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Elevated Inflammatory Markers in COVID-19 Patients in Relation to Symptom onset and Antiviral Therapy Options

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ABSTRACT

The COVID-19 virus has become a terrible global pandemic and has even caused severe trauma for all citizens in the world. Even though the number of cases is starting to decline, mutations of this virus are still possible and management is important to prevent serious fatalities. CRP and D-dimer have been widely studied as good markers of COVID-19 inflammation, and their application can even be used as a predictor of symptom severity. The rapid replication of the virus makes starting antiviral therapy from the onset of infection very crucial. Many previous studies have associated a worse prognosis in patients who receive antiviral therapy more slowly. The choice of antiviral is also important in order to effectively reduce viral replication and reduce the patient's severity. This study aims to compare the onset of symptoms and the choice of antiviral therapy in relation to suppressing the increase in inflammatory markers, namely CRP and D-dimer. This study uses a retrospective cohort model with a simple random sampling method that collects data on patients with COVID-19 who underwent treatment at a private hospital in Tangerang during the period January – December 2021 with a complete examination of CRP and D-dimer at the time the patient first arrived and on the day of the birth. 5 treatments. Data collected included age, gender, history of hypertension, diabetes mellitus, antiviral therapy used, onset of symptoms when the patient came to the hospital and CRP and D-dimer lab values. All of this data was then analyzed bivariately using the paired T test or Wilcoxon test method to determine the statistical significance of the data. The number of research subjects was 84 patients with an average age of 45.20 ± 15.02 years. Of all the patients, 14 patients had severe symptoms and 2 of them died. The CRP value at the time the patient first arrived was found to be lower in patients who came with symptom onset ≤ 2 days compared to those with symptom onset > 2 days with values respectively 12.55 and 33.01 mg/L, P value = 0.005. The D-dimer values in the two groups were also significantly different with values of 379.68 and 720 ng/mL, P value = 0.005. Based on the symptom onset category, it was found that patients who received antiviral therapy with symptom onset ≤ 2 days were found to have no significant differences in CRP and D-dimer values between the first day and the 5th day of treatment. This shows the effectiveness of the therapy provided. However, the group of patients who received antiviral therapy after the onset of symptoms > 2 days had significantly higher CRP and D-dimer values. The CRP values for the first day and the 5th day were 33.00 and 42.66 with a P value = 0.008 and the D-dimer values were 720 and 835.03 with a P value = 0.0029. In selecting the antiviral used, it was found that the remdesivir group provided a better prognosis with CRP values of 31.30 (H-1) and 40.93 (H-5), P value = 0.39. However, the same as favipiravir there was still a significant increase in D-dimer. Thus, starting antiviral therapy early with symptom onset ≤ 2 days is better for patient prognosis. The therapy chosen can be assumed to be that remdesivir is more effective than favipir avir in suppressing the increase in inflammatory markers, namely CRP and D-dimer .

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1. INTRODUCTION

The first case of COVID-19 was discovered due to the rapid and fatal spread of cases of lung infection/pneumonia from a market in Wuhan, China. (1) The spread of this terrible case forced further research into pneumonia and a new variant of the virus was discovered which was later named by WHO as Coronavirus disease 2019 (COVID-19). On March 11 2020, WHO then declared COVID-19 a global pandemic. (2) Since the initial reports of this disease in China, COVID-19 cases have spread rapidly with the number of cases increasing exponentially. The first case in Indonesia was first discovered on March 2 2020 after 2 Indonesian citizens met a Japanese citizen who tested positive for COVID-19 on February 27 2020. (3)

As of the time this research was written, the total number of COVID-19 cases globally had reached 771,549,718 cases with total deaths reaching 6,974,473 patients. This prevalence has begun to decline since mid-2022 and the completion of the COVID-19 vaccination dose for most of the global population. The spread of the COVID-19 virus is through droplets or splashes of saliva from sneezing or coughing. After virus entry, the median virus incubation period is estimated to be 5.1 days, and most patients will develop symptoms within 11.5 days of virus entry. (4) The symptoms that will appear are very diverse, ranging from asymptomatic to critical illness, including respiratory failure requiring mechanical ventilation, septic shock, and multiple organ failure. (5,6) Because the progression of COVID-19 disease can worsen over time, therapy given early is expected to reduce the risk of more severe symptoms or death.

A study compared the administration of remdesivir with placebo in patients who had symptoms in the last 7 days with risk factors for severe symptoms (age ≥ 60 years, obesity, or certain existing medical conditions in the patient) and undergoing outpatient therapy. From this study it was found that the group that received remdesivir had a significantly lower mortality rate and need for treatment compared to the placebo group. (7) In COVID-19 therapy using favipiravir, on the other hand, it was found that there was no effectiveness in reducing the virus clearance time or improving symptoms when compared with placebo. (8) In cases of COVID-19 in Indonesia, the commonly used antivirals are remdesivir and favipiravir. However, the effectiveness of this therapy has not yet been demonstrated in many studies in Indonesia.

