ORIGINAL ARTICLE

Correlation of D-dimer value with Lipid Levels in COVID-19 Patients at Tertiary Gresik Hospital

Nia Dyah Rahmianti[1], Hani Rahmantyo Akbar[2]

[1] Department of Cardiology and Vascular Medicine, RSUD Dr.Soetomo, Surabaya 60286, Indonesia
[2] Petrokimia Gresik Hospital, Gresik, East Java 61119, Indonesia

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) has infected millions of people worldwide, which is characterized by the manifestation of symptoms from coagulopathy to disseminated intravascular coagulation (DIC). This study aimed to investigated the correlation of D-dimer with lipoproteins values in COVID-19 patients. **Methods:** Observational cross-sectional analysis, using secondary data from medical records, based on the sample size formula it takes 78 samples, the data analysis method uses the SPSS program version 24. **Results:** From the results of the study, the number of patients with a D-dimer value of less than 0.5 ug/ml was 26%. While as many as 74% patients got the value of D-dimer increased by more than 0.5 ug/ml. Triglyceride and LDL levels were not associated with changes in D-dimer values. There is a correlation between the value of D-dimer with HDL (P = 0.024). High levels of D-dimer values are associated with the severity of symptoms and a poor prognosis. Excessive inflammatory processes will initiate coagulation via the extrinsic pathway, which progresses to disseminated intravascular coagulation (DIC) due to an imbalance between coagulation and fibrinolysis. Meanwhile, high HDL values reduce the risk of thrombotic events by initiating plasmin formation and are associated with low mortality rates. **Conclusion:** There is a statistically significant correlation between D-dimer values and HDL lipid levels. Suggestions, further research is needed to measure the correlation of D-dimer and HDL values in acute infection with the COVID-19 virus with a larger sample.
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Keywords: Covid-19, Coagulopathy, D-dimer, Lipid profile

Corresponding Author:
Hani Rahmantyo Akbar, PhD
Email: hanirahmantyo@yahoo.com
Tel: +62 813-3346-7548

INTRODUCTION

The 2019 coronavirus disease or better known as coronavirus disease 2019 (COVID-19) was first reported in December 2019 in the city of Wuhan, Hubei Province, China. As a newly discovered β-coronavirus, COVID-19 has spread widely and rapidly throughout the world, making COVID-19 a global pandemic problem with a very high mortality rate and multidisciplinary impact. The high infectivity of the virus and the limited understanding of the disease cause great challenges in handling this disease (1).

Data from WHO shows that in the early period of the COVID-19 pandemic on March 30, 2020, there were 693,224 cases and 33,106 deaths worldwide. In Indonesia, the first case was found on March 2, 2020, there were two cases. Then the number increased rapidly on July 17, 2021, it was reported that there were 2,832,755 confirmed cases with 72,489 deaths. The COVID-19 mortality rate in Indonesia is 2.6%, this figure is the highest in the Southeast Asia region. Meanwhile in Gresik Regency on July 17, 2021, COVID-19 incidents were reported with 1,480 active cases, 242 deaths, with a Fatality Rate of 5.44% (2).

In COVID-19 patients, severe clinical manifestations can occur including severe pneumonia (3), sepsis, septic shock, acute respiratory distress syndrome (ARDS) (4), multiple organ dysfunction syndrome (MODS) (5), and often have systemic coagulation disorders (coagulopathy) such as disseminated intravascular coagulation (DIC), thrombosis microangiopathy and macroangiopathy (6,7).

Signs of coagulation in the blood can be predicted through examination of D-dimer levels. D-dimer is a fibrin degradation product formed during the degradation of blood clots by fibrinolysis ((8)5). In the case of COVID-19, there was an increase in the value of D-dimer in 3.75-68% of cases in the world (9).

Lipid profile is a pattern of lipids in the blood consisting of total cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Lipoproteins

are known to be involved and play a role in the process of thrombosis and fibrinolysis. Increased HDL levels will reduce the risk of thrombosis by initiating the formation of plasmin so that the fibrinolysis process occurs (10).

