***Original Research Article***

# Profile of D-Dimer Levels in Patients Confirmed Positive for COVID-19 at the Indonesian Christian University Hospital



**ABSTRACT**

**Aims:** the research aimed to determine the profile of d-dimer levels in patients confirmed positive for COVID-19 at UKI Hospital from December 2020 to September 2021
**Study design:** This type of research is descriptive research with a retrospective cross-sectional research design, namely using secondary data in the form of UKI RS medical records.
**Place and Duration of Study:** The research was carried out in the medical records section of RS UKI from May to October 2021.
**Methodology:** The research samples were all medical records of patients suffering from COVID-19 with an age range of 18 to 45 years and their D-Dimer levels were checked during treatment at UKI Hospital for the period December 2020 to September 2021, totaling 148 samples. This data will be processed and analyzed using the Chi-Square Test.
**Results:** From the results of the study, it was found that there were 129 patients (87.2%) with COVID-19 who had normal D-Dimer levels and 19 patients (12.8%) who had elevated D-Dimer levels. Obtained a p-value of 0.677, which means that there is no statistically significant relationship between clinical symptoms and increased levels of D-Dimer in COVID-19 patients. However, there is a statistically significant relationship between the administration of anticoagulants and an increase in D-Dimer levels in COVID-19 patients with a p-value of 0.015.
**Conclusion:** It can be concluded that there is a significant relationship between anticoagulants and D-Dimer levels in COVID-19 patients with moderate and severe symptoms (in this case administration of anticoagulants can inhibit the increase in D-Dimer), but researchers did not find a significant relationship with mild symptoms..

*Keywords: D-Dimer Level, Anticoagulation, Covid-19*

## 1. INTRODUCTION

The World Health Organization China Country Office reported the problem of pneumonia of unknown cause in Wuhan City, Hubei Province, China, precisely on December 31, 2019 [1]. China designated the case of pneumonia of unknown cause as a new type of Coronavirus. The World Health Organization has determined the official name of this disease, namely COVID-19, and is caused by the SARS-CoV-2 virus, which has changed its name from the previous one, namely "2019 Novel Coronavirus or 2019 nCoV". Transmission of the virus can occur from human to human and has spread widely in China and other countries in less than a month [2]. WHO declared this incident a public health emergency that is worrying the world. On January 30, 2020, COVID-19 was designated as a pandemic on March 3, 2020. There is a close relationship in the form of homology between the SARS-CoV-2 virus and the types of Coronaviruses originating from bats, namely batSLCoVZC45 and bat-SLCoVZXC21 [3]. Because of the identity between the genomes, wild animals, including bats, are thought to be the natural hosts SARS-CoV-2 virus [4]. Transmission of COVID-19 can occur between humans through droplets containing SARS-CoV-2 from symptomatic patients when they cough or sneeze, talk, or sing from a distance of one meter. Apart from that, transmission can come from asymptomatic carriers, that is, the person has no

symptoms but has been infected with the SARS-CoV-2 virus. Transmission from carriers can occur by direct or indirect contact [2,6]. A person can also be exposed if they touch a surface that has been contaminated by the virus through the eyes, nose, and mouth [5].
The incubation period for COVID-19 is usually 5-6 days and the longest is 14 days (RI Ministry of Health, 2020). The clinical manifestations of COVID-19 patients vary, ranging from asymptomatic, very mild symptoms, to patients falling into ARDS which requires patients to use ventilation or breathing aids. Fitriani (2020) stated that clinical symptoms in COVID-19 patients include fever, dry cough, shortness of breath, headache, muscle pain, and weakness. 6 There are also disorders of the digestive tract such as abdominal pain, diarrhea, and vomiting [7]. Ministry of Health of the Republic of Indonesia (2020), states that the clinical symptoms caused by SARS-CoV-2 are acute respiratory disorders such as fever, cough, and shortness of breath, in severe cases of COVID-19 it can cause pneumonia, acute respiratory syndrome, kidney failure and even death. The clinical manifestations of COVID-19 are dominated by respiratory symptoms, but it turns out that COVID-19 infection can cause disorders outside the lungs, namely systemic inflammation, thromboembolic disease, or blood vessel coagulation disorders, such as DVT [8]. Current evidence shows that COVID-19 patients severe, often experience coagulation disorders such as DIC. Diagnostic examination can be carried out by testing by amplifying nucleic acids using RT-PCR using specimens taken from nasopharyngeal swabs and oropharyngeal swab specimens.
Blood clotting is an event where there is an excessive systemic inflammatory response in the form of cytokines and inflammatory cells which are abundant in the blood vessels to fight Coronavirus. The body has a natural process of stopping bleeding and keeping the blood fluid through the blood clotting mechanism. This excessive inflammatory response will cause systemic vascular endothelial injury, and the inflamed vascular endothelium will release ULVWF. The release of ULVWF will bridge endothelial injury with platelet activation. Neutrophils, monocytes, and platelets in the blood vessel circulation will bind to the injured endothelium, triggering the coagulase process and producing thrombin [26]. Blood clotting occurs through two pathways, namely the intrinsic pathway involving F. Intrinsic factor will be activated when there is contact between F.XII and collagen fibers, which will activate F.XII to become F.XIIa. The action of F.XIIa will convert prekallikrein to kallikrein with the cofactor HMWK and will increase F.XII activation. Next, there is activation of F.XI to become F.XIa by F.XIIa with HMWK as a cofactor. F.XIa will change F.IX to F.IXa with the help of calcium ions. The interaction between F.IXa, F.VIII, PF 3, and calcium ions will activate F.X. The extrinsic pathway consists only of F.VII which will be activated to become F.VIIa with the help of calcium ions, kallikrein, tissue thromboplastin released by endothelial injury [27,28]. The common pathway involves F.X which will become the active form of F.Xa by the complex formed in the intrinsic pathway and F.VIIa from the extrinsic pathway. F.Xa with F.V, PF 3, and calcium ions will form a prothrombin-converting complex which will convert prothrombin into thrombin. Thrombin itself has the function of converting fibrinogen into fibrin, stimulating platelet release and platelet aggregation, and increasing F.V and F.VIII [27,28]
D-dimer is the end product of fibrin degradation. The D-Dimer examination is useful for detecting abnormalities in blood clot formation and for detecting the presence of a fibrinolytic process, namely the process of clot reduction through the hydrolytic enzyme plasmin by digesting fibrin and fibrinogen. Willim et al said there was an increase in D-Dimer which is a marker of coagulopathy in patients who were confirmed positive for COVID-19. Rusdiana et al also said that patients with confirmed COVID-19 experienced an increase in D-Dimer which indicated that there was a thrombosis event [8]. Therefore, the latest guidelines recommend administering anticoagulants to patients who are suspected of having thrombosis or not, as prophylaxis for COVID-19 patients who are hospitalized [9].
Based on the high possibility of thrombus occurring in patients who were confirmed positive for COVID-19, researchers were therefore interested in examining D-Dimer levels in patients who were confirmed positive for COVID-19 using RT-PCR examination at RS UKI. In this study, D-Dimer levels were checked on the first day the patient underwent a swab test with RT-PCR