Earlier therapy became a subject of frequent research during the initial spread of COVID-19. Researchers around the world hope to find a solution to prevent the severity of COVID-19 symptoms. A study by Shimizu et al, showed that the interval between the onset of the disease and the start of COVID-19 therapy was longer in patients who received treatment in hospital compared to those who received outpatient treatment. (9) However, not all therapies given early have significant effects. The study by Baksh et al, compared the administration of convalescent plasma which is known to provide symptomatic improvement in patients with COVID-19. This therapy was given to patients who had symptoms for a maximum of 9 days and were undergoing outpatient treatment, then interviews were conducted again on the 14th day and it was found that there were no significant differences between the groups that received plasma and those that did not receive plasma. (10)

Studies comparing symptom improvement with the use of favipiravir and remdesivir in hospitalized patients have not been studied previously. Earlier initiation of therapy with a better prognosis has also never been done in Indonesia. Therefore, this study aims to compare inflammatory biomarkers (D-dimer and CRP) in patients with COVID-19 undergoing treatment and assess the effect of early therapy or antiviral selection in patients to prevent disease progression and improve inflammatory biomarkers .

2. METHOD

The research was conducted as a retrospective cohort study at a private hospital in Tangerang where researchers worked with patients who received COVID-19 treatment between January 2021 and January 2022, collected randomly until there were sufficient research samples. The research inclusion criteria were all COVID-19 patients receiving treatment at Mentari Hospital aged 18 - 90 years including mild to severe symptoms. The study exclusion criteria were subjects who did not have inflammatory biomarkers re-examined.

Data collection used simple random sampling using secondary data, namely hospital medical records. Data collection has gone through a research ethics review while keeping patient identities confidential. Data collected were age, gender, disease onset, history of hypertension, diabetes mellitus, and inflammatory biomarkers, namely D-dimer and CRP.

Analysis of demographic data/patient characteristics using frequencies and percentages for categorical variables and mean or median for numerical data depending on the normality of the data. The bivariate test will compare the D-dimer and CRP values between the patient's initial admission and the 5th day of treatment compared based on the covariates studied in the study including the onset of the disease and the antiviral used.

3. RESULTS AND DISCUSSION

Research data collected over a 1 year period showed that there were 84 patients with COVID-19, of which 49 cases were male (58.3%) and 35 cases were female (41.7%) with an average age of 45.2 ± 15.02 year. Of the total patients, 14 of them were in the severe COVID-19 category and 2 of them died due to respiratory failure. The inflammatory markers assessed in this study were CRP and D-dimer with the average CRP value at the start of the examination being 23.99 ± 29.22 mg/L and after 5 days it was found to be 30.99 ± 32.38 mg/L. Meanwhile, the D-dimer value at the start of the examination found an average of 570.09 ± 416.22 ng/mL and after 5 days of treatment the average was 654.09 ± 536.57 ng/mL. Patient demographic data can be seen in table 1 below.

Table 1. Demographic Data of Patients with COVID-19

Variable	n (%)	Mean ± SD / Median (range)	P Value Normality Test
Gender			
Man	49 (58.3%)		-
Woman	35 (41.7%)		
Age (years)		45.20 ± 15.02	0.193
Anti virus			
Remdesivir	30 (35.7%)		
Favipiravir	54 (64.3%)		
Onset during treatment (days)			
≤ 2	37 (44.0%)		
> 2	47 (56.0%)		
Diabetes mellitus			
Yes	8 (9.5%)		
No	76 (90.5%)		
Hypertension			
Yes	14 (16.7%)		
No	70 (83.3%)		
Severity Level			
Light	54 (64.3%)		
Currently	16 (19.0%)		
Heavy	14 (16.7%)		
Initial D-dimer (ng/mL)		460.42 (190 – 2250)	0.0005
D-dimer Day 5 (ng/mL)		500.46 (147.09 – 2670)	0.0005
Initial CRP (mg/L)		12.70 (0.10 – 167.30)	0.0005
CRP Day 5 (mg/L)		20.95 (0.2 – 198.70)	0.0005

Source: Primary data, 2021

Based on the onset of the patient's symptoms when they arrived, bivariate analysis was carried out using the chi-square and T test to assess differences between groups of patients with symptom onset ≤ 2 days and those with symptom onset > 2 days. From the results of this test, it was found that most of the group of patients who came with the onset of symptoms ≤ 2 days were significantly younger than those who came after symptoms > 2 days. There was also a statistical difference in the choice of antiviral, which showed that most patients with symptom onset ≤ 2 days received

favipiravir. This is possible because most of the patients who came earlier had milder symptoms. Clinicians in Indonesia tend to give favipiravir for mild cases and reserve remdesivir only for severe cases. This is proven by the CRP and D-dimer values which are also significantly different. The symptom onset group > 2 days was found to have higher CRP and D-dimer values compared to the symptom onset group ≤ 2 days.

