

Original Article

**Comparison of D-dimer Levels Based on COVID-19 Severity Degree in Third-trimester Pregnant Women at dr. Doris Sylvanus Hospital**

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**ABSTRACT**

*Pregnant women are vulnerable to COVID-19 due to the physiological adaptive changes and immunosuppressive state during pregnancy. Various studies on COVID-19 patients have shown the prognostic value of elevated D-dimer. Pregnant women with COVID-19 experience hypercoagulability and hyperfibrinolysis, as indicated by the increased D-dimer levels that exceed normal limits during pregnancy. This study aims to determine the comparison of D-dimer levels based on the COVID-19 severity degree in third-trimester pregnant women at dr. Doris Sylvanus Hospital Palangka Raya. This research is an analytical observational study with a cross-sectional design. It used the medical record data of third-trimester pregnant women confirmed positive for COVID-19 who underwent D-dimer examination at dr. Doris Sylvanus Hospital, Palangka Raya, during November 2020–October 2021, and limited to be generalized to places that has similarity with this hospital. Descriptive analysis in this study used the Kruskal Wallis test and Mann Whitney test. There is a significant difference in D-dimer levels based on the severity of COVID-19 with mild and moderate severity as indicated by the  $p=0.000$  value. In mild and severe severity, the value of  $p=0.001$  means that there is a significant difference, whereas in moderate and severe severity showed a value of  $p=0.101$  which means there was no significant difference. Mild severity has median 1.21, Moderate 2.71 and Severe 4.20. D-dimer and SpO2 data showed non-normally distributed data. It is an important topic to be studied because D-dimer levels can be the parameter for patients with COVID-19 severity status.*

**Keywords:** Pregnant women, D-dimer levels, COVID-19.

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**INTRODUCTION**

The Severe Acute Respiratory Syndrome Coronavirus-2, or also known as SARS-CoV-2 virus infection is the cause of COVID-19 disease. The disease was first reported in Wuhan, Hubei Province, China, in late December 2019. The WHO declared

COVID-19 a pandemic on March 11, 2020<sup>1</sup>. This disease has resulted in more than 6 million deaths worldwide<sup>2</sup>. The infection itself may be without or with symptoms, namely life-threatening sepsis and upper respiratory tract infection<sup>3</sup>. As many as 80% of COVID-19 infections are classified as asymptomatic or with mild symptoms, 15% with moderate

symptoms requiring oxygen, and 5% with severe symptoms requiring ventilators.

On January 30, 2020, WHO declared the this outbreak as a global public health emergency. It had been reported that, from around the world, there were about more than 80,000 confirmed cases since February 28, 2020<sup>4</sup>. In Indonesia, COVID-19 cases were first announced on March 2, 2020. Up until December 21, 2021, there were total 4,262,720 confirmed cases, where 4,292 of them are active cases. By age group, most COVID-19 cases occurred in the age groups 31–45 years (984,723 people), 19–30 years (863,297 people), and 46–59 years (740,913 people) and included both female and male sexes<sup>5</sup>. Transmission of the virus is possible to occur not only through respiratory droplets but also through direct contact with patients, which is also a source of transmission.

The Indonesian Ministry of Health reported that in 2021, there were 7,389 maternal deaths in Indonesia. In 2020–2021, there were 41,672 confirmed cases of COVID-19 in Central Kalimantan Province, including 1,063 deaths. Based on cumulative cases of COVID-19 by district or city and type of disease in Central Kalimantan in 2021, Palangka Raya City ranked first with the most confirmed cases of COVID-19, with a total of 13,127 cases. One group that contributes to the number of cases is pregnant women. Pregnant women are more vulnerable to COVID-19 since they experience physiological adaptive changes and immunosuppressive conditions during pregnancy<sup>6</sup>. A normal pregnancy lasts 280 days or within 40 weeks or 10 months (lunar months). There are three trimesters of pregnancy. The first trimester lasts about three months or 12 weeks, the second trimester happened from 13th to the 27th week, for about 15 weeks, and the last or third trimester happened from the 28th to the 40th week, for about 13 weeks<sup>7,8</sup>.

The probable length of pregnancy can be estimated from: 1) Duration of amenorrhoea. Sometimes pregnancy can occur after a period of physiological amenorrhoea, for example, during lactation. 2) Height of the fundus uteri. Before the third month, the fundus uteri cannot be palpated from the outside, and by the 9th month, the fundus uteri in primigravida falls again because the head begins to descend into the pelvic cavity. On lying down multigravida, the fundus uteri remain at the level of the arcus

costarum and is more prominent forward. 3) Gestational age, which can be seen from the size of the fetus, especially the size of the fetal head. The biparietal diameter can be measured precisely by ultrasound. 4) When movement and fetal heart sounds are felt. 5) Whether or not the head has entered the pelvic cavity. 6) Amniocentesis examination (orange-stained cells, creatinine, etc.)<sup>8,9</sup>.