## 2. MATERIAL AND METHODS

### 2.1. MATERIAL

#### 2.1.1. COVID-19 Diagnostic Examination

The World Health Organization recommends examining the NAAT method with rRT-PCR for the diagnosis of COVID-19.18 Samples required for carrying out the rRT-PCR test are specimens from the upper respiratory tract, namely from nasopharyngeal swab specimens and oropharyngeal swab specimens carried out by competent health workers using BSL-2 [19]. Diagnostic examination can be carried out by testing by amplifying nucleic acid to detect at least two RNA genome targets (Nucleocapsid, Envelope, Spike, or Membrane), but PCR can only amplify DNA nucleic acid while Coronavirus is a virus with RNA genetic material, so before the PCR process, Reverse Transcription enzyme is added at 50oC for 30 minutes to convert RNA into Complementary DNA. The PCR reaction components consist of Taq Polymerase in the form of a DNA Polymerase I enzyme which is stable at various temperatures and is useful for forming complementary DNA strands on the DNA template, dNTPs in the form of nucleotide material to form new DNA strands, MgCl2 in the form of ions needed for the enzymatic reaction, Buffer for To keep the pH optimal for enzyme work, the Forward Primer and Reverse Primer are short nucleotides that will bind to the antisense DNA and sense DNA templates, the template is a cDNA template that will be reproduced. The DNA amplification process consists of three stages, the first stage is denaturation to separate the double-stranded template DNA into single-stranded DNA by heating at a temperature of 90 - 95oC for 60 seconds. The second stage is annealing in the form of attaching Forward and Reverse

Forward Primers to a single strand of DNA template, carried out at a temperature of 50 – 60oC for 30-45 seconds. The third stage is elongation in the form of extending the new DNA strand on the template by the Taq Polymerase enzyme using dNTPs starting from the attached primer, elongating moving from 5' to 3', carried out at a temperature of 72 oC for 1-2 minutes. These three stages constitute one amplification cycle, in PCR generally 30-40 repeated cycles are carried out to obtain the DNA template. In one PCR cycle, the nucleotide bases that are amplified are twice the initial amount, so that for every n PCR cycle, 2n target DNA will be obtained. Amplification results from DNA can be analyzed conventionally or in real time [18].

Real-time PCR analysis uses a fluorogenic probe which produces a fluorescence signal and is converted into a digital signal that will be analyzed by a computer at each cycle. There are two fluorogenic probes in real-time PCR analysis, the first is the Strand-Specific Probe which uses the Taqman probe which is labeled by two dyes Reporter (R) and Quencher (Q). At the annealing stage, the probe will bind to the DNA template, at the elongation stage the probe will be cut off by the Taq Polymerase enzyme. Disconnection of the probe will cause a fluorogenic glow and will be read by the camera. The second is the Non-Specific Probe which uses SYBR Green I. In the annealing and elongation stages, SYBR Green I will bind to DNA and glow, this glow is captured by the camera at each cycle. The result of rRT-PCR is the Cycle threshold [18]. The Cycle threshold is the intersection between the threshold line and the amplification curve. Cycle Threshold refers to the number of cycles in the RT-PCR test required to amplify the viral RNA to reach a level that can be detected. Thus, the CT value can indicate the level of viral RNA in the specimen, a lower CT value indicates a higher level of virus. High [20].

**D-Dimer**

D-Dimer is a protein in the form of a natural end product from the degradation of cross-linked fibrin which is formed by the sequential action of three enzymes namely Thrombin, Factor fibrin degradation, high levels of thrombus formation and breakdown [27]. The results of fibrin degradation are fragments or molecules of fibrin monomers, X, Y, D, and E. D-Dimer is a strong bond between two D fragments and one E fragment. Abnormal blood clot formation and Knowing if there is a fibrinolytic process can be determined from the D-Dimer examination, namely the clot reduction process through the hydrolytic enzyme plasmin by digesting fibrin and fibrinogen [30]. D-Dimer increases one hour after the presence of a thrombus with a half-life of D-Dimer in plasma of eight hours, and clearance occurs through the kidneys and reticuloendothelial system [31]. D-dimer can increase in plasma in non-pathological conditions such as increasing age, race (dark skin population), smoking, pregnancy, postpartum period, and post-surgery. D-Dimer can also increase in plasma in pathological conditions, due to trauma, preeclampsia, malignancy, infection, chronic inflammatory diseases, disseminated intravascular coagulation, arterial or venous thromboembolism, and stroke [31].