When acute inflammatory reaction occurs excessively, it will cause disruption of the vascular endothelium (11), so that coagulopathy and thrombosis can trigger organ failure which it can be trigger dysregulation of lipid metabolism in the body (12). In the acute phase of sepsis and SIRS triglyceride levels were found to be increased and levels of HDL, LDL and VLDL decreased in the first 24 hours (13). These changes occur for 72 hours and will return to normal after more than 7 days. Based on this theory we want to know the description of D-dimer with lipoproteins values in acute phase of COVID-19 patients and this is what distinguishes our research with previous studies. Thus this study aimed to analyze the correlation between D-dimer levels and lipid profile levels in COVID-19 patients at the Petrokimia Gresik Hospital.

MATERIALS AND METHODS

This study used an observational analytical method with a cross sectional approach to assess the correlation between D-dimer values and lipid profile values of HDL, LDL, and Triglycerides in COVID-19 patients at Petrokimia Gresik Hospital. Data collection used secondary data from medical record data of COVID-19 patients treated at Petrokimia Gresik Hospital during July 2020 - July 2021. After screening to select samples based on inclusion and exclusion criteria, based on the sample size formula, 78 samples were needed. The sample was selected using a simple random sampling method where every patient has the same opportunity to be taken as a sample. Data analysis methods include descriptive statistics of patient data and regression analysis using SPSS version 24 software. Ethical approval was obtained from Komite Etik Penelitian Kesehatan (KEPK), Universitas Muhammadiyah Malang (No.E.5.a/240/KEPKUMM/VIII/2023).

RESULTS

Table I shows that the highest number of patients was in the age range of 50-69 years, namely 76.92%. The number of patients aged more than 70 years was only 10.25%, while the number of patients aged less than 50 years was 12.82%. Cases of COVID-19 are closely related to an increase in the value of D-dimer. Table II shows the frequency distribution of D-Dimer levels in COVID-19 patients.

In Table II, patients who had normal D-dimer values (less than 0.5 ug/ml) were 26% and patients who had increased D-dimer values (more than or equal to 0.5 ug/ml) were 74%. The increase in the value of D-dimer is closely related to changes in lipid levels in the blood.

Table I: Distribution of Patients by Age

Respondent's age	Frequency	Percentage
< 50	10	12.82%
50 – 69	60	76.92%
>70	8	10.25%
Total	78	100%

Table II: Frequency Distribution of D-Dimer Levels in COVID-19 Patients

D-dimer Value	Frequency	Percentage
<0.5 ug/ml	20	26%
≥0.5 ug/ml	58	74%
Total	78	100%

Table III: Frequency Distribution of HDL, LDL, and Triglyceride Levels in COVID-19 Patients

Variable	Value Category	n	%
HDL Cholesterol Level			
≤ 35 mg/dL	Dangerous	32	41.10%
36 - 44 mg/dL	Alert	22	28.20%
≥45 mg/dL	Optimal	24	30.70%
Total		78	100%
LDL Cholesterol Level			
< 130 mg/dL	Optimal	56	71.80%
130 – 159 mg/dL	Alert	16	20.50%
≥160 mg/dL	Dangerous	6	7.70%
Total		78	100%
Trigliserida Cholesterol Level			
< 200 mg/dL	Optimal	54	69.20%
200 – 399 mg/dL	Alert	20	25.60%
≥400 mg/dL	Dangerous	4	5%
Total		78	100%

The lipid profile consists of high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides. Table III shows HDL levels in COVID-19 patients.

HDL values in COVID-19 patients are divided into 3 categories, namely dangerous, alert, and optimal. The percentage of COVID-19 patients in the dangerous HDL category is 41.1%, the alert category is 28.2%, and the optimal category is 30.7%. The category with the highest number of patients was in patients who had HDL values 35 mg/dL. LDL values can be seen in Table III.

LDL values in COVID-19 patients are divided into 3 categories, namely optimal, alert, and dangerous. The percentage of COVID-19 patients with the optimal LDL category is 71.8%, the alert category is 20.5%, and the dangerous category is 7.7%. The category with the highest number of patients was in patients who had LDL values < 130 mg/dL. The results of the frequency

distribution for triglycerides can be seen in Table III.

