ORIGINAL ARTICLE

Association Between Serum D-dimer Levels and COVID-19 Severity Among Vaccinated and Non-vaccinated Individuals

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ABSTRACT

Introduction: Coagulopathy is commonly seen with coronavirus disease (COVID-19). Abnormal coagulation parameters are important to determine the prognosis and severity of the disease. There is scant evidence of coagulation in the Omicron variant of COVID-19. This study aimed to analyse the correlation between D-dimer level and clinical severity among 284 hospitalised patients with COVID in Jakarta, Indonesia. **Methods:** A retrospective cross-sectional study was conducted among 284 patients with COVID-19 admitted to Wisma Atlet Kemayoran COVID-19 Emergency Hospital between August 2021 and January 2022. D-dimer levels were determined on I-Chroma cs2100 and x-rays were taken with a Rotanode E7239X. $p<0.05$ was defined as statistically significant. The analytics were calculated using SPSS ver. 21. **Results:** Elevated D-dimer was discovered in 175 patients with the Omicron variant of COVID-19 (61.61%). Radiological signs of pneumonia were found in 38 patients (13.3%). Only one patient (0.35% severity rate) was diagnosed with a severe clinical case. A correlation was identified between an elevated D-dimer level and radiological signs of pneumonia in the Omicron variant of COVID-19 ($p=0.045$). **Conclusion:** The Omicron variant of COVID-19 tends to generate milder symptoms and less severe cases. Elevated D-dimer can be one of the signs of severity in the Omicron variant of COVID-19 due to its correlation with radiological signs of pneumonia.

Keywords: COVID-19, D-dimer, Omicron, Coagulopathy, Vaccination

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INTRODUCTION

Coronavirus disease (COVID-19) was first identified in Wuhan, China, in December 2019 and was declared a pandemic by WHO on March 11, 2020 (1, 2). It has become a global health threat with an increasing number of deaths linked to COVID-19 reported (3). As of January 25, 2022, the global tally of COVID-19 cases stood at 354,769,092, with 5,621,989 deaths (4). Indonesia has recorded the highest number of confirmed positive COVID-19 cases and deaths in South East Asia, second only in Asia to India (5). Indonesia's totals stand at 4,289,305 positive COVID-19 cases and 144,227 deaths. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of COVID-19, has undergone various mutations since the outbreak of the pandemic (6, 7). The latest variant of concern is the Omicron variant (B.1.1.529); this mutation is considered to lead to greater transmission, higher viral binding affinity, and higher antibody release compared to previous variants (8-10).

Coagulopathy is considered the leading cause of death in COVID-19 cases. Microvascular thrombosis has been identified in autopsies from COVID-19 patients. Clinical pictures of coagulopathy in patients with COVID-19 indicate an increase in D-dimer, fibrinogen, and platelet count, prolongation of PT, and APTT. Tang et al.'s research with 183 patients infected with SARS-CoV-2 showed an increase in D-dimer in 71.4% of the patients who died with Disseminated intravascular coagulation (DIC) (11-12). Several other studies have indicated D-dimer levels, fibrin degradation product (FDP) levels, prothrombin

time (PT) and activated partial thromboplastin time (aPTT) as parameters to identify patients at high risk for Venous thromboembolism (VTE) and predict disease severity. The evolution of COVID-19 is associated with the severity and mortality of the disease. Therefore, the early detection of COVID-19 patients with an elevation of these parameters is important to reduce mortality (12). Vaccination plays an important role in reducing mortality and morbidity. There has thus been a rapid intensification of vaccination in Indonesia to vaccinate all members of the population at risk, especially the elderly. In Indonesia, the majority of the population has received a second dose of vaccination and is awaiting a booster vaccination. Mohammed et al. found that vaccination reduces both the morbidity and mortality rate (15).

MATERIALS AND METHODS

Study Population

This study included 284 patients confirmed as having the Omicron variant of COVID-19 at Wisma Atlet Kemayoran COVID-19 Emergency Hospital during the period August 2021–January 2022. Blood samples were first taken before any medical intervention. Diagnosis of SARS-CoV-2 Omicron was carried out by whole genome sequencing. Chest radiographs were taken at the hospital. Medical records, including radiology and haematology test results, were tested using Chi-square from SPSS ver.21. A correlation in this study was identified as significant if it was less than 0.05.

Sample Collection And Analysis

A retrospective cross-sectional study was conducted among 284 patients with COVID-19 admitted to Wisma Atlet Kemayoran COVID-19 Emergency Hospital between August 2021 and January 2022. D-dimer levels were determined using an I-Chroma cs2100 and x-rays were taken with a Rotanode E7239X. Identification of the Omicron variant was referred to a centralised laboratory for gene sequencing.