The basis of checking D-Dimer uses a special monoclonal antibody that recognizes the epitope on the D-Dimer fragment. There are several ways to check D-Dimer levels in the blood, namely Latex agglutination, Immunoturbidometric assay, Whole blood agglutination, Immunofiltration assay, and ELISA [33].

The latex agglutination method is by obtaining lumps of granules or particles resulting from the antigen-antibody reaction in a visible/macroscopic way, the cut-off value for this method is 500ng/ml [27]. This examination method is most often used because it does not require special equipment and expertise and the cost is relatively cheap [34].

## 2.2. METHODS

### 2.2.1.Research design

This type of research is descriptive research with a retrospective cross-sectional research design (where all variables are both variablesindependent and dependent variablesobserved/measured at the same time.Measurement/observation results of the independent variableand dependent describe the conditions at that timeAlso), namely using secondary data in the form of UKI RS medical records

### 2.2.2. Place and time of research

The research was carried out in the medical records section of RS UKI from May to. October 2021.

### 2.2.3. Population

The population in this study were all COVID-19 sufferers who were treated and had their D-Dimer levels checked, which were recorded in the medical records at RS UKI from December 2020 to September 2021.

### 2.2.4. Research sample

The research samples in this study were all medical records of patients suffering from COVID-19 and whose D-Dimer levels had been checked during hospitalization at RS UKI in the period December 2020 to September 2021.

#### *2.2.4.1. Inclusion and Exclusion Criteria*

**Inclusion Criteria**

a. Age 18 to 45 years.
b. Positive RT-PCR COVID-19 results.
c. Supporting data, especially D-Dimer levels in medical records.
d. COVID-19 patients are being treated at RS UKI.

**Exclusion Criteria**

a. Age outside 18 to 45 years.

b. Having comorbid diseases that can increase D-Dimer levels such as deep vein thrombosis, trauma, preeclampsia, malignancy, infection, chronic inflammatory diseases, disseminated intravascular coagulation, arterial or venous thromboembolism, and stroke.
c. Incomplete medical record data for COVID-19 patients at RS UKI

**2.2.5. Data analysis**

2.2.5.1. Univariate

Univariate analysis is used to describe the frequency distribution of each independent variable and dependent variable. The aim is to understand the characteristics of respondents and analyze the data in further research

2.2.6.2. Bivariate

Bivariate analysis is used to see the relationship between the independent variable and the dependent variable to prove whether the two variables are significant or not. Using data analysis in the form of chi-square (X2) and probability value (P value). Presented in cross-tabulation form.

## 3. RESULTS AND DISCUSSION

### 3.1. RESULTS

Data collection in this study began on December 18 2021 to January 15 2022 and was obtained from medical records at UKI General Hospital. In this study, 689 patients were confirmed positive for COVID-19 and were treated at RS UKI in the period December 2020 to September 2021, and from this number, 148 research samples were obtained who met the inclusion criteria for the age range of 18 - 45 years. Data processing was carried out using an application. SPSS version 26, data is presented in the form of tables and diagrams

**Table 1. Distribution of Respondents Based on Gender and Age**

| **No** | Age | Jenis Kelamin | | Amount (n) | Percentage (%) |
|---|---|---|---|---|---|
| | | Male | Female | | |
| 1 | 18 – 25 year | 8 | 12 | 20 | 13.5 |
| 2 | 26 – 35 year | 22 | 31 | 53 | 35.8 |
| 3 | 36 – 45 year | 28 | 47 | 75 | 50.7 |
| | Total | 58 | 90 | 148 | 100.0 |

| Age | N | Mean | SD | Med | Min | Max |
|---|---|---|---|---|---|---|
| | 148 | 35 | 7,086 | 36 | 18 | 45 |

Based on gender, the number of respondents was dominated by women, namely 90 people (60.8%). Meanwhile, based on age, the largest age group is 36 - 45 years old, namely 75 people (50.75%), then 26 - 35-year-olds are 53 people (35.8%), and 18 - 25-year-olds are 20 people (13.5%). It was found that the average age of COVID-19 patients was 35 years.

The distribution of respondents based on the description of the clinical symptoms experienced by the patient is presented in Table 2 below:

**Table 2. The Distribution of Respondents Based on The Description of The Clinical Symptoms**

| **Clinical Symptoms** | **Amount (n)** | **Percentage (%)** |
|---|---|---|
| COVID-19 mild symptoms | 39 | 26.4 |
| COVID-19 moderate symptoms | 96 | 64.8 |
| COVID-19 severe symptoms | 13 | 8.8 |
| **Total** | **148** | **100.0** |

The research results based on the percentage of clinical symptoms with the highest number were COVID-19 with moderate symptoms, 96 people (64.8%), followed by COVID-19 with mild symptoms, 39 people (26.4%), followed by COVID-19 with severe symptoms, 13 people (8.8%).

