International Journal of Research and Review
Vol. 10; Issue: 8; August 2023
Website: www.ijrrjournal.com
Original Research Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

The Correlation between D-Dimer/Fibrinogen Ratio with the Severity of COVID-19 in Coronary Heart Disease Patients with Confirmed COVID-19 at H. Adam Malik General Hospital in 2021

Refli Hasan[1], Hadhinah Rasiqah Nasution[2], Naomi Niari Dalimunthe[3]

[1,3]Staff of Internal Department, Faculty of Medicine, Sumatera Utara University / Haji Adam Malik General Hospital, Medan, Indonesia
[2]Resident of Internal Department, Faculty of Medicine, Sumatera Utara University / Haji Adam Malik General Hospital, Medan, Indonesia

Corresponding Author: Refli Hasan

DOI: https://doi.org/10.52403/ijrr.20230848

ABSTRACT

Background: COVID-19 is a pandemic caused by SARS-CoV-2 and which became a worldwide pandemic. The virus enters and forms the bonds between the spike protein on the surface of the virus and the angiotensin-converting enzyme 2 (ACE2) receptor in the lungs, heart, kidneys, blood vessels. Cardiovascular diseases such as coronary heart disease (CHD) can exacerbate the severity of COVID-19 by triggering excessive inflammatory and coagulation responses. D-dimer/fibrinogen ratio (DFR) has been proven to be significant in assessing thrombosis. In several studies, DFR examination was considered more accurate than using D-dimer or fibrinogen examination alone.
Aim: To determine the correlation between the DFR value and the severity of COVID-19 in CHD patients with COVID-19 at H. Adam Malik General Hospital.
Method: This is a cross sectional study. The samples are the patients who are treated in isolation room at H. Adam Malik General Hospital who meet the inclusion and exclusion criteria. To analyze the correlation between the DFR value and the severity of COVID-19 in CHD patients with COVID-19 at H. Adam Malik General Hospital we conducted the chi-square test.
Results: From 39 samples, there is a significant correlation between the DFR value and the severity of COVID-19 in CHD patients with COVID-19 at H. Adam Malik General Hospital (p=0.0001).
Conclusion: There is a significant correlation between the DFR value and the severity of COVID-19 in CHD patients with COVID-19 at H. Adam Malik General Hospital.

Keywords: DFR, The severity of COVID-19, CHD, D-dimer, Fibrinogen

INTRODUCTION

Coronary heart disease (CHD) is a cardiovascular disease caused by atherosclerosis in the coronary arteries which causes 17.9 million deaths each year [1]. Atherosclerosis is caused by the accumulation of lipids which triggers inflammation and thrombosis which eventually causes narrowing of the lumen of the coronary arteries [2]. Coronary atherosclerosis remains to be the perpetrator of decreasing oxygen in the myocardium which leads to myocardial infarction and death [3].
COVID-19 is a pandemic caused by SARS-CoV-2 infection. A number of new cases and deaths have been reported to be increased daily [4,5]. The virus can be spread by droplets or aerosols. The spike protein on the surface of the virus binds to

the angiotensin-converting-enzyme 2 (ACE2) receptor after the protein is activated by a transmembrane protease serine. The ACE2 receptor is mostly found in the lungs, heart, kidney and blood vessels. The infection begins with the virus binding to the ACE2 receptor in the lung which is the port d'entrée of the infection and causes pneumonia. COVID-19 has been found to be the culprit of high morbidity and mortality worldwide. The higher severity degree of the diseases is mostly found in people with immunocompromised, especially in people with comorbid including cardiovascular disease [6,7]. The virus can trigger pro-inflammatory molecules, oxidative stress agents and pro-thrombotic agents and lead to the disruption of endothelial function which stimulates sympathetic nerve and increase vasomotility, coronary artery spasm and the coagulation markers [8,9].