Ethical Consideration

Ethical clearance was obtained and approved by the COVID-19 Emergency Hospital Kemayoran [Reference No: 039/KERSDCWA/2021]. All the personal identifying information and medical records were kept confidential.

Statistical Analysis

The association between D-dimer, COVID-19 severity, age group and gender was tested using Chi-square, with $p<0.05$ defined as statistically significant. We performed data editing, sorting, coding, classification, tabulation, and statistical analyses using IBM SPSS.

RESULTS

A total of 284 patients were diagnosed with the Omicron variant of SARS-CoV-2, comprising 118 male patients (41.8%) and 166 female patients (58.5%). This study included two age categories, namely geriatric patients and non-geriatric patients, with a mean age of 35.96±10.85 years. Of the 284 patients, only one was identified with a severe case of COVID-19. The mean length of stay in this study was 12.77 days. Among the 284 patients, there were 34 with comorbidity. Hypertension with no other comorbidities was identified as the most prevalent, with 26 patients (9.2%). The characteristics and haematological profiles of the patients are presented in Table I and Table II.

Table I: Demographic characteristics of COVID-19 Omicron variant

Variable	Frequency	Percentage
Gender	118	(41.5%)
Male	166	(58.5%)
Female		
Age	278	(96.8%)
Non-geriatric	6	(3.2%)
Geriatric		
Pre-existing Illness	4	1.4%
Diabetes	26	9.2%
Hypertension	2	0.7%
Acute Kidney Injury	2	0.7%
Hypertension and Diabetes		

Table II. Haematological profile of SARS-CoV-2 Omicron variant

Variable	Mean
Haemoglobin	13.99±1.95
Ureum	24.90±8.27
Creatinine	0.82±6.41
SGOT	26.77±17.68
SGPT	31.06±37.44
D-dimer	698.7±760.39

Aside from the D-dimer, there were no other significant findings from the laboratory profile of patients with the Omicron variant of COVID-19. A slight increase in the D-dimer level was observed; however, some cases showed a two- to threefold increase in the D-dimer level from the base level. The association between the severity of the COVID-19 Omicron variant and other parameters is shown in Table III.

In terms of the severity of the Omicron variant of SARS-CoV-2, a total of 246 patients (86.7%) were found to have asymptomatic or mild cases, while 38 patients (13.3%) indicated moderate or severe cases. In this study, there were 4 patients (1.4%) with diabetes, 26 (9.2%) with hypertension, 2 (0.7%) with acute kidney injuries, and 2 patients (0.7%) with diabetes and hypertension. This comorbidity demographic was supported by a public release from Indonesia's Ministry of Health in 2021, which stated that hypertension was the most common comorbidity found in COVID-19 infections (14).

In this study, an association was identified between comorbidity and case severity ($p=0.003$). Observed patients with underlying diseases were suffering from

Table III: Association between severity of COVID-19 Omicron and other parameters

Variable		COVID-19 Severity Cases		p-value
		Asymptomatic-Mild	Moderate-Severe	
Comorbidity	Without	221	28	0.003
	With	25	10	
Age	Non-geriatric	244	34	0.000
	Geriatric	2	4	
Gender	Male	100	18	0.434
	Female	146	20	
Radiological findings of pneumonia	No	145	12	0.002
	Yes	101	26	

hypertension, diabetes, and acute kidney injury. Patients with one or more of these underlying diseases were more likely to develop pneumonia. Similar results were indicated by Mi et al., whose study showed that patients with underlying diseases tend to develop pneumonia, hence the severity of the disease (13).

Pneumonia, which was diagnosed by chest radiographs, was identified in 38 patients (13.3%). This finding correlates with the last postulated theory that the Omicron variant most frequently infects the upper respiratory tract, which means this is the most common site for the inflammatory response. This study showed that an elevated D-dimer level was found in 175 patients (61.6%). A total of 146 patients had mild or asymptomatic cases and 29 patients had moderate or severe cases. During the study, there was no case indicating any clinical deterioration; therefore, moderate and severe cases were often declared by radiological findings. The magnitude of D-dimer levels in the Omicron variant of COVID-19 is presented in Table IV.

Table IV: Magnitude of D-dimer in COVID-19 Omicron variant

Variables		D-dimer level		p-value
		Normal	Elevated	
Age	Non-geriatric	108	170	0.269
	Geriatric	1	5	
Gender	Male	50	68	0.243
	Female	59	107	
Comorbidity	Without	96	153	0.693
	With	13	22	
Pneumonia	No	100	146	0.045
	Yes	9	29	

In this study, both the patients with comorbidity and those without comorbidity had an equal risk of developing pneumonia (p=0.693). This was possible since the population was dominated by non-comorbid patients. These findings differ from those reported by Zhang et al., who stated that comorbidity is a contributory factor to elevated D-dimer findings (17).