The results of this study are in accordance with the study published by Galindo et al where older patients tend to seek medical help later. In addition, with each additional day, there was an increase in mortality of 6.4%. (11) As these symptoms become more severe, it can also be proven by increasing CRP values. CRP is considered to be a predictor factor in the severity of COVID-19, where research by Nurshad Ali in 2020 showed that the CRP concentration in patients with mild symptoms usually has a value of around 23 mg/L, while in severe cases it is twice as high, namely 46 mg. /L. In fact, patients who died from COVID-19 had CRP values that were 10 times higher. (12–14)

Table 2. Bivariate analysis comparing the symptom onset group ≤ 2 days with the symptom onset group > 2 days

Variable	Onset of Symptoms		
	≤ 2 days	**> 2 days**	**P value**
Age	40.40 ± 14.09	48.98 ± 14.78	**0.008**
Gender			
Man	18 (36.7%)	31 (63.3%)	0.169
Woman	19 (54.3%)	16 (45.7%)	
Anti virus			
Remdesivir	8 (26.7%)	22 (73.3%)	**0.031**
Favipiravir	29 (53.7%)	25 (46.3%)	
DM			
Yes	3 (37.5%)	5 (62.5%)	1.00
No	34 (44.7%)	42 (55.3%)	
Hypertension			
Yes	3 (21.4%)	11 (78.6%)	0.08
No	34 (48.6%)	36 (51.4%)	
CRP (D-1)	12.55 ± 25.65	33.01 ± 28.95	**0.005** *
D-dimer (H-1)	379.68 ± 368.35	720.00 ± 392.79	**0.005** *

Information: * Test was carried out with MannWhitneyU because the data was not normally distributed

Source: Primary data, 2021

From the patient data, bivariate analysis was then carried out to compare the initial CRP and D-dimer values with the 5th day of treatment and it was found that there was a significant difference in these two variables with the p value for both being 0.01. This difference showed that the patient's CRP and D-dimer were higher on day 5 of treatment even with appropriate antiviral and supportive therapy. Of all the cases studied, it was found that the patient's CRP value increased by 7 mg/L. Even though the figure of 7 mg/L is a small difference in CRP values, statistically this value is found to be significantly different. This is possible because there are many variables involved between day 1 and day 5, including the severity of symptoms and extreme values that cannot be assessed with an average. Meanwhile, the D-dimer value also showed an increase of 84 ng/mL. The results of the bivariate analysis can be seen in table 2 below.

Table 3. Bivariate analysis with paired T test between CRP and D-dimer at the beginning of treatment and day 5 of treatment

Variable	Overall Data		
	D-1 (mean ± SD)	**D-5 (mean ± SD)**	**P value**
CRP	23.99	30.99	0.001 *
D-dimer	570.09	654.09	0.001 *

Note: the test was carried out using the Wilcoxon test because the data was not normally distributed

Source: Primary data, 2021

Bivariate analysis was then continued by categorizing the samples based on the onset of the patient's symptoms when they arrived and started treatment with antivirals at the hospital. It was also analyzed using a combination of the two to see possible interactions in these variables. It was found that the group of patients with symptom onset ≤ 2 days had CRP and D-dimer values that were not statistically significantly different between the first day of treatment and the 5th day. This means that patients who receive antiviral therapy as soon as possible have a better prognosis. Meanwhile, the group of patients with symptom onset > 2 days had significantly higher CRP and D-dimer values on the 5th day compared to the first day of treatment. The difference in CRP values was found to be 9.66 mg/L with a P value of 0.008 and the D-dimer value was 115.03 ng/mL with a P value of 0.029. Seeing this, it can be assumed that antiviral therapy in patients with symptom onset > 2 days is considered less effective in reducing the level of inflammation in the patient.