The distribution of respondents based on the comorbidities they suffer from is presented in table 3 below:

**Table 3. The Distribution of Respondents Based on The Comorbidities**

| **The Comorbidities** | **Amount (n)** | **Percentage (%)** |
|---|---|---|

| | | |
|---|---|---|
| Hypertension | 22 | 14.7 |
| Pulmonary TB | 4 | 2.7 |
| Type 2 Diabetes Mellitus | 3 | 2 |
| Type 2 Diabetes Mellitus and Hypertension | 2 | 1.4 |
| Hypertension with Coronary Artery Disease | 2 | 1.4 |
| HIV | 2 | 1.4 |
| Congestive Heart Failure | 1 | 0.7 |
| Acute psychotic disorders such as schizophrenia | 1 | 0.7 |
| Urinary tract infection | 1 | 0.7 |
| Bronchial Asthma | 1 | 0.7 |
| Transaminitis | 1 | 0.7 |
| Hypercoagulability | 1 | 0.7 |
| Chronic Kidney Disease | 1 | 0.7 |
| Allergic Rhinitis | 1 | 0.7 |
| Post-laparotomy acute appendicitis perforation | 1 | 0.7 |
| No disease | 95 | 64.2 |
| **Total** | **148** | **100.0** |

The data in Table 3 above explains that the most common comorbidities were hypertension, 22 people (14.7%), followed by ARDS, 6 people (4.1%), followed by pulmonary tuberculosis, 4 people (2.7%), followed by diabetes. Type 2 Mellitus, Type 2 Hypertension, Pregnancy with 3 people each (2%), followed by Type 2 Diabetes Mellitus and hypertension, Hypertension with CAD, 2 people each (1.4%), and the last one is Congestive Heart Failure, Schizophrenia, UTI, Bronchial Asthma, Transaminitis, CKD, Rhinitis, Post Laparatomy Acute Appendicitis with 1 person each (0.7%). There were 95 people (64.2%) who did not have comorbidities/diseases, the number of people who did not have the disease was greater than those who had the disease.

### 3.1.1. Relationship between Concomitant Diseases and D-Dimer Levels

The relationship between comorbidities and D-Dimer levels in patients confirmed positive for COVID-19 aged 18 - 45 years at RS UKI, East Jakarta for the period December 2020 - September 2021, is presented in Table 4 below:

**Table 4. The Relationship Between Comorbidities And D-Dimer Levels**

| | | | **D-Dimer Test Results ( ng/dl )** | | **Total** | ***p-value*** |
|---|---|---|---|---|---|---|
| | | | D-Dimer Increases | D-Dimer Decreases | | |
| **The Comorbidities** | Ada | Amount | 6 | 47 | 53 | 0.815 |
| | | Percentage | 4.1% | 31.8% | 35.8% | |
| | Tidak Ada | Amount | 12 | 83 | 95 | |
| | | Percentage | 8.1% | 56.1% | 64.2% | |
| **Total** | | Amount | 18 | 130 | 148 | |
| | | Percentage | 12.2% | 87.8% | 100% | |

Based on statistical analysis, a p-value of 0.815 > sig 0.05 was obtained, which means that there is no statistically significant relationship between comorbidities and increased D-Dimer levels in COVID-19 patients.

**3.1.2. The Relationship Between Anticoagulant Administration And D-Dimer Levels In Patients Who Have Comorbidities**

The relationship between anticoagulant administration and D-Dimer levels in patients who have comorbidities can be seen in the data presented in Table 5 below:

**Table 5. The Relationship Between Anticoagulant Administration And D-Dimer Levels**

| | | | D-Dimer Test Results (ng/dl) | | Total | *p-value* |
|---|---|---|---|---|---|---|
| | | | D-Dimer Increases | D-Dimer Decreases | | |
| Administration of Anticoagulants | There is | Amount | 4 | 16 | 20 | 0.0184 |
| | | Percentage | 7.5% | 30.2% | 37.7% | |
| | There isn't any | Amount | 2 | 31 | 33 | |
| | | Percentage | 3.8% | 58.5% | 62.3% | |
| Total | | Amount | 6 | 47 | 53 | |
| | | Percentage | 11.3% | 88.7% | 100.% | |

The data in table 5 explains that there were 20 people (37.7%) who were given anticoagulants, 16 people (30.2%) had normal D-Dimer levels, and 4 people (7.5%) had increased D-Dimer. Furthermore, there were 33 people (62.3%) who were not given anticoagulants, there were 31 people (58.5%) who had normal D-Dimer levels, and 2 people (3.8%) had increased D-Dimer. Based on statistical analysis, a p-value of 0.0184 was obtained, which means that there is a statistically significant relationship between anticoagulant administration and increased D-Dimer levels in COVID-19 patients who have comorbidities.

**3.1.3. Description of D-Dimer Levels**

**Table 6. Description of D-Dimer Levels**

| D-Dimer Level (ng/dL) | Amount | Percentage |
|---|---|---|
| <500 | 129 | 90.8 |
| >500 | 19 | 9.2 |
| Total | 148 | 100.0 |

The table explains that there were 129 people (90.8%) with normal D-Dimer levels, and 19 people (9.2%) had increased D-Dimer levels.

