

D-Dimer Levels in Covid-19 Patients with Moderate and Severe Symptoms

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ABSTRACT

COVID-19 is an infectious disease in humans. This disease is caused by a new virus similar to SARS-CoV, called SARS-CoV-2. This virus attacks the human respiratory system and causes symptoms such as cough, fever above 38°C, shortness of breath, muscle aches, malaise, and diarrhea. Elevated levels of D-Dimer are often found in patients with severe COVID-19 symptoms. Previous studies have shown that increased levels of D-Dimer can increase the risk of death and is also a marker of poor prognosis. The purpose of this study was to provide an overview of D-Dimer levels in patients confirmed by COVID-19 with moderate and severe symptoms at UKI General Hospital. This study is a cross-sectional study with descriptive and analytic data presentation from the Medical Record document of UKI General Hospital. Data that has been collected was processed using the Mann-Whitney test. The subjects of this study are 211 patients who were confirmed to have COVID-19 through RT-PCR examination and had checked for D-Dimer levels. The Mann-Whitney test that was carried out gave a p-value <0.05, which means a significant difference in the mean D-Dimer level between COVID-19 patients with moderate and severe symptoms. The average level of D-Dimer in moderate symptoms was 441.272 ng/mL with 154 patients. The average level of D-Dimer in severe symptoms is 1,231,630 ng/mL with 57 patients.

Key words: D-Dimer, COVID-19, mild symptoms, severe symptoms

INTRODUCTION

Coronavirus Disease – 19 (COVID-19) is experiencing a rapid increase in cases worldwide. The first case was found in Wuhan, China, on December 30, 2019, which was originally known as "Unexplained Pneumonia". On January 9, 2020, the World Health Organization (WHO) reported that the outbreak was caused by a new type of coronavirus (novel coronavirus). This virus is spreading rapidly around the world. Indonesia's first case occurred on March 2, 2020, when two patients were found positive for COVID-19 at a hospital in Depok. As of September 24, 2021, positive cases of COVID-19 in Indonesia totalled 4,206,253.

The government has made various efforts to prevent the spread of the COVID-19 virus, including by making policies and guidelines related to COVID-19. The government has also established a COVID-19 referral hospital to help people exposed to this virus. The Indonesian Christian University General Hospital (RSU UKI) is one of the COVID-19 referral hospitals designated by the Governor of the Special Capital Region of Jakarta [1; 2; 3; 4].

COVID-19 is a contagious disease in humans. This disease is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). This virus primarily attacks the human respiratory system. Symptoms

include fever above 38°C, shortness of breath, cough, muscle aches, malaise, and diarrhea. If it continues, COVID-19 can cause severe symptoms such as pneumonia, kidney failure, respiratory failure, and death. COVID-19 is differentiated based on the severity of the disease, namely asymptomatic, mild, moderate, severe, and critical symptoms [5; 6; 7].

D-Dimer is a product of fibrin degradation by plasmin in fibrinolysis. Fibrinolysis breaks down fibrinogen and fibrin to produce fibrin degradation products known as Fibrin Degradation Products (FDP). The products of fibrin degradation are E, D, X, and Y fragments. Two D fragments will bind to one E fragment to form D-Dimer [8; 9].

In various studies, D-Dimer levels have increased in COVID-19 patients with severe and critical symptoms. Elevated D-Dimer levels reflect a hyperinflammatory state and a cytokine storm, which then activates coagulation factors and causes thrombosis and thromboembolism in veins and arteries [10; 11]. Research by Fei Zhou et al. [12] proved that increased levels of D-Dimer in COVID-19 patients are directly proportional to mortality and morbidity. High D-Dimer levels also indicate a poor prognosis in COVID-19 patients. Hilda F.'s research [13] proved that increased levels of D-Dimer are often found in patients with severe symptoms of COVID-19.

RESEARCH METHODOLOGY

The research design is cross-sectional with descriptive and analytical data presentation.