D-dimer is a degradation product of cross-linked fibrin which increased in the presence of thrombotic events and circulating throughout the body [10]. Fibrinogen is a coagulation factor which is secreted by the hepatocyte and plays a role in the coagulation process [11]. D-dimer and fibrinogen were found to be increased in infection including COVID-19 and cardiovascular disease including CHD as the results of inflammation process which leads to coagulation and thrombotic events [4, 12,13]. Together, the increase of D-dimer and Fibrinogen can indicate the presence of thrombotic events [9]. In a few studies, D-dimer/fibrinogen ratio proven to be significantly useful in treating patients with thrombotic disease like deep vein thrombosis, pulmonary embolism [14]. Nonetheless, a few studies reported fibrinogen testing alone is not significant in evaluating coagulopathy in COVID-19 patients and must be combined with D-dimer testing too [12,13].

MATERIALS & METHODS

This research is analytical research with a cross sectional approach. The research is conducted using medical records from CHD patients with COVID-19 from January until December 2021.The minimal number of samples in this study is 39 people with inclusion criteria are patients CHD or with history of CHD, age >18 years, patients without history of CHD but clinical appearance with ECG and/or cardiac biomarkers supports the diagnosis of CHD, COVID-19 patients with confirmed by antigen swab or polymerase chain reaction (PCR) testing. Exclusion criteria in this study were patients with incomplete medical records, patients with myocardial infarction, cerebral infarction, deep vein thrombosis, pulmonary embolism.

The occlusion of coronary artery is determined by ECG findings showing elevated ST segment for total occlusion and depressed ST segment for partial occlusion. The severity of COVID-19 is classified based on COVID-19 guidelines by The Indonesian ministry of Health which includes the assessment of clinical manifestations, respiration rate, SpO2 and the requirement of mechanical ventilation or vasopressor. D-dimer, fibrinogen and DFR value are considered to be increased if the values are higher than 500ng/mL; 400mg/dL; 0,61, respectively [15].

STATISTICAL ANALYSIS

Bivariate analysis is conducted to assess the correlation between the D-dimer/fibrinogen ratio with the severity of COVID-19 using the chi-square test. The analytical test result is determined to be significant if $p<0.05$.

RESULT

There are 39 research subjects which meet the inclusion and exclusion criteria in this study.

Table 1. Characteristics of research subjects

Variables	Frequency (n)	Percentage (%)
Gender		
Male	35	89,7%

Female	4	10,3%
Age (years)		
Mean ± SD	57,49 ±10,49	
20 – 29	1	2,6%
30 – 39	1	2,6%
40 – 49	3	7,7%
50 – 59	19	48,7%
60 – 69	12	30,8%
70 – 79	2	5,1%
80 – 89	1	2,6%
Comorbid		
None	5	12,8%
Hypertension	22	56,4%
Type 2 DM	8	20,5%
Hypertension and type 2 DM	4	10,3%
ECG findings		
Depressed ST segment	18	46,2%
Elevated ST segment	21	53,8%
Severity of COVID-19		
Moderate	16	41,0%
Severe	23	59,0%
D – dimer		
Normal	8	20,5%
Increase	31	79,5%
Fibrinogen		
Normal	10	43,6%
Increase	29	51,3%
DFR		
Normal	15	38,5%
Increase	24	61,5%
Total	39	100%

Based on **table 1**, there are 35 males (89,7%) and 4 females (10,3%). The range of age is dominated by 19 samples who are in the range of age between 50-59 years. The average of the research sample's ages is 57,49 ±10,49. Comorbid in this research is dominated by hypertension in 22 samples (56,4%). The severity of COVID-19 was mostly found to be severe in 23 samples (59,0%). D-dimer, fibrinogen and DFR were mostly found to be increased in 31 (79,5%); 29 (51,3%) and 24 (61,5%) in number of samples respectively.

