Acta Medical and Health Sciences, 2(2): 81-87 (2023)

Advance Access Publication Date: October 2023
DOI : 10.35990/amhs.v2n2.p81-87

ORIGINAL ARTICLE

Relationship between D-dimer level and severity in COVID-19 cases at Dustira Hospital

Rini Roslaeni[1*], Eka N Nawangsih[2], Tristy Judarisa[3]

1) Department of Clinical Pathology, Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi, Indonesia.
2) Department of Microbiology, Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi, Indonesia.
3) Medicine Study Program, Faculty of Medicine, Universitas Jenderal Achmad Yani, Cimahi, Indonesia.

*Corresponding author. E-mail: rini.roslaeni@lecture.unjani.ac.id

ABSTRACT

Coronavirus Disease-2019 (COVID-19) is an emerging disease with clinical symptoms similar to severe pneumonia. It is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). COVID-19 encompasses various degrees of severity, including mild, moderate, severe, and critical. One of the supporting tests used to detect COVID-19 is the D-dimer test. This cross-sectional study aims to investigate the relationship between D-dimer levels and the severity of COVID-19. The study was conducted at Dustira Hospital in West Java, Indonesia, from September 2022 to January 2023. D-dimer examination utilizes the Sysmex CS-2500 instrument, with a reference value of <0.5 mg/L. A sample of 42 patients was selected using the purposive sampling technique. The results revealed that the majority of confirmed COVID-19 cases were female (59.5%), with the highest proportion in the age groups of 41-50 years and 51-60 years (33.3%). Among the patients, 52.4% had moderate severity, and 64.3% had increased D-dimer levels. The average D-dimer levels in patients with moderate, severe, and critical symptoms were 0.97 mg/L, 2.33 mg/L, and 4.35 mg/L, respectively. The data were analyzed using the Kruskal-Wallis test, which indicated a significant difference in D-dimer levels based on the severity of COVID-19 (p=0.0001). Elevated D-dimer levels occur as a result of SARS-CoV-2 infection, which triggers an exaggerated inflammatory response leading to a cytokine storm. This, in turn, causes endothelial cell dysfunction and stimulates an excessive immune response, resulting in immune cells attacking healthy tissue. The severity of symptoms worsens as the D-dimer level increases.

Keyword: COVID-19, degree of severity, D-dimer level, predictor, prognosis

Received: 2023-06-12, Revised: 2023-08-07 Accepted: 2023-10-20, Published: 2023-10-31.

How to cite :
Roslaeni, R., Nawangsih, E. K., and Judarisa, T. (2023) "Relationship between D-dimer level and severity in COVID-19 cases at Dustira Hospital", Acta Medical and Health Sciences, 2(2).p81–87. doi: 10.35990/amhs.v2n2.p81-87

INTRODUCTION

COVID-19, or coronavirus disease 2019, is a newly discovered disease that was first identified in December 2019 in Wuhan, China. It shares clinical symptoms similar to severe pneumonia and is caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). The infection rapidly spread across countries and was declared a pandemic by the World Health Organization (WHO) on March 11st, 2020.[1,2,3] Data from the Ministry of Health of the Republic of Indonesia indicates a significant increase in confirmed COVID-19 cases during the period of July - October 2021.[4] Based on its clinical manifestations, COVID-19 can be classified into five different levels of disease severity. These levels include asymptomatic cases, mild cases without evidence of viral pneumonia or hypoxia, moderate cases with clinical symptoms of pneumonia but no signs of severe pneumonia, severe cases with clinical signs of pneumonia and additional respiratory distress symptoms, and lastly, critical cases with symptoms of acute respiratory distress syndrome (ARDS), sepsis, or other conditions requiring advanced medical interventions such as mechanical ventilation or vasopressor therapy.[5] This study will focus more on cases with moderate, severe, and critical manifestations since patients with asymptomatic and mild cases were not hospitalized and their D-dimer levels were not examined.

