The Correlation between Initial D-dimer Levels and the Length of ICU Stay of the COVID-19 Patients in Dr. Soetomo General Hospital from April 2020 to March 2021

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Abstract

Approximately 10-15% of COVID-19 patients become severely ill and require intensive care. One of the laboratory tests used in monitoring patients in the ICU is D-dimer. Elevated levels of D-dimer can predict the disease severity and mortality. The aim of this study was to analyze the relationship between D-dimer levels and ICU length of stay in patients with COVID-19. This was an analytical observational study with a cross-sectional design and a retrospective approach. The secondary data were in the form of confirmed COVID-19 patients at Dr. Soetomo General Hospital Surabaya from April 2020 to March 2021. The median of continuous variables was compared with the Mann-Whitney U test. The correlation was determined using the Spearman's Rank Correlation Coefficient test. Based on the criteria, it was obtained a sample of 120 patients with the median of initial D-dimer 2225 (855 – 6122.5) ng/mL FEU and the median duration of the ICU stay 9 (1 – 32) days. The result of the comparative analysis of the initial D-dimer levels on clinical outcomes indicated a p-value of 0.012. Patients with life clinical outcomes showed a relationship between initial D-dimer levels and the length of ICU stay ($p = 0.328$; (r^2) = 0.309) while in patients with death clinical outcomes was ($p = 0.023$; (r^2) = -0.219). Elevated D-dimer levels as a marker of thrombosis were reported. Increased D-dimer levels correlated with mortality. Thus, there was a correlation between initial D-dimer levels and length of ICU stay in COVID-19 patients with death clinical outcome.

Keywords: D-dimer; ICU stay; COVID-19

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has caused the coronavirus disease 2019 (COVID-19) pandemic since it was first identified in Wuhan, China in late December 2019. The pandemic has affected more than 500 million people in various countries.[1] Clinical manifestations of COVID-19 range from asymptomatic illness to severe viral pneumonia with respiratory failure, multiple organ and systemic dysfunction, and death.[2] Furthermore, COVID -19 can be divided into asymptomatic, mild, moderate, severe and critical.[3]

An epidemiological study showed that approximately 10-15% of COVID-19 patients become severely ill.[4] Severe cases of COVID-19 need to be treated immediately in the ICU for acute hypoxemic respiratory failure (SpO2 < 93%). Most patients admitted to the ICU will eventually experience diffuse lung injury and ARDS which require IMV. In addition, extrapulmonary complications are also significant contributors to poor outcomes.[5]

Previous studies reported that the mortality of patients with severe COVID-19 in the ICU ranged from 50-65 %.[5] Mortality in severe COVID-19 patients is often caused by pulmonary complications such as ARDS followed by various complications including shock, myocardial dysfunction, and acute kidney injury. Elderly patients, patients with comorbidities (such as high blood pressure, DM, CVD, chronic lung disease, and cancer), high

disease severity scores, worsening respiratory failure, increased levels of D-dimer and C-reactive protein, total lower lymphocytes, and the appearance of secondary infections also affect mortality in COVID-19 patients.[6]

An increase in D-dimer levels indicates the presence of thrombosis which characterizes a coagulation disorder. The diagnosis of coagulation disorders can also be assessed from laboratory results of blood samples. In addition, elevated D-dimer levels can also predict disease severity and mortality. In patients hospitalized with SARS-CoV-2 infection, an increase in D-dimer above normal (500 ng/mL) may indicate a poor clinical outcome. The clinical outcome needs special care in the ICU, ARDS, or mortality from all causes.[7]

A study of COVID-19 patients at Pamukkale University, Denizli, Turkey, concluded that there was a positive correlation between D-dimer levels and length of hospital stay.[8] In Indonesia, D-dimer levels and COVID-19 relationship with duration of treatment in ICU patients has not been studied. Therefore, the current study aimed to examine the correlation between D-dimer level in a COVID-19 patient and length of stay in the ICU.

2. Method

This was an analytic observational study using a cross-sectional design with a retrospective approach. The data were in the form of secondary data obtained from the medical records of COVID-19 patients treated in the Special Isolation Room (RIK) 1 Dr. Soetomo General Hospital Surabaya from April 2020 to March 2021. The samples were collected by total sampling method, with the results of 120 patients. The samples were COVID-19 patients aged 18 years who had been diagnosed both clinically and by laboratory and treated in the RIK 1 Dr. Soetomo General Hospital Surabaya from April 2020 to March 2021. Patients who did not have complete laboratory data, patients who were still being treated at RIK 1 on March 31, 2021, and patients with several conditions, including acute coronary syndrome, chronic liver disease, cancer, hematological malignancies, pregnancy, surgery, or trauma within the last 30 days were excluded from this study. This research had obtained permission from the Health Research Ethics Committee of Dr. Soetomo General Hospital with Letter of Exemption number 0610/LOE/301.4.2/IX/2021.