Most of the triglyceride values in COVID-19 patients were in the optimal category at 69.2%, in the alert category at 25.6%, and in the dangerous category at 5%. The lipid profile was further analyzed in both living/recovering COVID-19 patients and deceased patients. Table IV shows the value of D-dimer with HDL levels in living COVID-19 patients.

The distribution of patients in Table IV shows that there are 47 COVID-19 patients living or recovering. Living patients who had normal D-Dimer values (less than 0.5 ug/ml) were 40.42%, while 59.58% of patients had high

Table IV: Distribution of Patients Based on D-Dimer Values with Category HDL Levels in Living COVID-19 Patients

D-Dimer value	HDL Value			Total	Percentage
	Optimal	Alert	Dangerous		
<0.5 ug/ml	12	5	2	19	40.42%
≥0.5 ug/ml	11	7	10	28	59.58%
Total				47	100%

D-Dimer values (more than equal to 0.5 ug/ml). HDL values are categorized into 3 groups, namely optimal, alert, and dangerous.

In the case of patients with increased D-dimer values (more than equal to 0.5 ug/ml), the optimal HDL levels were 11 patients, the alert category was 7 patients, and the danger category was 10 patients. Patients who have normal D-Dimer values have HDL values with the least danger category as many as 2 patients, followed by the alert category with 5 patients, and the optimal category with 12 patients. The distribution of COVID-19 patients who died in terms of HDL levels is shown in Table V.

The distribution of patients in Table V shows that 31 COVID-19 patients died. Patients who died and had normal D-Dimer values (less than 0.5 ug/ml) were 3.23%, while 96.77% of patients had high D-Dimer values (more than equal to 0.5 ug/ml).

In the case of patients who died with normal D-dimer values, HDL levels were only found in the danger category, which is 1 patient. Meanwhile, patients who died with high D-dimer values had HDL levels in the danger category as many as 18 patients, in the alert category as many as 10 patients, and in the optimal category as many as 2 patients.

Table V: Distribution of Patients Based on D-Dimer Values by Category HDL Levels in Covid-19 Patients who Died

D-Dimer Value	HDL Value			Total	Percentage
	Optimal	Alert	Dangerous		
<0.5 ug/ml	0	0	1	1	3.23%
≥0.5 ug/ml	2	10	18	30	96.77
Total				31	100%

In this study the correlation between D-Dimer with HDL, LDL, and Triglyceride values is using Pearson correlation

Table VI: Pearson Correlation Analysis between D-Dimer Values with HDL, LDL, and Triglycerides

	HDL	LDL	Triglyceride
D-Dimer	0.255	0.065	-0.172
P-value	0.024	0.571	0.133

analysis. The results of the Pearson correlation test on HDL, LDL, and Triglyceride values can be seen in Table VI.

Pearson correlation analysis showed that there was a correlation between D-Dimer values and HDL levels. This is indicated by the P-value less than 0.025, which is 0.024. Unlike the case with the correlation of D-dimer with LDL and Triglycerides. Pearson correlation analysis on D-dimer with LDL and Triglycerides showed that the two variables had no correlation. The P-value on the LDL value shows the number 0.571 which means that there is no correlation between the two variables. Likewise for the correlation of D-dimer with Triglycerides, the correlation analysis of -17.2% is not significant because the P-value is less than 0.025.

HDL levels in COVID-19 patients are known to be very closely related to D-dimer. The causal analysis between the two variables in this study used simple linear regression analysis. Table VII shows the results of the regression analysis on both variables.

The results of the simple linear regression analysis in Table VII show the regression equation

HDL=33.841+2.107 D-Dimer (1)

The regression model in equation (1) interprets the HDL value as 33,841 mg/dL when there is no increase in the D-dimer value (D-dimer = 0). HDL value will increase by 35,947 when the value of D-dimer increases by 1 ug/ml. The regression model formed has a coefficient of determination (R square) of 6.5%. The coefficient of determination in the regression analysis shows how much the HDL variable is explained by the D-dimer variable. In addition, the coefficient of determination also interprets how well the regression line formed from the regression model is.