**3.1.4. Description of D-Dimer levels based on clinical symptoms**

**Table 7. Description Of D-Dimer Levels Based On Clinical Symptoms**

| | | | D-Dimer Test Results (ng/dl) | | Total | *p-value* |
|---|---|---|---|---|---|---|
| | | | D-Dimer Increases | D-Dimer Normal | | |
| **Clinical** | Covid-19 severe | Amount | 2 | 11 | 13 | 0.677 |

| | | | | | |
|---|---|---|---|---|---|
| **Symptoms** | symptoms | Percentage | 1.4% | 7.4% | 8.8% |
| | Covid-19 mild symptoms | Amount | 6 | 33 | 39 |
| | | Percentage | 4.1% | 22.3% | 26.4% |
| | Covid-19 moderate symptoms | Amount | 11 | 85 | 96 |
| | | Percentage | 7.4% | 57.4% | 64.9% |
| **Total** | | Amount | 19 | 129 | 148 |
| | | Percentage | 12.8% | 87.2% | 100.0% |

The Table above explains that there were 96 people (64.9%) with moderate symptoms of Covid-19, there were 85 people (57.4%) who had normal D-Dimer levels, and 11 people (7.4%) who had increased D-Dimer levels. Furthermore, there were 39 people (26.4%) with mild symptoms of Covid-19, there were 33 people (22.3%) who had normal D-Dimer levels, and 6 people (4.1%) who had increased D-Dimer levels. Next, there were 13 people (8.8%) with severe Covid-19 symptoms, there were 11 people (7.4%) who had normal D-Dimer levels, and 2 people (1.4%) who had increased D-Dimer levels. Based on statistical analysis, a p-value of 0.677 was obtained, which means that there is no statistically significant relationship between clinical symptoms and increased D-Dimer levels in COVID-19 patients.

**3.1.5. Relationship between anticoagulant administration and D-Dimer levels in patients with mild clinical symptoms**

Table 8 below describes the relationship between Anticoagulant Administration and D-dimer levels in patients with mild clinical symptoms in Patients Confirmed Positive for COVID-19 aged 18 – 45 years at RS UKI, East Jakarta for the Period December 2020 – September 2021.

**Table 8. Relationship Between Anticoagulant Administration And D-Dimer Levels In Patients With Mild Clinical Symptoms**

| | | | D-Dimer Test Results (ng/dl) | | Total | *p-value* |
|---|---|---|---|---|---|---|
| | | | D-Dimer Increases | D-Dimer Normal | | |
| **Anticoagulant Administration** | There is | Amount | 3 | 3 | 6 | 0.110 |
| | | Percentage | 7.7% | 7.7% | 15.4% | |
| | There isn't any | Amount | 3 | 30 | 33 | |
| | | Percentage | 7.7% | 76.9% | 84.6% | |
| **Total** | | Amount | 6 | 33 | 39 | |
| | | Percentage | 15.4% | 84.6% | 100.0% | |

Based on statistical analysis, a p-value of 0.11 was obtained, which means that there is no statistically significant relationship between the administration of anticoagulants and increased D-Dimer levels in COVID-19 patients with mild symptoms. Based on mild clinical symptoms in the study, it was found that there were 33 people (84.6%) who were not given anticoagulants, 30 people (76.9%) had normal D-Dimer levels, and 3 people (7.7%) had increased D-Dimer levels. Furthermore, there were 6 people (15.4%) who were given anticoagulants, there were 3 people (7.7%) who had normal D-Dimer levels, and 3 people (7.7%) who had increased D-Dimer levels.

**3.1.6. Relationship between anticoagulant administration and D-Dimer levels in patients with moderate clinical symptoms**

The relationship between anticoagulant administration and D-Dimer levels in patients with moderate clinical symptoms in patients confirmed positive for COVID-19 aged 18 - 45 years at RS UKI, East Jakarta for the period December 2020 - September 2021 is presented in Table 9 below:

**Table 9. Relationship between anticoagulant administration and D-Dimer levels in patients with moderate clinical symptoms**

| | | | D-Dimer Test Results (ng/dl) | | Total | *p-value* |
|---|---|---|---|---|---|---|
| | | | D-Dimer Increases | D-Dimer Normal | | |
| **Anticoagulant Administration** | There is | Amount | 4 | 7 | 11 | 0.002 |
| | | Percentage | 4.2% | 7.3% | 11.5% | |
| | There isn't any | Amount | 14 | 71 | 85 | |
| | | Percentage | 14.6% | 74.0% | 88.5% | |
| **Total** | | Amount | 18 | 75 | 96 | |
| | | Percentage | 18.8% | 81.2% | 100.0% | |

Based on statistical analysis, a p-value of 0.002 was obtained, which means that there is a statistically significant relationship between the administration of anticoagulants and increased D-Dimer levels in COVID-19 patients with moderate symptoms. Based on moderate clinical symptoms in the study, it was found that there were 85 people (88.5%) who were not given anticoagulants, 71 people (74.0%) had normal D-Dimer levels, and 14 people (14.6%) had increased D-Dimer levels. Furthermore, there were 11 people (11.5%) who were given anticoagulants, there were 7 people (7.3%) who had normal D-Dimer levels, and 4 people (4.2%) who had increased D-Dimer levels.

### 3.1.7. Relationship between anticoagulant administration and D-Dimer levels in patients with severe clinical symptoms

The relationship between anticoagulant administration and D-Dimer levels in patients with severe clinical symptoms in patients confirmed positive for COVID-19 aged 18 - 45 years at RS UKI, East Jakarta for the period December 2020 - September 2021 is presented in Table 10 below:

**Table 10. Relationship between anticoagulant administration and D-Dimer levels in patients with severe clinical symptoms**

| | | | D-Dimer Test Results (ng/dl) | | Total | *p-value* |
|---|---|---|---|---|---|---|
| | | | D-dimer Increases | D-dimer Normal | | |
| **Anticoagulant Administration** | There is | Amount | 0 | 2 | 2 | 0.000 |
| | | Percentage | 0% | 15.4% | 15.4% | |
| | There isn't any | Amount | 11 | 0 | 11 | |
| | | Percentage | 84.6% | 0.0% | 84.6% | |
| **Total** | | Amount | | 11 | 13 | |
| | | Percentage | | 84.6% | 100.0% | |