Table 2. Laboratory results

Parameters	Minimum	Maximum	Mean	Total
D-dimer	232	4000	996,95	16 (41%)
Fibrinogen	150	2680	559,20	23 (59%)
DFR	0,11	11,56	2,37	39

In **table 2**, the average values of D-dimer, fibrinogen and DFR are increased and aligned with the results from **table 1**. The rest of the minimum and maximum values for each laboratory finding can be seen in **table 2.**

Table 3. Crosstabulation of DFR with Degree of COVID-19 severity

Degree of COVID-19 severity	DFR		Total
	Normal	Increased	
Moderate	13 (81,25%)	3 (18,75%)	16 (41%)
Severe	2 (8,7%)	21 (91,3%)	23 (59%)
Total	15 (38,5%)	24 (61,5%)	39

Table 3 showed from 16 samples in moderate category, most of the patients which are 13 samples (81,25%) have normal value of DFR. Otherwise, patients with the severe category which are 21 samples (91,3%) mostly have an increased value of DFR.

Table 4. Laboratory results per Degree of COVID-19 severity

Degree of COVID-19 severity	Mean		
	D-dimer	Fibrinogen	DFR
Moderate	523,63	742,07	0,75
Severe	1958,26	528,00	4,40

From **table 4**, we can conclude both moderate and severe COVID-19 have increased number of D-dimer, fibrinogen and DFR with the average values of each marker are 523,63; 742,07; 0,75 and 1958,26; 528,00; 4,40 respectively.

Table 5. Crosstabulation of D-dimer with ECG findings			
ECG findings	**D-Dimer**		**Total**
	Normal	**Increased**	
Elevated ST segment	4 (19,0%)	17 (80,95%)	21(53,8%)
Depressed ST segment	4 (22,22%)	14 (77,78%)	18(46,2%)
Total	8 (20,5%)	31 (79,5%)	39

Table 5 showed, the majority of both the elevated and depressed ST segment group of patients are have increase value of D-dimer with the number of samples are 17(80,95%) ;14(77,78%) samples, respectively. Table 6 showed the majority of both ECG findings groups have increased number of fibrinogens too.

Table 6. Crosstabulation of Fibrinogen with ECG findings			
ECG findings	**Fibrinogen**		**Total**
	Normal	**Increased**	
Elevated ST segment	5 (23,8%)	16 (76,19%)	21 (53,8%)
Depressed ST segment	5 (27,78%)	13 (72,22%)	18 (46,2%)
Total	10 (43,6%)	29 (51,3%)	39

Analytical test result is showed in **table 7.** From the table, we can conclude there is a significant correlation between DFR with the degree of COVID-19 severity (p<0,05).

Table 7. Crosstabulation of DFR with Degree of COVID-19 severity		
	DFR	**p**
	Value	
Degree of COVID-19 severity	20,986	0,0001*

***Chi-square test**

DISCUSSION

From the results above, most of the patients were male. Most studies showed the domination of gender in their studies were male [16,17]. According to the Association of Indonesian Cardiologists, age and males are the risk factors for CHD [18]. Along with our research results, the majority of the samples were old with the average of sample's age is 57,49 years old.

Comorbid is a factor that affects the severity of disease. Hypertension and type 2 DM still remain to be major risk factor and can be modified in cardiovascular disease. From this study, hypertension was found in the majority of the sample. But there are also 4 samples with both type 2 DM and hypertension. Guan *et al*., found that comorbids could affect COVID-19 and exacerbate the severity of COVID-19. Poor clinical outcome was mostly found in the samples with comorbids. The more comorbid, the poorer clinical outcome would be [16]. Type 2 DM and hypertension stimulates endothelial disfunction and lead to the accumulation of lipid and forms atherosclerosis. Also, these diseases contribute in destroying the plaque. Ruptured plaque stimulates pro-inflammatory molecules, induce coagulation pathway and thrombotic event. Eventually, the coronary vessels become narrowed and the oxygen cannot enter the myocardium adequately. On the other hand, hypertension stimulates the heart to pump even harder and makes the oxygen demand increase. These two combinations of mechanisms induce myocardial infarction [3,18].

In this study, both the elevated and depressed ST segment group of patients had increased value of D- dimer and fibrinogen. Elevated ST segment can denote a total occlusion in coronary artery disease. Meanwhile, depressed ST segment can indicate a partial occlusion. Most of the patients in this study have elevated ST segment or total occluded coronary artery. We can conclude that patients with total and partial occluded coronary artery have elevated coagulation markers. Han *et al*., found increased fibrinogen is correlated with severity of coronary stenosis which is determined by using Gensini score [13].