There are some typical symptoms found in hospitalized COVID-19 patients. Those symptoms are dry cough (60–86%), fever (70–90%), fatigue (38%), shortness of breath (53–80%), myalgia (15–44%), nausea/vomiting or diarrhea (15–39%), headache, weakness (25%), and rhinorrhea (7%). Various studies in COVID-19 patients have shown the prognostic value of elevated D-dimer. Several studies have revealed a correlation between elevated D-dimer (prevalence up to 46.4%) and increased severity and poor clinical outcomes in COVID-19 patients. The trend of D-dimer elevation experienced by the patient also affect the clinical outcome of COVID-19<sup>10</sup>.

D-dimer is a fibrin degradation fragment that indicates the occurrence of thrombosis and is an indicator of hemostasis and fibrinolysis. On the admission, the elevated D-dimer levels are linked with the elevation risk of disease severity and mortality in patients with the infection<sup>11</sup>. D-dimer examination is one of the parameters in the fibrinolysis examination that is important for monitoring disease progressivity, especially in the early phase of infection<sup>12</sup>.

People with more than 1000 ng/mL D-dimer may cause a 20-fold higher risk of mortality than those with a lower D-dimer. Thus, D-dimer examination is a probable screening tool for venous thromboembolism in confirmed COVID-19 patients. With reference to the elevated D-dimer value, administering therapeutic doses of anticoagulants is more beneficial than prophylactic doses. Therefore, it is important to monitored the D-dimer levels of these patients at the beginning of admission<sup>10</sup>.

Pregnant women who were infected by the COVID-19 experience hypercoagulability and hyperfibrinolysis, characterized by an increase in D-dimer levels that exceed normal limits in pregnancy. D-dimer in pregnant women with COVID-19 can increase 2–3 times. COVID-19 infection is associated with higher mortality rates<sup>6</sup>. In conditions such as

pregnancy, inflammation, malignancy, and surgery, D-dimer levels may increase. Age is a factor that can worsen the infection of COVID-19. The older a person is, the more likely the body's function will decline and the risk of pregnancy will also increase. Relatively weaker immune responses occur in older pregnant women compared to young pregnant women, so the severity caused by SARS-CoV-2 may be more severe. Pre-existing disease is also thought to be an additional factor that worsens the course of COVID-19<sup>13</sup>.

D-dimer and fibrinogen levels will increase in the primary phase of the COVID-19 infection. D-dimer levels can be used for early diagnosis and therapy to reduce morbidity and mortality, as high D-dimer levels are thought to predict COVID-19 severity, lung complications, and thromboembolic events<sup>14</sup>.

## METHOD

This research is an analytical observational study with a cross-sectional research design. It aims to determine the comparison of D-dimer levels based on the severity of COVID-19 in third-trimester pregnant women. The population used were the third-trimester pregnant women with D-dimer levels based on the severity of COVID-19 at dr. Doris Sylvanus Hospital Palangka Raya during the period of November 2020–October 2021.

The samples used were third-trimester pregnant women who were positive for COVID-19 and met the inclusion and exclusion criteria. The sampling techniques used is total population sampling. In the research process, out of 115 pregnant women with confirmed COVID-19, only 38 patients had records of D-dimer examinations, so all pregnant women who had this data (38 people) were used as research samples. The method of sample selection is probability sampling. The data was analyzed using the SPSS program. Descriptive analysis in this study used the Kruskal Wallis test which was used to determine the median difference of D-dimer levels comprehensively.

This research was done with the full consent of people who were chosen as the study sample. The ethical clearance was obtained from the research ethics team of dr. Doris Sylvanus Hospital, Palangka Raya. Letter number: 3955/UM-TU/RSUD/08-2023.

## RESULTS

After the analysis using the sample (38 pregnant women), the following test results were obtained. Table 1 contains the frequency distribution of characteristics based on age, occupation, and gestational age.

**Table 1. Frequency Distribution of Characteristics by Age, Occupation and Gestational Age (n=38).**

Characteristics	Positive COVID-19	
	Total	%
<b>Age</b>		
17-25 years (late teens)	9	23.7%
26-35 years (young adult)	16	42.1%
36-42 years (late adult)	13	34.2%
Total	38	100%
<b>Occupation</b>		
Housewife	14	36.8%
Civil servant	14	36.8%
Entrepreneur	8	21.0%
Student	2	5.2%
Total	38	100%
<b>Gestational Age</b>		
Preterm	23	60.5%
Aterm	11	28.9%
Post Date	4	10.5%
Total	38	100%

According to the table 1, the pregnant women in their third trimester who are confirmed positive for COVID-19 are mostly between 26-35 years old, namely 16 pregnant women (42.1%) out of the total sample, working as housewives and civil servants, with 14 pregnant women with a percentage of 36.8% in each category. The most cases occurred in preterm pregnancy, with 23 pregnant women (60.5%). The following Table 2 shows the frequency distribution of characteristics based on regional origin.