Table 2. Characteristics of Research Subjects Based on Gender

| Gender | Moderate Symptoms | | Severe Symptoms | |
|--------|-------------------|----------------|-----------------|----------------|
| | Total (n) | Percentage (%) | Total (n) | Percentage (%) |
| Male | 72 | 46,8 | 27 | 47,4 |
| Female | 82 | 53,2 | 30 | 52,6 |
| Total | 154 | 100 | 57 | 100 |

Based on Table 2, the number of COVID-19 study subjects with moderate and severe symptoms was almost equal between men and women. The moderate symptom group comprised 72 men (46.8%) and 82 women (53.2%). The severe symptom group

The study was conducted at UKI General Hospital from January to March 2022. The study population was all confirmed COVID-19 patients at UKI General Hospital with moderate and severe symptoms from June to September 2021. There were 211 samples in this study with inclusion criteria, namely patients aged ≥ 18 years, confirmed positive for COVID-19 based on RT-PCR results, moderate and severe symptoms, and D-Dimer examination. Exclusion criteria in this study, namely patients who are pregnant and post-surgical patients. The research instrument was in the form of medical record data of patients confirmed positive for COVID-19 at UKI General Hospital in June-September 2021. All data were initially created in Microsoft Excel, which was further processed using SPSS.

RESEARCH RESULT

Subjects who met this study's inclusion and exclusion criteria totalled 211 people. The research subjects were divided into two groups: the moderate symptom group and the severe symptom group. The moderate symptom group consisted of 154 patients (73%), and the severe symptom group consisted of 57 patients (27%). The research subjects comprised 112 women (53.1%) and 99 men (46.9%) with 18-89 years of age.

Table 1. Characteristics of Research Subjects Based on Symptom Groups

| Symptom Group | Total (n) | Percentage (%) |
|-------------------|-----------|----------------|
| Moderate Symptoms | 154 | 73 |
| Severe Symptoms | 57 | 27 |
| Total | 211 | 100 |

consisted of 27 men (47.4%) and 30 women (52.6%).

In the moderate symptom group, the most age was 46-65 years; 77 people (50%), and the least number was >65 years, namely six people (3.9%). The highest number in the severe symptom group was >65 years old,

namely 22 people (38.6%). There were no subjects aged 18-25 in the severe symptoms group. Can be seen in Table 3.

In this study, D-Dimer levels were divided into two groups: normal (D-Dimer <500

ng/ml) and increased (D-Dimer ≥500 ng/ml). Table 4 shows that in both groups of study subjects, both moderate and severe symptoms, normal D-Dimer levels were higher than increased D-Dimer levels.

Table 3. Characteristics of Research Subjects by Age

| Age (year) | Moderate Symptoms | | Severe Symptoms | |
|------------|-------------------|----------------|-----------------|----------------|
| | Total (n) | Percentage (%) | Total (n) | Percentage (%) |
| 18-25 | 11 | 7,14 | 0 | 0 |
| 26-45 | 60 | 38,96 | 14 | 24,6 |
| 46-65 | 77 | 50 | 21 | 36,8 |
| >65 | 6 | 3,90 | 22 | 38,6 |
| Total | 154 | 100 | 57 | 100 |

Table 4. Number of COVID-19 Patients Based on D-Dimer Levels

| D-Dimer levels (ng/mL) | Moderate Symptoms | | Severe Symptoms | |
|------------------------|-------------------|----------------|-----------------|----------------|
| | Total (n) | Percentage (%) | Total (n) | Percentage (%) |
| <500 | 126 | 81,8 | 33 | 57,9 |
| ≥500 | 28 | 19,2 | 24 | 42,1 |
| Total | 154 | 100 | 57 | 100 |

Table 5. Average D-Dimer Levels for Moderate and Severe Symptom Groups

| Symptom Group | Average (ng/mL) |
|-------------------|-----------------|
| Moderate Symptoms | 441,3 |
| Severe Symptoms | 1.231,6 |

Based on Table 5, the average D-Dimer level in the moderate symptom group was 441.3 ng/mL and in the severe symptom group was 1231.6 ng/mL.

Table 6. Mann-Whitney Test Results

| | Median (Minimum-Maximum) | p-value |
|---|--------------------------|---------|
| D-Dimer levels in patients with moderate symptoms of COVID-19 (n=154) | 237 (25-5000) | 0,000 |
| D-Dimer levels in patients with severe symptoms of COVID-19 (n=57) | 422 (26-5000) | 0,000 |

The normality test results in this study were not normal (p<0.05). For this reason, the difference in mean D-Dimer levels between the moderate and severe symptom groups was measured using the Mann-Whitney test. The results of the Mann-Whitney test for D-Dimer levels in each group are shown in

Table 6. Based on the results of the Mann-Whitney test in Table 6, a value of 0.000 was obtained, meaning that there was a significant difference in the average D-Dimer level in patients with moderate and severe symptoms.

