the official confirmed the first case in Thailand, which was the first case outside China ^(1,2). Based on the distribution of WHO data dated February 17, 2021, at 09.30 WIB, 223 countries were affected by the pandemic. A total of 108,822,960 confirmed world

population and 1,403,641 people died. Confirmation cases for each region were 48,457,101 cases in America, Europe with 36,806,380 cases, and Southeast Asia with 13,225,290 cases. Meanwhile, the confirmed cases for each country are the United States 27,309,503 cases, India's 10,925,710 cases, and Brazil's 9,834,513 cases ⁽³⁾. Based on data from the Committee for Handling COVID-19 and Indonesian National Economic Recovery, dated February 17,

2021, at 09.30 WIB, confirmed patients were 1,233,959 people, 1,039,674 people recovered, 86,960 people suspected, and 33,596 people died. The highest number of confirmed cases was DKI Jakarta 317,432 cases, West Java 175,950 cases, and Central Java 142,318 cases⁽⁴⁾.

During a pandemic, the need for intensive care rooms exceeds availability. Based on research at the AdventHealth Health System, Orlando, Florida from March 11 to May 18, 2020, there were a total of 1,283 COVID-19 patients with 131 (10.2%) meeting the ICU admission criteria (median age 61 years [IQR 49.5-71.5]; 35.1% female). Based on 131 ICU patients, there were 109 patients (83.2%) requiring mechanical ventilation and 9 patients (6.9%) receiving extracorporeal membrane oxygenation (ECMO). General hospital mortality was 19.8% and MV-related mortality was 23.8% after exclusion of inpatient⁽⁵⁾. The high mortality and morbidity rate due to COVID-19 is due to sepsis⁽⁶⁾. The pathomechanism of sepsis due to hypercoagulation in COVID-19 is still debated because it is due to hypercoagulability that triggers thrombosis, not the usual consumptive coagulopathy⁽⁶⁾.

Existing research states that the value of D-dimer is a prognostic factor in COVID-19, although there is no agreement on the best cut-off point for specificity and sensitivity^(7,8). D-dimer describes the condition of hypercoagulability and increased lactic acid in severe sepsis. Until now, there has been no study evaluating the results of this laboratory as a determinant of the prognosis of COVID-19 in Indonesia. And there has been no study of the relationship between sepsis and hypercoagulability with the dominance of thrombosis in COVID-19 patients in Indonesia. This research is needed to see the correlation between

the D-dimer value with the prognosis of COVID-19, sepsis cases, and hypercoagulability in ethnic groups in Indonesia, especially patients at the Gadjah Mada University Academic Hospital which is expected to be the basis for other research as well as to see the role of ethnicity in the variables that will be investigated.

2. Materials and Methods

2.1 Research Type and Design

This study is a retrospective cohort analytic observational study. Retrospective data were taken using secondary data in the form of medical records of COVID-19 patients who met the inclusion criteria at the Gadjah Mada University Academic Hospital.

2.2 Place and time

This research was conducted at the Academic Hospital of Gadjah Mada University. The time of this research is from April 2021 to October 2021.

2.3 Population and Sample

2.3.1 Population

The target population of this study is patients who have been diagnosed with PCR-confirmed COVID-19 with severe-critical severity. The population covered by this study were patients with severe-critical COVID-19 who were hospitalized at the Gadjah Mada University Academic Hospital.

2.3.2 Sample

The subjects involved in this study were selected by consecutive sampling, that is, all samples that met the inclusion criteria were included in the study. The samples were then recapitulated by using Microsoft Office software.

2.4 Inclusion and Exclusion Criteria

2.4.1 Subject inclusion criteria

- a. Patients with confirmed severe or critical severity of COVID-19 based on the Guidelines for the Management of COVID-19 5OP Edition 3 who was diagnosed in July 2020 to July 2021 and were hospitalized at the Gadjah Mada University Academic Hospital
- b. >18 years old

2.4.2 Subject exclusion criteria:

The patient has a history of blood clotting disorders such as von Willebrand disease or hemophilia

2.5 Types and Methods of Data Collection

2.5.1 Data Type

The type of data used in this study is qualitative and quantitative data sourced from the medical records of COVID-19 patients treated at the UGM Academic Hospital.