Table 4. Bivariate analysis with paired T test between CRP and D-dimer at the beginning of treatment and the 5th day of treatment based on disease onset category

Variable	n (%)	CRP			D-dimer		
		H-1	H-5	P value	H-1	H-5	P value
Onset of Symptoms							
≤ 2 days	37 (44.05%)	12.54	16,16	0.17	379.68	424.25	0.079
> 2 days	47 (55.95%)	33.00	42.66	**0.008**	720.00	835.03	**0.029**
Antiviral Therapy							
Remdesivir	30 (35.71%)	31.30	40.93	0.39	736.84	863.54	**0.022**
Favipiravir	54 (64.29%)	19.93	25.47	**0.014**	477.46	537.74	**0.011**
Onset and Therapy							
≤ 2 days + Remdesivir	8 (9.52%)	14.37	28.85	**0.036**	634.98	784.86	0.484
≤ 2 days + Favipiravir	29 (34.52%)	12.04	12.67	0.088	309.25	324.77	0.112
> 2 days + Remdesivir	22 (26.19%)	37.46	45.31	0.212	773.87	892.15	**0.036**
> 2 days + Favipiravir	25 (29.77%)	29.08	40.33	0.060	672.58	784.77	0.088

Note: the test was carried out using the Wilcoxon test because the data was not normally distributed

After grouping based on the category of symptom onset and antiviral therapy, it was found that the group of patients with symptom onset > 2 days had statistically significantly higher CRP and D-dimer values on day 5 regardless of the antiviral therapy used. The patient's CRP value was found to continue to increase significantly with a value on the first day of 33.00 and increased to 42.66 on the 5th day with a P value = 0.008. Meanwhile, the D-dimer results also showed that there was still a significant increase with a value on the first day of 720 and on the fifth day of 835.03 with a P value = 0.029. This shows that patients with symptom onset > 2 days who are given therapy still have a worse prognosis compared to patients who are treated early before 2 days of symptoms. Although this still has the possibility of bias considering the different incubation periods from the onset of infection to the appearance of symptoms, the onset of these symptoms can be a fairly good indicator in predicting the prognosis of patients with COVID-19.

In the selection of antivirals, it was also found that in the group of patients who received remdesivir, the difference in CRP values on day 1 and day 5 was not significantly different (31.30 and 40.93; P value = 0.39), although in D- dimer still shows a significant increase with a value on the first day of 736.84 and a value on the 5th day of 863.54 with a P value = 0.022. Meanwhile, in the favipiravir group, it was found that there were still significant differences in both CRP and D-dimer, which were always higher. By looking at these data, it can be assumed that therapy with favipiravir is inferior to remdesivir in relation to inflammatory markers in patients with COVID-19. However, this still requires further research to focus on looking at the effectiveness and efficacy of therapy. In further analysis using symptom onset categorization and antiviral therapy simultaneously

A comparative retrospective study in China also showed that patients with COVID-19 had a better prognosis with earlier therapy as evidenced by 7 days earlier viral clearance and milder symptoms. (15) Although favipiravir showed therapeutic efficacy in several previous studies, in this study it was found that there was no suppression of inflammatory markers in patients. (16) So, in accordance with recommendations based on the CDC, the best therapy to use is remdesivir for inpatients and molnupiravir for outpatients. (17) .

4. CONCLUSION

COVID-19 disease must be treated as quickly as possible and receive appropriate antiviral therapy. The more you delay therapy, the worse the patient's prognosis is, as evidenced by a significant increase in inflammatory markers, both CRP and D-dimer. Regardless of the therapy used, the faster COVID-19 is treated, the faster virus replication will be suppressed. By reducing the replication of the virus, it is hoped that COVID-19 infection will become easier with milder symptoms and a lower mortality rate. In selecting antivirals, remdesivir was also found to be superior compared to favipiravir. This is in accordance with previous studies which found that remdesivir can accelerate virus clearance and reduce the mortality rate of patients with COVID-19. Although, favipiravir was found to be less good at suppressing inflammatory markers, its use can still be considered in cases of patients with mild symptoms and without comorbid factors. On the other hand, patients with moderate-severe symptoms or comorbidities with the possibility of severe symptoms are better treated with remdesivir to get a better prognosis. Even with convincing study results that earlier treatment with appropriate antiviral therapy can suppress inflammatory markers, there remains the possibility of bias that is difficult to investigate. Including when the virus enters the body, of course each individual has a different incubation period, so that the onset of symptoms is an indicator that can be measured by anamnesis. Further research with a larger sample size and different research methods can be carried out to further demonstrate the effectiveness of antiviral therapy and the influence of early therapy on the prognosis of patients with COVID-19. As a suggestion, medical personnel can use this study as a reference for educating patients that it is better to treat COVID-19 symptoms immediately. It is better to have symptoms of cough, cold or fever immediately checked before 2 days have passed so that appropriate diagnosis and treatment can be carried out before the symptoms become severe. Even in selecting antivirals, medical personnel can prioritize the use of remdesivir in cases that are deemed to have a high risk of developing serious symptoms. This is because in this study it was found that favipiravir was less effective in suppressing inflammatory markers, so the possibility of the patient's prognosis being worse was higher.

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