Table 7. D-Dimer Levels in Moderate Symptoms of COVID-19 Patients

| Age (year) | D-Dimer levels (ng/mL) | | | |
|------------|------------------------|----------------|-----------------|----------------|
| | <500 (normal) | | ≥500 (increase) | |
| | Total (n) | Percentage (%) | Total (n) | Percentage (%) |
| 18-25 | 11 | 8,7 | 0 | 0 |
| 26-45 | 51 | 40,5 | 9 | 32,1 |
| 46-65 | 59 | 46,8 | 18 | 64,3 |
| >65 | 5 | 4,0 | 1 | 3,6 |
| Total | 126 | 100 | 28 | 100 |

If D-Dimer levels are related to age in the moderate symptom group, it can be seen that normal and high D-Dimer levels are most prevalent at the age of 46-65, as shown in Table 7.

Table 8. D-Dimer Levels in Patients with Severe Symptoms of COVID-19

| Age (year) | D-Dimer levels (ng/mL) | | | |
|------------|------------------------|----------------|-----------------|----------------|
| | <500 (normal) | | ≥500 (increase) | |
| | Total (n) | Percentage (%) | Total (n) | Percentage (%) |
| 18-25 | 0 | 0 | 0 | 0 |
| 26-45 | 7 | 21,2 | 7 | 29,2 |
| 46-65 | 12 | 36,4 | 9 | 37,5 |
| >65 | 14 | 42,4 | 8 | 33,3 |
| Total | 33 | 100 | 24 | 100 |

In the severe symptom group, normal D-Dimer levels mainly occurred at age >65 years, while high D-Dimer levels occurred in

almost every age group except 18-25 years old, as shown in Table 8.

Table 9. D-Dimer Levels of Survivor and Non-Survivor Group COVID-19 Patients

| D-Dimer levels (ng/mL) | Survivor | | Non-Survivor | |
|------------------------|-----------|----------------|--------------|----------------|
| | Total (n) | Percentage (%) | Total (n) | Percentage (%) |
| <500 (normal) | 132 | 75 | 20 | 57,1 |
| ≥500 (increase) | 44 | 25 | 15 | 42,9 |
| Total | 176 | 100 | 35 | 100 |

In this study, subjects were further divided into survivor and non-survivor groups. Survivors are COVID-19 patients who have successfully recovered/lived, while non-survivors are COVID-19 patients who have died. Based on Table 9, out of a total of 211 research subjects, there were 176 survivors of COVID-19 and 35 non-survivors of COVID-19. Out of a total of 176 survivors (alive), 132 patients (75%) had normal D-Dimer levels, and 44 patients (25%) had elevated D-Dimer levels. Of the 35 non-survivor subjects (who died), there were 20 patients (57.1%) with normal D-Dimer levels and 15 patients (42.9%) with increased D-Dimer levels.

Based on Table 10, the average D-Dimer level for survivors of COVID-19 is 817.5 ng/ml, and the average D-Dimer level for non-survivors of COVID-19 is 1,158.7 ng/ml.

Table 10. Average D-Dimer Levels of COVID-19 Patients Survivor and Non-Survivor groups

| Group | Total (n) | Percentage (%) | Average |
|--------------|-----------|----------------|---------|
| Survivor | 176 | 83,4 | 817,5 |
| Non-Survivor | 35 | 16,6 | 1.158,7 |

Table 11. Types of Comorbidities in COVID-19 Patients at UKI Hospital

| Comorbid | Total (n) | Percentage (%) |
|------------------------|-----------|----------------|
| Hypertension | 75 | 35,9 |
| Diabetes mellitus | 43 | 20,6 |
| Heart disease | 15 | 7,2 |
| Chronic Kidney Disease | 14 | 6,7 |
| Electrolyte Imbalance | 13 | 6,2 |
| Lung Disease | 12 | 5,7 |
| Anemia | 9 | 4,3 |
| Transaminitis | 5 | 2,4 |
| Obesity | 3 | 1,4 |
| Etc | 20 | 9,6 |

Table 11 shows that of the 211 study subjects, the most common comorbid was hypertension, namely, 75 subjects (35.5%), followed by Diabetes Mellitus with 43 subjects (20.4%).