The data included patient characteristics such as age, gender, comorbidities, oxygen therapy, clinical outcomes, D-dimer levels with a normal limit of 500 ng/mL FEU, and the length of ICU stay expressed in days. The data were collected using Microsoft Excel 2016 and then analyzed using the IBM SPSS Statistic version 23 application. The first test was the Kolmogorov-Smirnov and Shapiro-Wilk normality tests to determine the distribution of the data. The data were reported as percentages for categorical variables and as mean ± SD on normally distributed numerical data or median (IQR) on non-normally distributed numerical data. Initial D-dimer levels between patients with clinical outcomes who died and lived will be compared with the Mann-Whitney U test. The Spearman's Rank Correlation Coefficient test was used to determine the correlation between D-dimer levels and the length of ICU stay. The statistical significance was determined at $p<0.05$.

3. Results

A total of 120 patients met the inclusion and exclusion criteria and became study participants. The characteristics of the participants are shown in Table 1. The average age was 51.08 years. The percentage of male (73.3%) was higher than female (26.7%).

Table 1. The COVID-19 patients characteristics in RIK 1 of Dr. Soetomo General Hospital Surabaya from April 2020 to March 2021

Variables	Total (120)
Age (years)	51.08 ± 11,695
Gender	
Male	88 (73.3%)
Female	32 (26.7%)
Comorbidities	
Diabetes Mellitus	71 (32.9%)
Kidney Disease	45 (20.8%)
Obesity	42 (19.4%)
Hypertension	38 (17.6%)
No Comorbidity	15 (6.9%)
Cardiovascular Disease	5 (2.3%)
Oxygen Therapy	
Ventilator	115 (95.8%)
No ventilator	5 (4.2%)
Clinical Outcome	
Life	12 (10%)
Death	108 (90%)
Initial D-dimer Levels (ng/mL FEU)	2225 (855 – 6122.5)
The Length of ICU Stay (Days)	9 (5.25 – 14)

Data are mean ± SD, median (IQR), and n (%).

Initial D-dimer levels in died patients were relatively higher than those who were survived. Differences between the two groups were analyzed using the Mann-Whitney U test, as the initial D-dimer levels were not normally distributed. As shown in Table 2, Mann-Whitney U test results showed significant differences in initial D-dimer levels between died and survived clinical outcomes ($p<0.05$).

Table 2. The Correlation between Initial D-dimer Levels and Clinical Outcome

	Frequency (n)	Initial D-dimer Levels (ng/mL FEU)	p
Life	12	810 (632.5 – 2740)	0.012
Death	108	2405 (1152.5-6240)	

Mann-Whitney U test. Statistical significance was determined at $p<0.05$

Initial D-dimer levels in each clinical outcome group were then correlated with the length of ICU stay. First, a normality test was performed by either Kolmogorov-Smirnov or Shapiro-Wilk to confirm the distribution of the data. In the survival group, initial D-dimer levels were abnormally distributed ($p<0.05$). Both initial D-dimer levels and residence times were abnormally distributed in the dead group ($p<0.05$). As the data were not normally distributed, we performed Spearman's rank correlation coefficient test for each group. The correlation between initial D-dimer levels and length of stay in the ICU is shown in Table 3.

Table 3. The Correlation between Initial D-dimer Levels on the Length of ICU Stay

Variables	Initial D-dimer Levels			
	Life (12)		Death (108)	
	p	r^2	p	r^2
The Length of ICU stay	0.328	0.309	0.023	-0.219

Spearman Rank Correlation Coefficient test. Statistical significance was determined at $p<0.05$

Patients who survived showed a non-significant correlation between initial D-dimer levels and the length of ICU stay ($p = 0.328$; (r^2) = 0.309) with a fairly strong and linear correlation. Patients with death clinical outcomes showed a significant correlation between initial D-dimer levels and the length of ICU stay ($p = 0.023$; (r^2) = -0.219) with a weak and opposite correlation strength.

4. Discussions

The median test result for the D-dimer level on the first day of admission to the ICU was 2225 ng/mL FEU. This is higher than the normal limit for D-dimer in healthy individuals, which is 500 ng/mL FEU. An increase in D-dimer levels was also observed by Huang et al., (2020) who stated that the median D-dimer levels of the patients requiring ICU care was 2.4 mg/L.[9] Mubarak et al., (2021) compared D-dimer levels between severely symptomatic and asymptomatic patients. The results showed a significant difference ($p<0.001$) between non-severe (0.31 ± 0.38 g/L) and severe (3.09 ± 2.56 g/L) patients.[10] Meta-analysis by Nugroho et al. (2021) obtained the similar findings. This study stated that the average D-dimer levels at the time of hospital admission was higher in patients with severe degrees and requiring ICU care.[11]