DISCUSSION

Based on patient data distribution, patient in the age

Table VII: Simple Linear Regression Analysis

Model	Regression Coefficient	*P-Value*
(Constant)	33.841	0.000
D-Dimer	2.107	0.024

range of 50-69 years is 76.92% (60 patients), patients with age less than 50 years is 12.82% (10 patients), and age more than 70 years is 10.25% (8 patients). In previous meta-analysis concerning the odds of severe COVID-19 associated with D-dimer greater than 0.5 µg/ml. Conversely a D-dimer value less than 0.5 µg/mL is usually considered normal, and values increase with increasing age. The explanation for the increasing levels of D-dimer in the elderly is uncertain. An intriguing hypothesis is that the rising levels of D-dimer with aging is due to a mild pro-inflammatory state and increasing levels of co-morbidities

Elevated D-dimer was independently associated with total cholesterol, total triglyceride and BMI which are components of the metabolic syndrome. In the previous study, age was also found to be an independent factor extensively associated with lipid levels in both sexes when adjusted for serum glucose, body mass index, lifestyle, drinking and smoking (14), but in this study we did not look at these factors.

The distribution of increased D-dimer values in this study sample was found in 74% of the sample (58 patients), while samples with normal D-dimer values were 26% (20 patients). The average distribution of HDL values in this study sample was included in the category of dangerous HDL values (≤ 35 mg/dl) as many as 32 patients, and only 24 patients were in the category of optimal HDL values (≥ 45 mg/dL).

Data on the distribution of respondents based on D-dimer values with HDL values in COVID-19 patients showed that most of the COVID-19 patients who died was in conditions of increased D-dimer values (≥0.5 ug/ml) in as many as 18 patients and with lower HDL levels (≤ 35 mg/dl). These data are consistent with a previous study conducted by Long et al. (15) that high D-dimer values were associated with the severity of symptoms and poor prognosis in COVID-19 patients.

On the other hand, most of the surviving COVID-19 patients had low D-dimer values (<0.5 ug/ml) and 12 patients with optimal HDL values (≥45 mg/dl). Interestingly, in 11 living patients, the D-dimer values increased (≥0.5 ug/ml), but HDL levels were in the optimal category. From these findings, it can be concluded that an increased D-dimer value is not a major predictor of mortality in COVID-19 patients. HDL values also seem to affect the mortality rate in COVID-19 patients at the Petrokimia Gresik Hospital. This finding is in line with the research conducted by Jose et al which showed that in COVID-19 patients with high HDL-C values, it is associated with a low mortality rate (16).

There are several possible explanations for aberrant lipid levels in COVID-19 patients. First, it may result from a liver injury. Although liver functions only exhibit mild abnormalities in protein synthesis, whether lipid biogenesis has been impaired is yet to be determined. Second, viral infection induced proinflammatory cytokines modulate lipid metabolism including oxidation of LDL by reactive oxygen species singling to facilitate LDL clearance. A measurement of oxidized LDL in patient's serum will aid in determining this mechanism. Third, COVID-19 patients may have an increased vascular permeability caused by viral-induced inflammation. Exudates have been found evidently in the early phase of COVID-19 lung pathology. Exudative fluids, containing high levels of protein and cholesterol, are caused by inflammation related vascular permeability (17), which may be one possible mechanism underlying our data.

Corona virus disease or currently better known as COVID-19 is an RNA virus that can cause Severe Acute Respiratory Illness (SARS) symptoms. COVID-19 infection can cause clinical manifestations such as severe pneumonia, sepsis, septic shock, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome (MODS), and systemic coagulation disorders (coagulopathy) such as disseminated intravascular coagulation (DIC) (6,7).

COVID-19 infection occurs when the viral S protein binds to the ACE2 receptor on the endothelium of blood vessels (18). The aggregation of COVID-19 virus in the lungs causes disruption of alveolar epithelial and endothelial cells. This process occurs simultaneously with the infiltrating activity of inflammatory cells that initiates the production of proinflammatory cytokines (IL-1, IL-6, and TNFα, etc.) as the body's defense mechanism against infection (19).