D-dimer examination is a supportive laboratory test that aids the diagnosis of COVID-19. It is used to assess coagulation disorders and monitor the occurrence of severe symptoms associated with COVID-19, as well as to determine the prognosis of the patient.[6,7] The elevation of D-dimer levels in COVID-19 is attributed to a cytokine storm and both local and systemic inflammatory responses. These processes contribute to a state of hypercoagulability, endothelial dysfunction, and the activation of endothelial cells (ECs), platelets, and monocytes. Consequently, this can lead to the development of macro-thrombosis (venous and arterial thromboembolism) as well as micro-thrombosis (microangiopathy and multi-organ failure). Such thrombotic events can give rise to complications, such as pulmonary embolism and acute respiratory distress syndrome (ARDS) in patients with COVID-19 patients.[7] Various studies have found the utility and significance of D-dimer in determining the prognosis and predicting the severity of COVID-19.[8,9] However, there has never been a study that reported D-dimer level at different severity of COVID-19 at Dustira hospital. Therefore based on this background, we aim to investigate the correlation between D-dimer levels and the severity of COVID-19 symptoms at Dustira Hospital, which is one of the COVID-19 referral hospitals in West Java, Indonesia.

METHODS AND SUBJECT

This study is a cross-sectional analytic study that aims to investigate the relationship between D-dimer levels and the severity of COVID-19. Based on the Lemeshow formula, the minimum number of subjects of the study is 38 subjects. The subjects were selected from medical records of patients with confirmed COVID-19 at Dustira Hospital, from July to October 2021. Sampling was conducted using the purposive sampling technique. Inclusion criteria in this study were patients aged 18-60 years with a confirmed diagnosis of COVID-19 by PCR test who underwent D-dimer testing, patients were admitted to Dustira Hospital during the July-October 2021 period, and they were classified as having moderate, severe, or critical severity. We chose to focus on cases with moderate, severe, and critical symptoms because during that period, there were a high number of COVID-19 cases, so hospitals had to limit inpatient care and D-dimer testing only for those with moderate, severe, and critical symptoms.

D-dimer examination at Dustira Hospital utilizes the Sysmex CS-2500 instrument, which operates based on the Transmitted Light Detection Method. The reagent used is Innovance D-dimer, with a reference value of <0.5 mg/L FEU (Fibrinogen Equivalent Unit).

Data analysis for this study used univariate and bivariate analysis. Univariate analysis on the patient's D-dimer level was presented in the mean value, while the severity of COVID-19 was presented in the percentage for categorical data. Bivariate analysis was used to determine the relationship between D-dimer levels and the severity of COVID-19. The statistical analysis was carried out with the Kruskal-Wallis and the Post Hoc Mann-Whitney tests using SPSS Statistics for Windows version 26.

We maintain the confidentiality of patient's identity and other data from medical records as a form of application of autonomy and beneficence. This study has been granted an ethical clearance from Dustira Hospital with number: Ethics.RSD/003/1/2023 on January 5, 2023.[10]

RESULTS AND DISCUSSION

From the collected data, a total of 42 subjects who met the inclusion criteria were included in the study. The characteristics of the subjects in this study included age, sex, D-dimer levels, and the severity of COVID-19.

Table 1. The Subjects' characteristics based on Sex and Age

Characteristics	Frequency (N)	Percent (%)
Age (Years old)		
18-30	6	14,3
31-40	8	19,0
41-50	14	33,3
51-60	14	33,3
Sex		
Male	17	40,5
Female	25	59,5