The regional origin of patients who dominate in this study is Palangka Raya City, with 26 pregnant women (68.4%) out of the total sample. The D-dimer and SpO2 data showed non-normally distributed data. Comparison of haematological features based on the severity of COVID-19 in third-trimester pregnant women is the D-dimer level. For more detailed information, the data can be seen in Table 2 below.

**Table 2.** Frequency Distribution of Characteristics Based on Regional Origin

Regional Origin	Positive COVID-19	
	Total	%
Palangka Raya	26	68.4%
Katingan	4	10.5%
South Barito	2	5.3%
Murung Raya	2	5.3%
Pulang Pisau	2	5.3%
Others	2	5.3%
Total	38	100%

The results of the comparative analysis of D-dimer levels based on the severity of COVID-19 in third-trimester pregnant women can be seen in Table 3.

**Table 3.** Results of Descriptive Analysis Comparison of D-dimer Levels based on the severity of COVID-19 in Third-trimester Pregnant Women

COVID-19 severity	Median	Minimum	Maximum	P*
Mild (SpO2 >=96%)	1.21	0.20	4.69	
Moderate (SpO2 =94-95%)	2.71	1.19	6.04	0,000
Severe (SpO2 <=93%)	4.20	1.89	46.0	

\*Kruskal Wallis test

Kruskal Wallis analysis technique were chosen to determine the difference between the three sample groups. By the results, a value of p=0.000 was obtained. In conclusion, there were differences in D-dimer levels in each sample group. The Mann-Whitney test was done to determine the median difference in D-dimer values. It was found that the more severe, the higher the median of D-dimer level will be. D-dimer and SpO2 data showed that the data were not normally distributed. The median value of the D-dimer examination based on the degree of severity of mild COVID-19 is 1.21 (>=96%), the median value of the moderate degree is 2.71 (94-95%), and the median value of the severe degree is 4.20 (<=93%). It can be concluded that the more severe the severity of COVID-19, the higher the median value.

**Table 4.** Results of Comparative Test Analysis of D-dimer Levels based on the severity of COVID-19 in Third-trimester pregnant women

Group 1	Group 2	P*
Mild	Moderate	0.000
Mild	Severe	0.001
Moderate	Severe	0.101

\*Mann Whitney test

From Table 4, it can be seen that there is a significant difference in D-dimer levels based on the severity of COVID-19 in the group of third-trimester pregnant women with mild and moderate severity, as indicated by the p=0.000. In mild and severe severity, the value of p=0.001 shows that there is a significant difference. Whereas the group of moderate and severe level of severity showed a value of p=0.101 which means there was no significant difference.

## DISCUSSION

Lowering the rate of maternal mortality to less than 70 cases per 100,000 live births by 2030 is one of the Sustainable Development Goals targets. Globally, in 2020, maternal deaths are estimated to be 287,000 cases, leading to an overall MMR of 223 cases per 100,000 births<sup>15</sup>. Pregnant women are very vulnerable of the risk of infection due to the body's physiological changes and a decrease in the immune system<sup>16, 17</sup>.

Physiological changes in the body during pregnancy have an impact on reducing the ability of the body's immune system, which causes an increased risk of infection. Early detection of infectious diseases needs to be done for pregnant women to avoid complications during pregnancy until delivery and reduce the risk of death<sup>18</sup>. One of this infectious disease is COVID-19. Pregnant women who are infected with COVID-19 are very possible to experience harms and issues that can affect the pregnancy and the baby's development. During pregnancy, COVID-19 may increase the risk of delivering a premature (less than 36 weeks) or stillborn baby<sup>19</sup>.

The Centers for Disease Control and Prevention (CDC) concluded that the following are significantly associated with increased risk of severe COVID-19: cerebrovascular disease, chronic kidney disease, cancer, chronic obstructive pulmonary disease (COPD), type 1 and type 2 diabetes mellitus, etc.<sup>20</sup>. The severity

of COVID-19 affects the high level of inflammation that occurs in the body, so the higher the severity of COVID-19, the higher the D-dimer levels in the body<sup>21</sup>.

Based on the result of this study, the highest number of pregnant women confirmed positive for COVID-19 was found in the age group of 26–35 years (42.1%). This age group is a productive age to experience pregnancy and childbirth<sup>16</sup>. The majority of them had a relatively low risk of labor complications when concluded based on age only<sup>22</sup>. Schwartz et al. analyzed 38 pregnant women in the age range of 26–40 years with confirmed COVID-19 in China<sup>23</sup>. During pregnancy with symptomatic conditions, severe complications of COVID-19 were found<sup>1</sup>.