2.5.2 Data Collection Method

Patient data taken from medical records are recorded and recapitulated in a case report form created in Microsoft Office Excel software.

2.6 Data Analysis

Data on the frequency of confirmed severe-critical COVID-19 patients are presented in proportions. Overall survival in this study was carried out by looking at the Kaplan-Meier curve to see the general survival of patients. Determination of the cut-off for the D-dimer, lactic acid, and AGD variables (pH, PaO₂, PaCO₂, PaO₂/fiO₂) was carried out

using the Receiver Operating Curve (ROC) so that the sensitivity and specificity values were obtained. After that, the Youden Index is calculated and the highest value is chosen to be the cut-off value. Survival analysis for each marker was performed using the Kaplan-Meier curve and the hazard ratio was determined by cox regression. The value that is considered significant is the p-value <0.05.

All independent variables with p < 0.25 in bivariate analysis were then entered into multivariate analysis using the Cox regression time-independent method. In the results of multivariate analysis, the independent variable is said to be related to the dependent variable if p <0.05 and the confidence interval does not exceed the number 1. The strength of the relationship between the independent variable and the dependent variable is described by the magnitude of the hazard ratio (HR) value. Statistical analysis in this study used SPSS version 26 software and Medcalc Statistical Software. To determine the strength of the study based on the hazard ratio value using the PS Power and Sample Size Calculation software version 3.1.2.

3. Results

3.1 Characteristics of Research Sample

There were 222 patients with severe or critical symptoms of COVID-19 who were involved in this study, with the majority of men being 140 patients (63.1%) compared to women, which were 82 patients (36.9%). Most of the patients had comorbidities, namely, 140 (63.1%)

patients had comorbidities and 82 (36.9%) patients did not have comorbidities. Almost all COVID-19 patients with severe or critical symptoms in this study had a D-Dimer interpretation above the cut-off (>500 g/L) as many as 202 patients (91%) and for those below the cut-off (<500 g/L) as many as 20 patients (9%) (Table 1).

Table 1. Distribution of Research Sample Characteristics

Variable	Frequency	Percentage
Gender		
Men	140	63.1%
Women	82	36.9%
Total	222	100%
Interpretation of D-Dimer		
Above Cut-off (>500 µg/L)	202	91%
Below Cut-off (<500 µg/L)	20	9%
Total	222	100%
Status Comorbid		
Yes	140	63.1%
No	82	36.9%
Total	222	100%

3.2 The Correlation between Gender and Survivability of COVID-19 Patients with Severe or Critical Symptoms

In this study, it was found that 66 male patients (47%) survived, while 73 male patients (53%) did not survive. In women, it was found that the female patients who survived were 29 patients (35%), while the female patients who did not survive were 53 patients (65%). This difference was not significantly different

($p = 0.87$) so it was not clinically significant (Table 2).

3.3 The Correlation between D-Dimer Interpretation and Survival of COVID-19 Patients with Severe or Critical Symptoms

Based on the interpretation of D-Dimer, it was found that 85 patients (42%) who had D-Dimer above the cut-off (>500 g/L) survived and 117 patients (58%) did not survive. In patients who had D-Dimer

below the cut-off (<500 g/L) it was found that 10 patients (50%) survived and 10 patients (50%) did not survive. This difference was also not significantly different ($p = 0.495$), so it was not clinically significant (Table 2).

3.4 The Correlation between Comorbidities and Survival of COVID-19 Patients with Severe or Critical Symptoms

Based on comorbidities, it was found that 52 patients (37%) had comorbid and 88 patients (63%). Meanwhile, 43 patients (52%) who did not have comorbid survived, and 39 patients (48%). This difference was significantly different ($p = 0.026$), so it has clinical significance (Table 2).