According to Table 1, the majority of patients with confirmed COVID-19 fell within the age groups of 41-50 years and 51-60 years, accounting for 14 patients (33.3%). This finding is consistent with a report from the Centers for Disease Control and Prevention (CDC), which indicates that between November 2022 and April 2023, the 40-50 age group had the highest number of confirmed COVID-19 cases.[11] In the elderly population, there is a presence of biological dysfunction in multiple organ systems, which greatly affects the health status of this population. Aging is also associated with an increased vulnerability to chronic health problems that tend to accumulate and become comorbidities when they are infected with COVID-19.[12] Liu et al. found that older COVID-19 patients have lower lymphocyte counts compared to younger patients. This is believed to influence the occurrence of COVID-19 in older individuals. Although the underlying mechanisms between age, lymphocyte counts, and severity of COVID-19 are still not fully understood, low lymphocyte levels can be a key mechanism for the severity of COVID-19 in the elderly.[13]

The sex data based on Table 1 indicates that the majority of confirmed COVID-19 patients are female, with a total of 25 patients (59.5%). These findings are consistent with a study conducted by Kurnianto et al. which suggested that females might be more vulnerable to COVID-19 infection due to several factors such as frequent handshakes, larger social gatherings, and less adherence to maintaining one meter distance.[14] Meanwhile, Khaerunnisa et al. stated that females are more vulnerable to stress when dealing with something new and easily experience anxiety, which makes them to be more likely to be infected.[15]

Table 2. Distribution of D-dimer levels to the degree of severity of COVID-19

Degree of severity	D-dimer (mg/L)		Total
	Normal	Increased	
Moderate	12 (54,5%)	10 (45,5%)	22 (100,0%)
Severe	3 (25,0%)	9 (75,0%)	12 (100,0%)
Critical	0 (0,0%)	8 (100,0%)	8 (100,0%)

Based on Table 2, the highest number of subjects was observed in the moderate severity group, with 22 subjects. Among these 22 subjects, 10 (45.5%) experienced an increase in D-dimer levels. On the other hand, a higher percentage of subjects with severe and critical severity showed an increase in D-dimer levels, with 100% of subjects in the critical group experiencing an increase in D-dimer levels.

Berger et al.'s studies described that patients with severe degrees of COVID-19 showed an abnormal coagulation function, where increased D-dimer levels were observed.[16,17] Berger et al. showed that patients with D-dimer levels > 2000 ng/dl (normal limit 230 ng/ml) had the highest risk of experiencing critical illness (36,9%), thrombosis (36,9%), and acute kidney injury (58,7%).[16] Furthermore, hypercoagulation and an increase in D-dimer as a response to prothrombotic phenomena were reported to be consistent findings in confirmed COVID-19 patients with severe illness. High D-dimer indicates thrombosis, pulmonary embolism, and hemorrhage.[18,19]

Data processing in this study used Shapiro-Wilk analysis for the normality test since the sample size was less than 50. The p-value was < 0,0001, indicating that the data were not normally distributed. Therefore, the statistical tests used were Kruskal-Wallis, followed by the Post Hoc Mann-Whitney test, as shown in Tables 3 and 4.

Table 3. D-dimer Levels in Relation to the Severity of COVID-19

Degree of severity	N	D-Dimer (mg/L) Mean	St. Deviation	P-Value
Moderate	22	0,97	1,49	
Severe	12	2,33	1,44	0,0001
Critical	8	4,35	0,64	

Based on Table 3, the mean D-dimer level o the patients in the moderate severity group was 0.97±1.49 mg/L, in the severe group it was 2.33±1.44 mg/L, and in the critical group it was 4.35 ± 0.64 mg/L. These results were then subjected to statistical tests and obtained a value of p = 0.0001, so at 5% alpha, it can be concluded that there are significant differences in D-dimer levels in the three degrees of severity of COVID-19.

Table 4. Mann Whitney Post Hoc Test Result

Degree of severity	P-Value	
Moderate vs severe	0,04	Significant difference
Moderate vs critical	0,0001	Significant difference
Severe vs critical	0,02	Significant difference

Table 4 presents the results of the Mann-Whitney Post Hoc test, indicating the significant differences between the patient groups with different severity levels. The comparison between the moderate-severity group and the severe-severity group, as well as the moderate-severity group and the critical-severity group, showed significant differences. Additionally, the comparison between the severe-severity group and the critical-severity group also revealed a significant difference. These findings suggest that there are distinct variations in D-dimer levels among patients with different severity levels of COVID-19.