Based on statistical analysis, a p-value of 0.000 was obtained, which means that there is a statistically significant relationship between the administration of anticoagulants and increased D-Dimer levels in COVID-19 patients with severe symptoms. Based on severe clinical symptoms in the study, it was found that there were 11 people (84.6%) who were not given anticoagulants. Furthermore, there were 2 people (15.4%) who were given anticoagulants and had normal D-Dimer levels

## 3.2. DISCUSSION

COVID-19 is a disease caused by Coronavirus. 10 COVID-19 causes systemic inflammation which will cause systemic endothelial injury and increased production of cytokines, and blood clotting products to repair endothelial damage in blood vessels [9]. The products of blood clotting will be degraded into D-Dimer 27 Of the 148 research samples, the gender profile of COVID-19 sufferers was found to be mostly female, namely 90 people (60.8%). This research is by research by Putri et al in West Sumatra, which stated that in this study more women were affected by COVID-19 compared to men [38]. However, the results of this study contradict Aulia and Khemasili's research in North Kalimantan, which found that the percentage of men affected by COVID-19 was higher than the percentage of women. This is because men only have one X chromosome, while women have two X chromosomes, where the X chromosome is linked to genes related to the innate and adaptive immune system, and inflammation such as IL-8 [37]. Aulia's research also states that men are more often affected by COVID-19 because as many as 64.9% of men in Indonesia are active smokers, the nicotine content in cigarettes will activate the receptor of the virus, namely ACE2, the large number of active ACE2 receptors will make binding easier. with SARS-CoV-2.

According to the author, this research may not follow much of the literature due to the imbalance in the number of samples between men and women in this study. Based on age, the largest age group is in the 36 – 45 year age range, totaling 75 people (50.75%). This is following epidemiological research carried out by the Indonesian Ministry of Health in 2020, stating that the age group most positively infected with COVID-19 is the 31 - 45 year age range. This age is a productive age, which is more active in activities outside the home such as work, which will facilitate the transmission of COVID-19 in that age range [39] This research contradicts research by Widjaja et al, which states that the largest age range for COVID-19 patients is 51 – 60 years [40]. Based on comorbidities, this research shows that the most common comorbidity was hypertension in 22 people (14.7%), this research follows research by Widjaja et al at Immanuel Hospital Bandung, which stated that the most common comorbidity in COVID-19 patients was hypertension. The relationship between COVID-19 and hypertension is based on studies, namely through ACE-2 which is an activator of the renin-angiotensin aldosterone system to regulate blood pressure and fluid homeostasis in the body. There are many ACE-2 receptors in Hypertension patients. SARS-CoV-2 in the body of a COVID-19 patient will bind to the ACE-2 receptor in various tissues of the human body, the binding to this receptor will interfere with the process of regulating blood pressure [40].

Based on the relationship between comorbidities and D-Dimer levels, there were 53 people (35.8%) who had comorbidities, of which 6 people (4.1%) had increased D-Dimer and 47 people (31.8%) had D-Dimer levels normal. Furthermore, there were 95 people (64.2%) who did not have comorbidities, of whom there were 12 people (8.1%) who had increased D-Dimer, and 83 people (56.1%) who had normal D-Dimer levels. The number of people who have normal D-Dimer levels is greater than people who have increased D-Dimer levels, this is supported by statistical tests, where a p-value of 0.815 is obtained, which means that there is no statistically significant relationship between comorbidities and D levels -Dimers are increased in COVID-19 patients. Based on the relationship between anticoagulant administration and D-Dimer levels in patients with comorbidities, there were 20 people (37.7%) who were given anticoagulants, of whom 16 people (17.7%) had normal D-Dimer levels, and 4 people (7.5%) experienced an increase in D-Dimer. The number of patients who have normal D-Dimer levels is greater due to anticoagulant administration, compared to patients who have increased D-Dimer levels. This is supported by the statistical test p-value 0.0184, which means that there is a statistically significant relationship between the administration of anticoagulants and increased D-Dimer levels in COVID-19 patients who have comorbidities. In the research, it was found that there were 96 people (64.9%) with moderate symptoms of Covid-19, of which there were 85 people (57.4%) who had normal D-Dimer levels, and 11 people (7.4%) who had increased D-Dimer levels. Furthermore, there were 39 people (26.4%) with mild Covid-19 symptoms, of whom there were 33 people (22.3%) who had normal D-Dimer levels, and 6 people (4.1%) had increased D-Dimer levels. Next, there were 13 people (8.8%) with severe Covid-19 symptoms, of whom there were 11 people (7.4%) had normal D-Dimer levels, and 2 people (1.4%) had increased D-Dimer levels.

The normal level of D-Dimer at the RS UKI Laboratory is <500 ng/dL. From the data above, as many as 129 (87%) COVID-19 patients treated at RS UKI did not have an increase in D-Dimer levels. Meanwhile, there were 19 patients (13%) who experienced an increase in D-Dimer levels of >500 ng/dL, this increase in D-Dimer levels was accompanied by comorbidities, namely hypertension, CKD, and pneumonia. This is following research by Permana et al at Haji Hospital Jakarta, which stated that there was an increase in D-Dimer in patients with confirmed COVID-19 [41]. This is following research by Qiu H et al in China, that there was a significant relationship between increased D-Dimer levels and severity. disease. Storch de Gracia P et al, in Spain, also stated that there was an increase in D-Dimer in COVID-19 patients who had comorbidities. Saleh N et al, in Egypt, also stated that there was an increase in D-Dimer in COVID-19 patients with moderate-severe symptoms compared to patients with mild symptoms [43].