Table 2. Analysis of the Relationship between the Characteristics of the Study Sample and the Survivability of COVID-19 Patients with Severe or Critical Symptoms

Variable	Indicator	Survive	Not Survive	Total	P-value
Gender	Male	66 (47%)	74 (53%)	140 (100%)	0.87
	Female	29 (35%)	53(65%)	82 (100%)	
Interpretation of D-Dimer	Above cut-off (>500 µg/L)	85 (42%)	117 (58%)	202 (100%)	0.495
	Below cut-off (<500 µg/L)	10 (50%)	10 (50%)	20 (100%)	
Status Comorbid	Yes	52 (37%)	88 (63%)	140 (100%)	0.026*
	No	43 (52%)	39 (48%)	82 (100%)	

4. Discussion

The COVID-19 pandemic has caused increased morbidity and mortality rates worldwide. Previous studies have shown that serum D-dimer levels can be used to diagnose the presence of a pro-thrombotic condition. Serum D-dimer levels were significantly higher in patients with severe or critically ill COVID-19 symptoms. This suggests that D-dimer levels can be useful for the rapid identification of COVID-19 patients at high risk for pulmonary and venous thromboembolic complications⁽⁹⁾. So, this study

complements previous research, namely in examining the relationship between D-Dimer levels and the survival of COVID-19 patients with severe or critical symptoms.

D-dimer is a product of fibrin degradation, in the form of protein fragments present in the blood after the degradation of blood clots by fibrinolysis. Measurement of D-Dimer levels is a sensitive test in clinical practice to determine thrombotic conditions, including pulmonary embolism and DIC⁽¹⁰⁾. Therefore, the presence of elevated D-dimer levels in COVID-19 patients

can help predict the severity of COVID-19 disease. There is evidence to suggest that SARS-Cov 2 can also cause a cytokine storm that can trigger the coagulation cascade and cause thrombotic complications. This manifests clinically as disseminated intravascular coagulation (DIC). Compared to SARS-Cov in 2003, DIC in COVID-19 was more common. The autopsy results of COVID-19 patients with DIC showed that there was a fibrin thrombus, endothelial swelling, and the presence of megakaryocytes in the pulmonary arteries and capillaries⁽¹¹⁾.

The cut-off levels of D-dimer used in each study were different. This study uses a cut-off value of D-dimer levels of 500 g/L FEU (fibrinogen equivalent units) which is following the SI (International System of Units)⁽¹²⁾. The figure of 500 g/L is the result of a study that explains that the cut-off value for COVID-19 patients who develop pulmonary embolism complications with DVT is 500 g/L with a sensitivity of 96% and a specificity of 10%⁽¹³⁾. Meanwhile, for COVID-19 mortality markers based on D-dimer levels, the cut-off value was 1500 g/L FEU with a sensitivity of 70.6% and a specificity of 78.4%⁽¹⁴⁾.

The results obtained from this study are in patients with D-dimer interpretation above the cut-off, there is a difference in the percentage of patients who do not survive and survive as much as 16%. Meanwhile, in patients with D-dimer interpretation below the cut-off, there was no difference in the percentage of not surviving and surviving. In this study, the difference in the percentage of patients who did not survive and survive in the D-dimer group above the cut-off was higher than the percentage of patients who did not survive and survive in the D-dimer group below the cut-off. This is in line with research who

explained that the cut-off value of D-dimer levels in COVID-19 patients who experienced complications in the form of thromboembolism was in patients with D-dimer levels of more than 500 g/L⁽¹³⁾.

However, in this study, the difference in the percentage of patients who survived and did not survive in patients with D-dimer interpretation above the cut-off and below the cut-off did not show significant results ($p = 0.495$) (Table 2). This may be because the cut-off for D-dimer levels used by researchers still uses the cut-off for morbidity, which is 500 g/L. Meanwhile, the cut-off for mortality in COVID-19 patients with severe or critical symptoms with thromboembolic events is at least 1500 g/L.

Another outcome obtained by this study was the relationship between gender and comorbidities on the survival of COVID-19 patients with severe or critical symptoms. Table 2 shows that there is no significant relationship between gender and the survival of COVID-19 patients with severe or critical symptoms where the p-value is 0.87 ($p > 0.05$). Meanwhile, between comorbidities and the survival of COVID-19 patients with severe or critical symptoms, there is a significant relationship where the p-value is 0.026 ($p < 0.05$).