The mothers mostly worked as civil servants and housewives. Each group consist of 14 mothers with a percentage of 36.8%. Working pregnant women can get health information more easily than the pregnant women who choose to be housewives<sup>24</sup>. The majority of the sample came from Palangka Raya City, with the total of 26 people with a percentage of 68.4%. This is in accordance with the cumulative data of confirmed cases of COVID-19 in 2021 which shows Palangka Raya City as the first rank with the most cases in Central Kalimantan, with the total of 13,127 cases<sup>25</sup>. The majority of the gestational age of pregnant women in this study was less than 37 weeks (preterm), namely 23 people with a percentage of 60.5%. A study at the University of California San Francisco found that the risk of preterm birth was higher by 60% in pregnancies less than 32 weeks, while the risk of preterm birth was higher by 40% in pregnancies less than 37 weeks<sup>26</sup>.

D-dimer is a readily-available and commonly-used indication of inflammation that have a very important role in pneumonia caused by the COVID-19 infection in assessing the disease severity and response to treatment during hospitalization. In this study, there was a significant difference in D-dimer levels based on the severity of COVID-19 in the group of third-trimester pregnant women with mild and moderate severity, as indicated by the  $p=0.000$  value. In mild and severe severity, the value of  $p=0.001$  was obtained, which means there is a significant difference. Whereas in moderate and severe severity, the value of  $p=0.101$  means that there is no significant difference. Nonetheless, the median difference of moderate and severe

severity are almost twice bigger. It can be considered that there was a quite big gap difference of these two groups. This is in accordance with a previous study<sup>27</sup> that found that there was a very significant difference in the average value of D-dimer in mild and severe severity with a value of  $p=0.000$ .

It was also found that D-dimer levels increased significantly with an increase in the severity of COVID-19 ( $p=0.000$ )<sup>28</sup>. Another similar study also found that D-dimer levels were associated with mortality in COVID-19 patients, showing  $p=0.000$ , which means that there is a significant relationship between D-dimer levels and mortality in COVID-19 patients<sup>1</sup>. The severity of COVID-19 affects the high level of inflammation that occurs in the body. The higher the severity of COVID-19 in pregnant women, the higher the D-dimer levels in the body. In pregnant women with severe COVID-19, a significant increase in D-dimer was found<sup>21</sup>.

Pregnancy is one of the factors that can cause an increase in D-dimer levels. Gestational age in pregnant women will affect the high and low levels of D-dimer in the body<sup>21</sup>. In normal pregnancy, there will be an increase in D-dimer levels from conception, labor, and postpartum. D-dimer levels can be used as an early and advanced screening test to identify women with high-risk pregnancies that require more intensive fetomaternal monitoring and management. D-dimer can also be used as an initial screening and follow-up test for coagulopathy and to identify whether an individual is at high risk for more severe disease. A positive D-dimer result indicates the presence of high fibrin degradation products in the body. This is characterized by the presence of a significant amount of thrombus. Pregnant women with high D-dimer levels will have increased chances of labor and possible placental abruption.

The D-dimer examination is one of the supporting assessment to examine the presence of coagulation disorders in patients with COVID-19<sup>29</sup>. D-dimer levels increase gradually during normal pregnancy and peak in the third-trimester of pregnancy. Evidence of coagulopathy reported in COVID-19 infection shows elevated D-dimer levels. COVID-19 infection in pregnant women has been associated with a higher rate of mortality<sup>6</sup>. Low oxygen saturation, also known as hypoxia, is a poor predictor of COVID-19 because hypoxia

is a trigger for excessive coagulation caused by an increase in hypoxia-inducible transcription factor which will increase D-dimer levels<sup>30</sup>.

## CONCLUSION

In third-trimester pregnant women who are confirmed positive for COVID-19 at dr. Doris Sylvanus Hospital Palangka Raya in November 2020–October 2021, the median value for mild D-dimer level is 1.21 ( $\geq 96\%$ ), the median value for moderate D-dimer level is 2.71 (94-95%), and the median value for severe D-dimer level is 4.20 ( $\leq 93\%$ ). There is also a significant difference of D-dimer. The degree of mild-moderate severity obtained a p value=0.000, the degree of mild-severe severity obtained a p value=0.001, and the degree of moderate-severe severity obtained a p value=0.101. It means that there was no significant difference in D-dimer levels. D-dimer levels increased significantly along the increase of COVID-19 severity.

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## CONFLICTS OF INTEREST

The authors declare no competing interests or conflicts that may have influenced the study outcome.

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