However, this contradicts several studies, including Graff K et al in Colorado, which stated that there was no correlation between increased D-Dimer levels and disease severity, research by Chao J et al in New York also stated that there was no increase in D-Dimer in COVID-19 patients. 19 were treated in the ICU due to comorbidities compared to those in the ward [43]. If we look at mild clinical symptoms, a p-value of 0.11 was obtained through statistical tests, which means that there is no statistically significant relationship between the administration of anticoagulants and increased D-Dimer levels in COVID-19 patients with mild symptoms. The P-value for moderate symptoms is 0.002, and for severe symptoms 0.000, so there is a relationship between anticoagulant administration and increased D-Dimer levels. If a COVID-19 patient with moderate or severe symptoms is given anticoagulants, the patient's D-Dimer levels will not increase.

The number of COVID-19 patients who did not experience an increase in D-Dimer levels was greater than those who experienced an increase, this could be because at the productive age, namely 18 - 45 years, there had not been a decline in anatomical, and physiological function, the body's immune system, and they did not have the disease. accompanying or comorbid compared with elderly people [36]. Based on anticoagulant administration, the study found that 109 people (73.6%) were not given anticoagulants. This is contrary to research by Rusdiana et al, which states that COVID-19 patients should be given anticoagulants for prophylaxis and intermediate or long-term definitive therapy. 8 Anticoagulants are drugs that can inhibit blood clotting by inhibiting fibrin formation. COVID-19 patients often experience coagulation disorders due to damage to blood vessels, which is characterized by increased levels of D-Dimer due to high fibrin degradation, therefore it is important to provide anticoagulants to prevent thrombus in blood vessels. There were 9 people (6.1% ) not given anticoagulants with increased D-Dimer levels. There is a significant relationship between administering anticoagulants and increasing D-Dimer levels in COVID-19 patients based on statistical tests with a p-value of 0.021. According to PDSPatklin, the administration of anticoagulants depends on the clinical symptoms of the COVID-19 patient. For patients with moderate clinical symptoms, anticoagulants are given for prophylaxis and are given if there is an increase in D-Dimer levels, anticoagulants can be given immediately if the patient's clinical symptoms are moderate-severe [42]

In this study there are several limitations, including that the research did not consider other factors that have the potential to influence whether D-Dimer levels rise or not, so this could contribute to increasing or maintaining D-Dimer levels apart from being influenced by anticoagulant administration.

## 4. CONCLUSION

There was a significant relationship between anticoagulant administration and D-Dimer levels in COVID-19 sufferers with moderate and severe symptoms, but researchers did not find a significant relationship for mild symptoms.

**Suggestions**

Based on the conclusions outlined by the author above, suggestions that can be taken into consideration and included are as follows:

1. For RS UKI and health workers, it is recommended to continue checking D-Dimer levels in COVID-19 patients who have been confirmed by RT–PCR, and always provide anticoagulants for prophylaxis, or therapy to prevent thrombus formation.
2. For future researchers, it is recommended to analyze the factors that can prevent D-Dimer levels from increasing

## Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of manuscripts.

Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc have been used during writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1.

2.

3.

## REFERENCES


[1] Ministry of Health of the Republic of Indonesia 2020. Guidelines for the Prevention and Control of CORONAVIRUS DISEASE 2019 (COVID-19). Downloaded from: https://detikemerging.kemkes.go.id/download/KMK_No._HK.01.07-MENKES-413-2020_ttg_Pedoman_Pemcepatan_dan_pengendalian_COVID-19.pdf . accessed on 16 May 2021.

[2] Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Herikurniawan, et al. Coronavirus Disease 2019: A Review of Recent Literature. Indonesian Journal of Internal Medicine. 2020: 7 ( 1 ):45-6. Downloaded from: http://jurnalpenyakitdalam.ui.ac.id/index.php/jpdi/article/view/415/228. Accessed May 19, 2021. Doi: http://dx.doi.org/10.7454/jpdi.v7i1.415

[3] Prastyowati A. Understanding the Characteristics of the SARS-CoV-2 Virus That Causes COVID-19 Disease as a Basis for Efforts to Develop Antiviral Drugs and Vaccines. 2020: 11 (1): 4-6. Downloaded from: https://terbitan.biotek.lipi.go.id/index.php/biotrends/article/view/275/235. Accessed May 17, 2021.