The majority of the samples are diagnosed with severe COVID-19. Zhang *et al*., found that from 140 patients with COVID-19 in Wuhan, the majority of the cases are severe COVID-19 [19]. Another study was conducted by Liu *et al*., showed in 30 healthcare workers in Jianghan University Hospital, China there is about 87% of the samples were severe COVID-19 cases [12].

D-dimer and fibrinogen were also found to be higher in both moderate and severe COVID-19. The average of D-dimer, fibrinogen in this study were 996,9ng/mL and 559,2mg/dL respectively. We can conclude, the average of parameters is

above the baseline. Based on a study conducted by Liu *et al*., D-dimer is found to be higher in patients with severe than mild COVID-19 (with p<0,001). Also, elevated fibrinogen levels upon admission is considered correlated with poor outcome [12]. Sui *et al*., reported elevations in fibrinogen upon admission were significantly associated with disease severity and ICU admission in COVID-19 patients [20]. Fibrinogen plays a role as a biomarker in COVID-19 disease, as it is associated with both inflammation and coagulopathy [13]. Fibrinogen levels can be raised in critically ill COVID-19 patients. In the late stages, the thrombolysis lowers the level of Fibrinogen and increases fibrin-degradation products. D-dimer is one of the fibrin-degradation products (FDP). Raised D-dimer values contributed to poor prognosis and high mortality in COVID-19 with venous thromboembolic patients [21]. Another study by Tang *et al*., showed the laboratory parameter between survivors and non-survivors COVID-19. the non-survivors COVID-19 patients had significantly higher D-dimer and FDP levels, and longer prothrombin (PT) compared to survivors on admission [22]. COVID-19 is a systemic infection with significant impact on the coagulation system that often manifests in thrombotic complications and coagulopathy. There are some studies reported both D-dimer and fibrinogen are associated with the prognosis of the disease [20,23]. The raise of D-dimer is mostly found in patients with COVID-19 and it is more likely associated with inflammation than venous thromboembolism [24,25].

The average of DFR value was 2,37. We can see from the table 1 and 2, it can be concluded that the DFR was raised in most of the sample in this study. DFR baseline of 0,61 is considered have sensitivity and specificity for predicting the prognosis of coagulopathy [15]. Assessing the D-dimer, fibrinogen and DFR can be useful to detect coagulopathy and determine the prognosis of the disease. A combination of 2 or more coagulation parameters is better than only assessing 1 parameter. Zhang *et al*, showed statistically, the significancy of DFR using area under curve (AUC) value remains to be superior than using D-dimer or fibrinogen alone [26]. Murat *et al*., found heart failure (HF) patients diagnosed with COVID-19 have higher DFR value at admission and patients with history of HF diagnosed with COVID-19 have DFR at admission is associated with poorer outcomes [15]. Zhang *et al*., showed DFR value in COVID-19 with myocardial infarction is higher in the survivor than the non-survivor (0,4 vs 0,12, p<0,001) [19]. Bai *et al*., conducted a study using patients that performed percutaneous coronary intervention (PCI) and measured the DFR value pre and post PCI. It was found the DFR value is decreased post-PCI. The decrease of DFR value in this study remarks that there is a decrease in the coagulation process on patients post intervention [27]. Another study showed DFR is higher in patients with pulmonary embolism. Patients with the risk of pulmonary embolism tend to have a higher DFR value than without the risk [28]. A relationship is found between cardiovascular disease and infections [29,30]. Viral respiratory infection can raise the risk of myocardial infarction and other CVD. Higher mortality risk was found in patients with underlying CVD [31]. Hypoxemia in COVID-19 patients causes vasoconstriction, inflammation and thrombosis. CHD can be caused by atherosclerosis and leads to inflammation, narrowing lumen of the vessels and myocardial infarction. Hypercoagulation caused by inflammation can exacerbate the clinical outcomes and prognosis of the patients [32].