The results obtained are in line with research previously conducted by Yao et al., in 2020, with a case-control study designed to assess the ability of D-dimer levels as a predictor of disease course and COVID-19 disease outcomes. The study found that D-dimer levels > 2.0 mg/L obtained at the time of hospitalization were associated with a 10-fold increase in the risk of death, as evidenced by assessing the D-dimer levels of patients who died, who had significantly higher D-dimer levels than patients who recovered, with a ratio of 6.21 mg/L and 1.92 mg/L. Research conducted by Yao et al. also stated that D-dimer levels above 2.14 mg/L can be used as a predictor of mortality in COVID-19 patients with a sensitivity of 88.2% and a specificity of 71.3%.8 The research conducted by Yao et al. found that the D-dimer level of the patients in the moderate-severity group was 2.33 mg/L and in the severe group was 4.35 mg/L, which is consistent with the results of our own study. Therefore, it is necessary to give special attention in handling COVID-19 patients with D-dimer levels > 2 mg/L, as they are predicted to have a higher mortality rate.

D-dimer levels can be used as a mortality predictor for COVID-19 patients, because the SARS-CoV2 virus infects human cells when the S protein binds to the ACE-2 receptor on the plasma membrane. The virus then replicates and forms new virions that cause endothelial cell damage. When there is an exaggerated inflammatory response that stimulates the release of inflammatory mediators, it causes a cytokine storm that is exacerbated by endothelial damage, increasing the activation of the coagulation system.[9] When a cytokine storm is formed, the immune system is overactive, and immune cells attack healthy tissues, which can damage lung function and cause dyspnea to acute respiratory failure. Such a condition causes an increase in D-dimer levels, which explains why coagulopathy is commonly found in COVID-19 patients classified in the severe group. Symptoms that arise can include coagulation

disorders, where a prothrombotic state will be produced, and an increase in venous thromboembolism (VTE), which manifest as deep vein thrombosis (DVT) or pulmonary embolism, which can eventually block the patient's blood vessels and cause shortness of breath and death.[9,20]

According to the findings of this study, D-dimer levels in COVID-19 cases play a crucial role in patient management. Since moderate, severe, and critical symptoms indicate increased D-dimer levels, it is essential for COVID-19 patients with moderate, severe, and critical symptoms to undergo D-dimer testing, as it can serve as a reference for doctors in providing appropriate treatment such as anticoagulant therapy. This can help prevent worsening symptoms and mortality in patients at an earlier stage.

CONCLUSION

The D-dimer level in the critical severity COVID-19 cases was the highest compared to the moderate and severe severity cases. The highest mean value of the D-dimer level was in critical severity (4.35 mg/dL). There was a significant difference in the D-dimer levels in the severity group of COVID-19 with a p-value = 0.0001.

ACKNOWLEDGEMENTS

The author expresses gratitude to the Faculty of Medicine, Universitas Jenderal Achmad Yani. Special gratitude to Dustira Hospital, which has given permission to the author to collect research data.

DECLARATION OF INTERESTS

The authors declare that there is no conflict of interest involved in this research article.