Monitoring of D-dimer levels should be performed early after admission. D-dimer can be used to predict severe and fatal cases of COVID-19. Previous studies have shown that the D-dimer has moderate accuracy in predicting disease severity (77% sensitivity, 71% specificity, and 77% specificity)12.[13] A meta-analysis showed a strong relationship between patients at high baseline D-dimer risk for disease progression.[14]

A significant relationship was revealed between COVID-19 and D-dimer.[15] Elevated D-dimer levels indicate that COVID-19 patients are hypercoagulable and at risk for thrombosis. Hypercoagulability is triggered by a cytokine storm associated with excessive immune responses in SARS-CoV-2 infection and systemic inflammation. Stress conditions such as acute respiratory distress syndrome, sepsis, shock, and drug intoxication are associated with hypoxic reoxygenation, oxidative stress and acid-base imbalance and may contribute to high D-dimer. According to the Virchow triad, endothelial dysfunction, altered blood flow, hypoxia and immune response-induced hyperviscosity and platelet activation contribute to the development of thrombosis in COVID-19. Activation of the renin-angiotensin-aldosterone system (RAAS) and increased plasminogen activator inhibitor (PAI-1) contribute to this thrombus formation mechanism.[15,16,17]

In this study, the median length of ICU stay was 9 days (1-32). There were various median values for the length of ICU stay ranging from 6-17 days in several previous studies.[5,18,19,20,21,22,23] Three previous studies resulted in data on the average length of ICU stay of 17.17±7, 18 days; 15±9 days; 10,59±6.53 days.[24,25,26] This difference in reported results is possibly due to the sample size, different ICU admission criteria in various places, availability

of ICU beds, differences in disease severity at the time of ICU admission, and other conditions that underlie each individual.

There was a significant difference between initial D-dimer levels and patients who survived and died (810 (632.5-2740) vs 2405 (1152.5-6240); $p<0.05$). These results are consistent with a study by Poudel et al., (2021). Mean initial D-dimer in surviving patients was 1067 g/mL (±1705 g/mL), but in dead patients was 3208 g/mL (±2613 g/mL).[26] A meta-analytic study by Nugroho et al., 2021, also found that a group of survivors had lower levels of D-dimer on admission.[11]

Abnormal D-dimer levels are common in hospitalizations for COVID-19 and are associated with the development of more severe disease symptoms, the presence of thrombosis, acute kidney injury, and death.[27] D-dimer levels at admission are an accurate biomarker to predict mortality in COVID-19 patients.[11,14,26] The optimal cut-off value for predicting mortality in COVID-19 patients is 1.5 g/mL.[26] Shah et al., (2020) mentioned that the risk of death in the patients with D-dimer levels above 0.5 mg/l were four times greater than patients with D-dimer levels below 0.5 mg/l.[13]

In patients with life clinical outcomes, the higher the initial D-dimer level, the longer the ICU stay will be. This is of course the opposite of the clinical outcome of death. In COVID-19 patients with death clinical outcomes, the higher the initial D-dimer level, the shorter the ICU stay.

No other studies have been performed that correlate D-dimer levels with length of stay in the ICU. However, an association between D-dimer levels and length of hospital stay has been demonstrated.[8] Compared with non-survivors, survivors had longer ICU stays [14 (IQR 7-24) vs. 9.5 (IQR 6-11), $p < 0.001$].[5] Patients who died in the ICU had a median length of stay of 10 (IQR, 5-16) days compared to 15 (IQR, 8-24) days for survivors.[20] Consistent results were also reported by Nadeem et al., (2021). The survivor group spent more days in the ICU (median [IQR] 18 [6.5–29.5] vs. 11 [4–18], p-value 0.003 and hospital (32 [14.5–49.5] vs. 14 [7-21], p-value 0.001 compared with non-survivors.[21] Another study by Briguglio et al., (2021) also provided data that non-surviving patients required 16.00 ± 5.31 days of intensive care, while surviving patients stayed for 19.00 ± 9.63 days. [24] Patients who did not survive stayed 4.3 days in the hospital's ICU (6.0 ± 2.1 vs 10.3 ± 10.0, p: 0.10).[28]

Conclusions And Suggestions

This study figured out a relationship between initial D-dimer levels and the length of ICU stay in COVID-19 patients with clinical outcome of death. In this study, there are several limitations including the nature of the study that is non-randomized controlled trial so that it cannot be compared to the control group. Researchers suggest further research to use a control group by considering the effects of using therapy such as anticoagulants to determine the differences between each group. In addition, it is necessary to search for the relationship between other factors such as the use of a ventilator and secondary infections that may affect the clinical outcome and the length of ICU stay.

Acknowledgements

The authors would like to express their deepest gratitude to the Dr. Soetomo General Hospital, Faculty of Medicine of Airlangga University, and to other parties who have helped the authors in completing this article.

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