Table 12. Average D-Dimer Levels in Comorbid and Non-Comorbid Patients

| Group | Total (n) | Percentage (%) | Average |
|---------------------------|-----------|----------------|---------|
| Patients with Comorbid | 138 | 65,4% | 897,4 |
| Patients without Comorbid | 73 | 34,6% | 308,1 |

Table 12 shows that the average D-Dimer level in COVID-19 patients with comorbidities was 897.4 ng/ml, and those without comorbidities were 308.1 ng/ml.

Table 13. Mann-Whitney Test Results

| | Median (Minimum-Maximum) | P Value |
|--|--------------------------|---------|
| D-Dimer levels in COVID-19 patients with comorbidities (n=138) | 305,5 (25-5000) | 0,000 |
| D-Dimer levels of COVID-19 patients without comorbidities (n=73) | 208,5 (26-2037) | 0,000 |

The normality test results in this study were not normal ($p < 0.05$). For this reason, the difference in mean D-Dimer levels between groups of patients with comorbidities and without comorbidities was measured using the Mann-Whitney test. The results of the Mann-Whitney test for D-Dimer levels in each group are shown in Table 13. Based on

the results of the Mann-Whitney test in Table 13, a value of 0.000 is obtained, meaning that there is a significant difference in the average D-Dimer levels in patients with comorbidities and patients without comorbidities.

DISCUSSION

This study consisted of 211 subjects who met the inclusion and exclusion criteria. The subjects were divided into two groups: the moderate and severe symptoms of COVID-19. Of the 211 people, most subjects were from the moderate symptom group, namely 154 people (73%), while the severe symptoms were 57 (27%). It is similar to the study by Yu et al. 33 out of a total of 1561 research subjects there were 1196 people (76.6%) with moderate COVID-19 symptoms and the remaining 365 (23.4%) with severe symptoms. [14]

The subjects of this study consisted of 112 (53.1%) women and 99 (46.9%) men. It is in line with research by Hilda F. [13], who found that out of 287 research subjects, there were more women (151 people/52.6%) than men (136 people/47.4%). It is different from the study by Zhou et al, who found that of 191 research subjects, there were fewer women (72 people/38%) than men (119 people/62%). [12]

Of all the study subjects, the most age group was 46-65 years old, with a total of 98 patients (46.4%), and the second most was aged 26-45 years, with 74 patients (35.1%). It is slightly different from the research conducted by Elviani et al [15] in his research at RSMH Palembang. They get the most age is 26-45 years totalling 122 patients (39.4%), and the second most in the age range 46-65 years totalling 114 patients (36.8%). This difference can occur due to differences in the criteria of research subjects. The subjects in this study came from the moderate and severe symptom groups, while the subjects in Elvani's study were all treated COVID-19 patients. The age range of 26-65 years is the largest age group in these two studies; this could happen because this age is productive. People of productive age have a lot of activities outside the home, so the risk of getting COVID-19 will increase. [15]

In Table 4, out of a total of 154 moderately symptomatic COVID-19 patients, 126 patients (81.8%) had normal D-Dimer levels more than those with high D-Dimer levels. The same thing happened with COVID-19

patients with severe symptoms, out of a total of 57 subjects, who had more normal D-Dimer levels, namely 33 patients (57.9%), compared to those who had high D-Dimer levels, namely 24 patients (42.2%).). The results of this study are different from those of Hilda F. [13] found that normal D-Dimer levels were lower (77 patients/33.5%) compared to those with elevated D-Dimer levels (153 patients/66.5%) in the non-severe group. In the severe group, fewer patients had normal D-Dimer levels (3 patients/5.3%) than those with high D-Dimer levels (54 patients/94.7%). This difference in results occurred due to differences in the distribution of subject groups, namely the moderate and severe symptom groups in this study, and the severe and non-severe groups in Hilda's study. In addition, differences in the number of samples also affect. In this study, out of 211 research subjects, there were more patients with normal D-Dimer levels (159 people/75%) compared to the number of patients with high D-Dimer levels (52 people/25%). In Hilda's study, fewer patients had normal D-Dimer levels (80 people / 27.9%) than those with high D-Dimer levels (207 people / 72.1%) of 287 research subjects. [13]