Excessive inflammation will initiate coagulation through the extrinsic pathway. In COVID-19 patients who experience coagulopathy (DIC) there is an imbalance between coagulation and fibrinolysis (20). In which when there is hypercoagulation and thrombosis the body compensates by increasing the fibrinolysis process which will cause D-dimer levels to increase in the blood as a product of fibrin degradation. If this coagulopathy condition is not treated immediately, there will be excessive thrombus blockage in the blood vessels resulting in organ failure.

Lipoproteins are known to be involved and play a role in the process of thrombosis and fibrinolysis. Low density lipoprotein (LDL) pro-atherogenic lipoproteins are associated with an increased risk of thrombosis. In contrast, many epidemiological studies have shown an inverse correlation between HDL levels and the risk of thrombosis (21).

From the results of this study, it was found that the value of D-dimer was positively correlated with the value of HDL lipids which was statistically proven with a significant value of P<0.05. If there is an increase of 1

unit of D-dimer it will increase the HDL value by 33.84.

Based on the results of this study, we suspect that in the acute inflammatory phase of COVID-19 infection (less than 7 days), the body's efforts to compensate by increasing plasma HDL levels in the blood. The results of this study are in line with Fernandes et al. (22) findings in 2021 which showed that in acute inflammatory conditions, there is an adaptive role of the immune system that inhibits the activity of cholesteryl ester transfer protein (CETP), thus affecting lipid metabolism in the body, especially HDL lipoproteins. Plasma HDL concentrations will be maintained to remain high as an anti-inflammatory agent (23).

The results of Helena's research are also supported by Feingold's findings in 2019 which showed that during the process of inflammation and acute infection, pro-inflammatory cytokines will decrease the activity of CETP (cholesterol ester transerin protein), which will cause a decrease in cholesterol shift from HDL to Apo B containing lipoproteins (24).

In addition, in COVID-19 virus infection, there is an increase in the activity of pro-inflammatory cytokines which will disrupt the physiological processes of lipid metabolism. One of the most widely used mechanisms currently is the disruption of cholesterol synthesis in the liver, thereby inhibiting the absorption of lipids in the intestine and the synthesis of ApoA1 which then causes changes in HDL concentrations in the blood (25). A previous study showed that in a group of COVID-19 patients who had just been hospitalized (<7 days) IL-26 levels were positively correlated with ceramide lipid levels in the blood. Ceramide itself is a sphingolipid family found in HDL lipoproteins (26).

The results of research from van der Stoep et al. (21) showed that HDL-C levels and HDL size correlated with D-dimer levels as a product of fibrin degradation. Increased levels of HDL-C will reduce the risk of thrombotic events by initiating the formation of plasmin and the process of fibrinolysis. In addition, increased HDL-C levels are associated with increased fibrin clot permeability and accelerated fibrin clot breakdown time. HDL-C levels and HDL size are inversely proportional to the levels of plasminogen activator inhibitor (PAI-I), tPA inhibitor (tissue plasminogen activator) and uPA (urokinase plasminogen activator), so that the fibrinolysis process can occur properly (21).

Our study has limitations. Additional important markers of inflammation such as IL-6 and Creactive protein levels were not available at the time of this analysis. Ideally, future analyses should include a broad panel of inflammatory markers to verify the hypothesis that the D-dimer value associated pro-inflammatory state is also associated with up-regulation of coagulation and fibrinolysis. Major limitation of our study is selection bias because of its retrospective study. Only patients admitted to the hospital were included in the study. Some otherwise eligible cases also had to be excluded due to incomplete laboratory tests and medical records, specifically D-dimer and Trygliceride, LDL, HDL on admission. Time from disease onset to hospital admission may affect D-dimer and lipid values but we did not evaluate these points because we had limited data.

CONCLUSION

There is a statistically significant correlation between D-dimer values and HDL lipid levels in COVID-19 patients who were hospitalized for less than 7 days at Petrokimia Gresik Hospital. If there is an increase of 1 unit in the value of D-dimer, it will increase the HDL value by 33.84. This study still has weaknesses, so that in the next research we recommend to measure the correlation of D-dimer and HDL values in acute infection of the COVID-19 with a larger sample and needed to see serial HDL levels in the first 7 days of patients COVID-19 being hospitalized. Moreover we needed to see the activity of cholesteryl ester transfer protein (CETP) on HDL values in acute infection of COVID-19.

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