CONCLUSION

There is a significant correlation between the DFR value and the severity of COVID-19 in CHD patients with COVID-19 at H. Adam Malik General Hospital.

Declaration by Authors

Ethical Approval: Approved

Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Wang, M. (ed.) (2020) *coronary artery disease: Therapeutics and Drug Discovery*, *Advances in Experimental Medicine and Biology*. Singapore: Springer Singapore. Available at: http://link.springer.com/10.1007/978- 981-15-2517-9%0Ahttp://www.springer.com/series/5584.
2. World Health Organization (2021) *cardiovascular diseases (CVDs)*. Available at: https://www.who.int/news- room/fact-sheets/detail/cardiovascular-diseases-(cvds) (Accessed: 10 January 2023).
3. Lilly, L. S. (2016) *Pathophysiology of Heart Disease Fifth Edition*. 6th edn, *Havard Medical School*. 6th edn
4. Huang, C. *et al.* (2020) 'Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China', *The Lancet*, 395(10223), pp. 497– 506. doi: 10.1016/S0140-6736(20)30183-5
5. Yonas, E. *et al.* (2021) 'Effect of heart failure on the outcome of COVID- 19 — A meta-analysis and systematic review', *The American Journal of Emergency Medicine*, 46, pp. 204–211. doi: 10.1016/j.ajem.2020.07.009.
6. Madjid, M. *et al.* (2020) 'Potential Effects of Coronaviruses on the Cardiovascular System', *JAMA Cardiology*, 5(7), p. 831. doi: 10.1001/jamacardio.2020.1286.
7. Zheng, Y.-Y. *et al.* (2020) 'COVID-19 and the cardiovascular system', *Nature Reviews Cardiology*, 17(5), pp. 259–260. doi: 10.1038/s41569- 020-0360-5.
8. Esposito, L. *et al.* (2021) 'COVID-19 and Acute Coronary Syndromes: From Pathophysiology to Clinical Perspectives', *Oxidative Medicine and Cellular Longevity*, 2021. doi: 10.1155/2021/4936571
9. Yang, J. *et al.* (2020) 'Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta- analysis', *International Journal of Infectious Diseases*, 94, pp. 91–95. doi: 10.1016/j.ijid.2020.03.017
10. Kikkert, W. J. *et al.* (2014) 'D-dimer levels predict ischemic and hemorrhagic outcomes after acute myocardial infarction: A HORIZONS- AMI biomarker substudy', *Journal of Thrombosis and Thrombolysis*, 37(2), pp. 155–164. doi: 10.1007/s11239-013-0953-5.
11. Buljubasic, N. *et al.* (2017) 'Fibrinogen in relation to degree and composition of coronary plaque on intravascular ultrasound in patients undergoing coronary angiography', *coronary artery disease*, 28(1), pp. 23– 32. doi: 10.1097/MCA.0000000000000442.
12. Hayıroğlu, M. İ., Çınar, T. and Tekkeşin, A. İ. (2020) 'Fibrinogen and D- dimer variances and anticoagulation recommendations in COVID-19: current literature review', *Revista da Associação Médica Brasileira*, 66(6), pp. 842–848. doi: 10.1590/1806-9282.66.6.842.
13. Han, H. *et al.* (2020) 'Prominent changes in blood coagulation of patients with SARS-CoV-2 infection', *Clinical Chemistry and Laboratory Medicine (CCLM)*, 58(7), pp. 1116–1120. doi: 10.1515/cclm-2020-0188
14. Hajsadeghi, S. *et al.* (2012) 'Accuracy of D-dimer: fibrinogen ratio to diagnose pulmonary thromboembolism in patients admitted to intensive care units: cardiovascular topic', *Cardiovascular Journal of Africa*, 23(8), pp. 446–456. doi: 10.5830/CVJA-2012-041.
15. Murat, S. *et al.* (2021) 'Prognostic value of D-dimer/fibrinogen ratio on in-hospital outcomes of patients with heart failure and COVID-19', *Biomarkers in Medicine*, 15(16), pp. 1519–1528. doi: 10.2217/bmm-2021- 0341.
16. Guan, W. *et al.* (2020) 'Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis', *European Respiratory Journal*, 55(5), p. 2000547. doi: 10.1183/13993003.00547-2020.
17. Zeymer, U. *et al.* (2022) 'Effects of the COVID-19 pandemic on acute coronary syndromes in Germany during the first wave: the COVID-19 collateral damage study', *Clinical Research in Cardiology*, 112(4), pp. 539–549. doi: 10.1007/s00392-022-02082-3.
18. Perki (2018) *Pedoman Tatalaksana Sindrom Koroner Akut*. 4th edn. doi: 10.5694/j.1326-5377. 2007.tb01292. x.
19. Zhang, J. jin *et al.* (2020) 'Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China', *Allergy:*