Based on Table 4, increased D-Dimer levels were more common in the severe symptom group (42.1%) compared to the moderate symptom group (28.2%). It is in line with a study by Hilda F., who found D-Dimer increased severe symptoms. [13]

Based on Table 7 and Table 8, increased levels of D-Dimer are most often found in the age group of 46-65 years. It shows that age is inversely proportional to immunity; the higher the age, the lower a person's immunity. In the elderly, there is a defect in the function of T cells and B cells so that the proinflammatory response slows down and the body's ability to control viral replication decreases, worsening the patient's clinical condition. [12]

In this study, three things were found that increased D-Dimer levels: the clinical degree of patients with severe symptoms, non-

survivors, and the presence of comorbidities. In this study, the average D-Dimer level for moderate symptoms was 441.3 ng/mL and 1,231.6 ng/mL for severe symptoms. The average D-Dimer level in severe symptoms is much higher than in moderate. It is reinforced by the results of the Mann-Whitney test (Table 6), which proves a significant difference between the mean D-Dimer levels in moderate and severe COVID-19 patients. Research by Yu et al. [14] also obtained results similar to this study. They found that the average D-Dimer level in patients with moderate symptoms of COVID-19 was 500 ng/ml, while those with severe symptoms were 1,800 ng/ml. The more severe the symptoms of a COVID-19 patient, the greater the number of pro-inflammatory cytokines. The excessive immune response will cause a systemic cytokine storm and trigger the occurrence of injury to the endothelium. This endothelial injury will cause hypercoagulation, which will eventually increase D-Dimer levels. [14] Hypercoagulation is often found in patients with severe symptoms of COVID-19. Hypercoagulation in COVID-19 also increases the risk of death. An increase in D-Dimer in the blood indicates hypercoagulable events. The average D-Dimer level in the non-survivor group of COVID-19 (dead subjects) was 1,168.7 ng/mL higher than the average D-Dimer level in the group of survivors of COVID-19 (living subjects), which was 817.5 ng/mL (Table 10). This is in line with the research of Fogarty et al. [16], who stated in their research that the average D-Dimer level in the non-survivor group of COVID-19 was higher, namely 1,210 ng/mL compared to the average D-Dimer level in the group of survivors of COVID-19, namely 803 ng /mL. These researchers concluded that elevated levels of D-Dimer in COVID-19 patients indicate a poor prognosis. This was reinforced by the research of Tang et al. [17], who stated in their research that the average D-Dimer level in the non-survivor group of COVID-19 was higher, namely 4700 ng/mL compared to the average D-Dimer level in

the group of survivors of COVID-19, namely 1,470 ng /mL. In Tang et al.'s study, the average D-Dimer was much higher than the average D-Dimer in this study. This difference can occur due to differences in the criteria of research subjects. The subjects in this study came from the moderate and severe symptom groups, while the study subjects of Tang et al only came from the severe symptom group. [16; 17]

In this study, it was seen whether there were comorbid factors affecting D-Dimer levels. Table 11 shows some of the most common comorbidities in patients treated at UKI Hospital. The two highest were hypertension with 75 patients (35.5%) and Diabetes Mellitus with 43 patients (20.4%). This is similar to the study by Zhou et al [12] which found the most types of comorbidities were hypertension in 58 patients (30%), Diabetes Mellitus in 36 patients (19%), and heart disease in 15 patients (8%). In this study, the average D-Dimer level in COVID-19 patients with comorbidities was higher, namely 897.443 ng/mL, compared to the average D-Dimer level in COVID-19 patients without comorbidities, 308.081 ng/mL [12]

CONCLUSION

The number of patients with moderate symptoms of COVID-19 who checked their D-Dimer levels was greater than the number of patients with severe symptoms of COVID-19 who checked their D-Dimer levels. Of all the research subjects, the number of men and women was almost equal, with an age range of 18-89 years. There was a significant difference between the mean D-Dimer levels in the moderate and severe symptom groups, which was higher in severe symptoms. For future researchers, it is hoped that they can conduct descriptive and analytical research on D-Dimer levels with more COVID-19 patients with severe symptoms.

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