In patients with male sex, the difference in the percentage of patients who did not survive and survived was 8%. Meanwhile, in female patients, the difference between the percentages of not surviving and surviving was 24%. In this study, the difference in the percentage of patients who did not survive and survived in women was more than the percentage of patients who did not survive and survived in men. This is not in line with research which explains

that men have a greater chance of being infected than women ⁽¹⁵⁾. It is known that men are 28% more likely to be infected with COVID-19 than women. This is comparable to research on the relationship between sex and mortality which shows that men are 1.8% at risk of death compared to women.

However, in this study, the difference in the percentage of patients who survived and did not survive in male and female patients did not show significant results ($p = 0.87$). It is known that men have higher ACE-2 expression. This is related to sex hormones that cause men to be at greater risk for infection with SARS-CoV-2. ACE2 expression is encoded by a gene on the X chromosome. Females are heterozygous while males are homozygous. Thus, the male sex has the potential to increase ACE2 expression. SARS-CoV-2 infection and other clinical symptoms can be neutralized by women because women carry the heterozygous X allele ⁽¹⁶⁾.

The results of this study are not in line with the literature, perhaps due to the lack of completeness of patient data, especially in terms of age. In premenopausal women, endogenous estrogen has a protective effect against cardiovascular disease and COVID-19. The higher levels of estrogen and progesterone in premenopausal women, can increase the immune response and reduce the severity of COVID-19. Research in America shows that there is an increase in the mortality ratio of COVID-19 in women aged 45-54 years who have experienced menopause ⁽¹⁷⁾.

In patients with comorbidities, the difference in the percentage of patients who did not survive and survived was 26%. Meanwhile, in patients without comorbidities, the difference

between the percentages of surviving and not surviving was 4%. In this study, the difference in the percentage of patients who did not survive and survive in patients with comorbidities was significantly higher than the percentage of patients who did not survive and survive in patients without comorbidities where the p-value was 0.026 ($p < 0.05$). This is in line with research which explains that there is a significant correlation between comorbidities and their role in COVID-19 exacerbations in patients leading to death ⁽¹⁸⁾.

Previous research explained that hypertension, obesity, and diabetes mellitus were the most common comorbidities in COVID-19 patients. Recent studies have reported that hypertension and diabetes can increase the incidence of thrombotic events. COVID-19 is associated with increased thrombus strength, increased D-dimer levels, and hyperfibrinogenemia ⁽¹⁸⁾.

Chronic medical conditions are similar to infectious diseases, which can cause inflammation and a decreased immune response in affected individuals. This is due to a decrease in macrophage and lymphocyte activity ⁽¹⁹⁾. This is a predisposing factor for patients to be infected and experience complications of the disease. The high prevalence of fatal cases in COVID-19 patients with hypertension and diabetes mellitus as comorbidities can be caused by cytokine storms. Cytokine storms can cause hyperinflammation and be a marker of severe SARS-Cov 2 infections ⁽²⁰⁾.

The use of immunosuppressive drugs in autoimmune and cancer patients can also experience weakened immune function ⁽²¹⁾. This explains that there is an increased risk of

hospitalization in critically ill patients. Thus, patients with comorbidities, especially cancer, hypertension, and diabetes, have a higher risk of mortality. Obesity cannot be an independent predictor of mortality. Obesity does not play a direct role in ACE2 expression, but obese patients have ACE2-expressing adipose tissue which indirectly increases ACE2-expressing cells⁽²²⁾. Another factor is the abnormality of cytokines and complement production which can lead to decreased activity that inhibits inflammation. In addition, in treating obese patients several difficulties can affect the prognosis such as difficult intubation, weight restrictions on imaging machines, and difficulty in performing prone position which can cause ventilation dysfunction⁽²³⁾.

5. Conclusion

There is an insignificant correlation ($p > 0.05$) between the interpretation of D-Dimer and the survival of COVID-19 patients with severe or critical symptoms where the p-value is 0.495. In this study, another outcome was obtained, namely, there was an insignificant difference ($p > 0.05$) between gender and the survival of COVID-19 patients with severe or critical symptoms where the p-value was 0.87. Meanwhile, based on the history of comorbidity with the survival of COVID-19 patients with severe or critical symptoms, significant results were obtained ($p < 0.05$) where the p-value was 0.026.

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