European Journal of Allergy and Clinical Immunology, 75(7), pp. 1730–1741. doi: 10.1111/all.14238
20. Sui, J. et al. (2021) 'Elevated Plasma Fibrinogen Is Associated with Excessive In fl ammation and Disease Severity in COVID-19 Patients', 11(August), pp. 1–7. doi: 10.3389/fcimb.2021.734005
21. Eljilany, I. and Elzouki, A. N. (2020) 'D-dimer, fibrinogen, and il-6 in covid-19 patients with suspected venous thromboembolism: A narrative review', Vascular Health and Risk Management, 16, pp. 455–462. doi: 10.2147/VHRM.S280962.
22. Tang, N. et al. (2020) 'Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia', Journal of Thrombosis and Haemostasis, 18(4), pp. 844–847. doi: 10.1111/jth.14768.
23. Nemec, H. M. et al. (2022) 'Correlation of D-dimer and Outcomes in COVID-19 Patients', American Surgeon, 88(9), pp. 2115–2118. doi: 10.1177/00031348221091940
24. Wang D, Hu B, Hu C et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus- infected pneumonia in Wuhan, China. JAMA 323(11), 1061–1069 (2020).
25. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J. Thromb. Thrombolysis doi:10.1007/s11239-020-02105-8 (2020)
26. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV2 and non-SARS-CoV2. J. Thromb. Thrombolysis doi:10.1007/s11239-020-02105-8 (2020)
27. Zhang, L. et al. (2022) 'Prognostic value of D-dimer to fibrinogen ratio for patients with acute myocardial infarction', European Journal of Inflammation, 20. doi: 10.1177/1721727X221132381
28. Bai, Y., Zheng, Y. Y., et al. (2020) 'D-Dimer to Fibrinogen Ratio as a Novel Prognostic Marker in Patients After Undergoing Percutaneous Coronary Intervention: A Retrospective Cohort Study', Clinical and Applied Thrombosis/Hemostasis, 26. doi: 10.1177/1076029620948586.
29. Corrales-Medina VF, Alvarez KN, Weissfeld LA, Angus DC, Chirinos JA, Chang C-CH, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. JAMA. 2015;313(3):264- 74.
30. Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, et al. Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. Eur Heart J. 2007;28(10):1205-10
31. Dhainaut J-F, Claessens Y-E, Janes J, Nelson DR. Underlying Disorders and Their Impact on the Host Response to Infection. Clinical Infectious Diseases. 2005;41(Supplement_7):S481-S9.
32. Kara, H. et al. (2014) 'D-dimer and D-dimer/fibrinogen ratio in predicting pulmonary embolism in patients evaluated in a hospital emergency department', Acta Clinica Belgica, 69(4), pp. 240–245. doi: 10.1179/2295333714Y .0000000029

How to cite this article: Refli Hasan, Hadhinah Rasiqah Nasution, Naomi Niari Dalimunthe. The correlation between D-dimer/fibrinogen ratio with the severity of COVID-19 in coronary heart disease patients with confirmed COVID-19 at H. Adam Malik General Hospital in 2021. *International Journal of Research and Review*. 2023; 10(8): 403-409.
DOI: *https://doi.org/10.52403/ijrr.20230848*

******