REFERENCES

1. World Health Organization. WHO Official COVID-19 Info [Internet]. 2022 [cited 2022 Jul 17]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019
2. Magdalena, Sugiri Y jane, Tantular R, Listyoko A. Karakteristik Klinis Pasien COVID-19 di Rumah Sakit Dr. Saiful Anwar, Malang. J Respirologi Indones. 2021;41(1):7–14.
3. Susilo A, Rumende CM, Pitoyo CW, Santoso WD, Yulianti M, Herikurniawan H, et al. Coronavirus Disease 2019: Tinjauan Literatur Terkini. J Penyakit Dalam Indones. 2020;7(1):45–67.
4. Kemenkes RI. Peta Sebaran Transmisi Lokal dan Wilayah Terkonfirmasi [Internet]. [cited 2022 Jul 18]. Available from: https://infeksiemerging.kemkes.go.id/dashboard/covid-19
5. Burhan E, Susanto AD, Nasution SA, Eka G, Pitoyo ceva W, Susilo A, et al. Pedoman Tatalaksana Covid-19. 4th ed. Pedoman tatalaksana COVID-19 edisi 4. jakarta; 2022. 1–10 p.
6. Willim HA, Hardigaloeh AT, Supit AI. Koagulopati pada Coronavirus Disease -2019 (COVID-19): Tinjauan pustaka. Intisari Sains Medis. 2020;11(3):749–56.
7. Akbar MNA, Rahardjo AM, Parti DD, Sakinah elly nurus. Analisis Hubungan NLR, D-dimer dan Saturasi Oksigen dengan Derajat Keparahan COVID-19 di RSU Kaliwates Jember. J Agromedicine Med Sci. 2022;8(1):51–5.
8. Yao Y, Cao J, Wang Q, Shi Q, Liu K, Luo Z, et al. D-dimer as a biomarker for disease severity and mortality in COVID-19 patients: a case control study. J intensive care. 2020;8(49):2–11.
9. Nemec HM, Ferenczy A, Iii BDC, Ashley DW, Montgomery A. Correlation of D-dimer and Outcomes in COVID-19 Patients. Am Surg. 2022;88:2115–8.

10. Afandi D. Kaidah dasar bioetika dalam pengambilan keputusan klinis yang etis. Majalah Kedokteran Andalas. 2017;40(2):111–21.
11. Centers for Disease Control and Prevention. Provisional COVID-19 Deaths by Sex and Age. 2023.
12. Neves MT, de Matos LV, Vasques AC, Sousa IE, Ferreira I, Peres S, et al. COVID-19 and aging: Identifying measures of severity. SAGE Open Med. 2021;9:1–6.
13. Liu Y, Mao B, Liang S, Yang JW, Lu HW, Chai YH, et al. Association between age and clinical characteristics and outcomes of COVID-19. Eur Respir J. 2020 Apr;55(5).
14. Kurnianto E, Putra DH, Fannya P, Dewi DR. Tinjauan karakteristik pasien dengan kasus positif COVID-19 di Puskesmas Kecamatan Matraman. Indones Heal Inf Manag J. 2021;9(2):102–8.
15. Khaerunnisa R, Rumana NA, Yulia N, Fannya P. Gambaran Karakteristik Pasien Covid-19 di Rumah Sakit Mekar Sari Bekasi Tahun 2020-2021. J Manaj Inf Kesehat Indones. 2022;10(1):72.
16. Berger JS, Kunichoff D, Adhikari S, Ahuja T, Amoroso N, Aphinyanaphongs Y, et al. Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19. 2020;(October):2539–47.
17. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J Thromb Haemost. 2020;18(4):844–7.
18. Roslaeni R. Telaah Pustaka: D-Dimer Pada Pasien COVID-19. Med Kartika. 2022;5(3):332–42.
19. Atmaja KS, Wicaksana AAGOS, Putra IWAS, Putra WWS. Hubungan konsentrasi serum C-Reactive Protein dan D-dimer dengan derajat keparahan dan mortalitas pasien COVID-19. Intisari Sains Medis. 2021;12(2):680.
20. Ardiani S, Tursinawati Y, Wahab Z. Hubungan D-Dimer dengan Ketahanan Hidup Pasien Covid-19 Derajat Berat - Kritis di RSUD Tugurejo Semarang. Heal Med J. 2022;5(1):44–9.