[4] Cui J, Li F, Shi ZL. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol. 2019;17(3):181-192. Downloaded from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7097006/. Accessed May 17, 2021. doi:10.1038/s41579-018-0118-9
[5] Bender L. Main Messages and Activities for Preventing and Controlling COVID-19 in Schools. 2020.Downloaded from https://www.who.int/docs/defaultsource/searo/indonesia/covid19/pesan-dankegiatan-utama-pengengahan-dan-pengendalian-covid-19-di-school-- indonesian--march- 2020.pdf?sfvrsn=5cdfea17_2 , on May 17, 2021
[6] Fitriani NI. Literature Review COVID-19: Virology, Pathogenesis and Clinical Manifestations. Malahayati Medical Journal.2020:4(3)196-198Downloadedfrom: http://ejurnalmalahayati.ac.id/index.php/medika/article/viewFile/3174/pdf, on 19 May 2021.
]7] Kumar CVS, Mukherjee S, Harne PS, Subedi A, Ganapathy MK et al . Novelty in the Gut: A Systematic Review Analysis of the Gastrointestinal Manifestations of COVID-19. BMJ Open Gastroenterology. 2020: 7 ( e0000417 ), 5-8. Downloaded from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7252994/. On May 17, 2021. doi: https://doi.org/10.1136/bmjgast2020-000417
[8] Rusdiana T, Akbar R. Recent Developments in Anticoagulant Therapy in COVID-19 Patients with Severe Symptoms. Journal of Pharmaceutical & Clinical Sciences. 2020: 7 (3). 244. Downloaded from: http://jsfk.ffarmasi.unand.ac.id/index.php/jsfk/article/view/755/242. On May 17, 2021. Doi: 10.25077/jsfk.7.3.244-250.2020
[9] Willim HA, Hardigaloeh AT, Supit AI, Handriyani. Coagulopathy in Coronavirus Disease -2019 (COVID-19): Literature Review. Medical Science Digest. 2020: 11 {3). 749-56. Downloaded from: https://isainsmedis.id/index.php/ism/article/viewFile/766/642. On May 18, 2021. Doi: 10.15562/ism.v11i3.766
[10] Juliana. Corona Virus Disease (Covid-19); A Literature Review. Wellness and Health Magazine. 2020: 2 (1). 188-9. Downloaded from: https://wellness.journalpress.id/wellness/article/view/21026/pdf. On June 26, 2021.
[11] World Health Organization: Transmission of SARS-CoV-2: Implications for infection prevention precautions. WHO. 2020: 1-5. Downloaded from: https://www.who.int/docs/default-source/searo/indonesia/covid19/transmisi-sars-cov-2---imklik-untuk-terhadap-kewaspadaan-pengepenangan-infection---statement -keilmuan.pdf?sfvrsn=1534d7df_4. On May 20, 2021.
[12] Doremalen NV, Morris DH, Gamble A, Williamson BN, Tamin A, Harcourt JL et.al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. The New England Journal of Medicine. 2020: 382 (16): 1564-1567. Downloaded from: https://pubmed.ncbi.nlm.nih.gov/32182409/. On May 20, 2021. Doi: 10.1056/NEJMc2004973.
[13] Gennaro FDi, Pizzol D, Marotta C, Antunes M, Racalbuto V, Veronese N et al. Coronavirus Diseases (COVID-19) Current Status and Future Perspectives: A Narrative Review. International Journal of Environmental Research and Public HealthEnvironmental Research and Public Health.2020: 17(2690), 1–11. Downloaded from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7215977/. On June 26, 2021. https://doi.org/10.3390/ijerph17082690
[14] Handayani D, Hadi DR, Isbaniah F, Burhan E, Agustin H. Corona Virus Disease 2019. Indonesian Respirology Journal. 2020: 40 (2). 121-2. Downloaded from: https://jurnalrespirologi.org/index.php/jri/article/view/101/110. On May 19, 2021.
[15] Hoffmann M, Kleine-Weber H, Schroeder S et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020 Apr 16;181(2):271-280.e8. Downloaded from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102627/. On May 19, 2021. doi : 10.1016/j.cell.2020.02.052.
[16] Association of Indonesian Internal Medicine Specialists. Ministry of Health's Readiness in Facing Outbreak of Novel Coronavirus (2019-nCoV). PAPDI. 2020: 6. Downloaded from: https://www.papdi.or.id/pdfs/817/dr%20Siti%20Nadia%20-%20Kemenkes%20RI.pdf . On June 26, 2021.
[17] Kushner A, West WP, Pillarisetty LS. Virchow Triad. 2020. Downloaded from: https://www.ncbi.nlm.nih.gov/books/NBK539697/. on May 19, 2020.
[18] Agustiningsih, Nugraha AA, Daryanto, Pawestri HA, Ikawati HD, Harianja H et.al. SARS-CoV-2 PCR Examination Guidelines for Laboratory Staff. Edition 1. Jakarta: Publishing Institution, Health Research and Development Agency (LPB); 2020. pp. 136-152.
[19] Caliendo AM , Hanson KE . COVID-19: Diagnosis. Downloaded from https://www.uptodate.com/contents/covid-19-diagnosis?topicRef=126981&source=related_link#H1282456413. on May 18, 2021
[20] Infectious Disease Society, Association for Molecular Pathology: The use of SARS-CoV-2 PCR Cycle Threshold (CT) Values for clinical decision-making. IDSA, AMP. 2021 downloaded from https://www.idsociety.org/globalassets/idsa/public-health/covid-19/idsa-amp-statement.pdf. On May 19, 2021.
[21] Dinnes J, Deeks JJ, Berhane S, Taylor M, Adriano A, Davenport C, et al. Rapid, point-of-care antigen and molecular-based tests for diagnosis of SARS-CoV-2 infection. Cochrane Database Syst Review. 2021: 3(3):1-6 . Downloaded from: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013705.pub2/full. On June 25, 2021. doi: 10.1002/14651858.CD013705.pub2.
[22] Pray IW, Ford L, Cole D, Lee C, Bigoutte JP, Abedi GR et al. Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020. MMWR ( Morbidity and Mortality Weekly Report). 2021: 69 ( 51-52 ). 1642-1647. Downloaded from:

https://www.cdc.gov/mmwr/volumes/69/wr/pdfs/mm695152a3-H.pdf. On June 27, 2021. Doi: http://dx.doi.org/10.15585/mmwr.mm695152a3.

[23] Hansen KE, Caliendo AM, Arias CA, et al. Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Serologic Testing. 2020. Downloaded from https://www.idsociety.org/practice-guideline/covid-19-guideline-serology/. on May 20, 2021