This study also identified that an elevated D-dimer level is found not only in geriatric patients with pneumonia but also in geriatric patients without pneumonia (p=0.121). Patients younger than 30 years of age had a similar risk of developing elevated D-dimer levels (p=0.269) as geriatric patients. This was due to the fact that the geriatric patient sample in this study was not normally distributed. The data for geriatric magnitude to an elevated D-dimer are shown in Table V.

Table V: Geriatric magnitude to elevated D-dimer

Variable		Elevated D-dimer level		p-value
		No	Yes	
Geriatric	Without pneumonia	1	1	0.121
	Pneumonia	0	4	

This study also assessed the vaccination status of patients infected with the Omicron variant of COVID-19. It was discovered that even with a full dose of vaccination, the risk of developing pneumonia was similar to patients that were not fully vaccinated (p=0.666). However, patients with a full dose of vaccination are unlikely to develop severe cases of COVID-19 with the Omicron variant (p=0.034). The vaccination status of the patients in this study is presented in Table VI.

Table VI: Vaccination status of COVID-19 Omicron variant

Variable		Vaccination status		p-value
		Not fully vaccinated	Fully vaccinated	
D-dimer level	Non-elevated	18	91	0.537
	elevated	34	141	
COVID severity	Asymptomatic-mild	46	200	0.666
	Moderate-severe	6	32	
COVID severity	Non-severe	51	232	0.034
	Severe	1	0	

DISCUSSION

The present study identified more non-geriatric than geriatric patients. This was due to an increase in the number of Indonesian migrant workers of productive age admitted to the hospital during the study period. The Omicron variant cases were associated with milder severity as it has been proposed that such infections occur more frequently in the upper than the lower respiratory tract. ACE-II receptors are postulated to be the entry point for infection and are more common in the lower respiratory tract; therefore, the inflammatory response in the Omicron variant of SARS-CoV-2 is milder than in the other variants (9).

Elevated D-dimer level in patients with COVID-19 is associated with disease mortality (16). A study by Tang et al. in Wuhan postulated that four factors have a direct impact on case mortality, namely D-dimer levels, fibrin degradation product (FDP) levels, prothrombin time (PT) and activated partial thromboplastin time (aPTT) (11). Zhang et al. (17) also reported that D-dimer is among the parameters to predict mortality in COVID-19. They found that D-dimer predicts mortality with a sensitivity of 92.3% and a specificity of 83.3%. Their study also

found that a four-fold increase in D-dimer level can lead to a high mortality rate in hospitalised COVID-19 cases (17). This study shows an association between elevated D-dimer levels and the occurrence of pneumonia in COVID-19 patients with the Omicron variant (p=0.045). In this study, only one severe case of COVID-19 was identified. This corresponds to another study by Barek et al., which stated that the Omicron variant results in a milder infection compared to the Delta variant (18).

Geriatric patients are at elevated risk of developing pneumonia (96.8%). This study also correlates with another study in which geriatric patients were identified to be more likely to develop moderate or severe cases of COVID-19 (p=0.000). There, similar results were reported, whereby age was described as one of the risk factors in developing more severe cases (18).

Vaccination status is relevant in preventing the development of severe cases of COVID-19. In this study, only one patient had a severe case; it was discovered that the patient in question was not fully vaccinated, or more specifically not vaccinated. Even after receiving treatment in the facility, the patient still required a transfer to a higher-level facility due to the limitations in the emergency hospital. Fully vaccinated patients have been found not to develop clinical deterioration during the hospitalisation period, despite the development of elevated D-dimer and pneumonia. The study findings correlate with those reported by Mohammed et al., who concluded that vaccination reduces the morbidity and mortality rates of COVID-19 (15).

This study was limited to a single institution. The collected samples were not normally distributed, especially regarding comorbidity, while the population age was dominated by non-geriatric patients. Further research is therefore needed to address the limitations of this study in multicentered institutions with a normal distribution of certain variables.

CONCLUSION

The Omicron variant of COVID-19 tends to generate milder symptoms and less severe cases. Comorbidity and old age are risk factors for the development of moderate and severe cases of COVID-19 with the Omicron variant. An elevated D-dimer level is closely associated with the occurrence of pneumonia in COVID-19 patients with the Omicron variant. There is no correlation between vaccination and the occurrence of pneumonia and D-dimer elevation, although it significantly decreases the prevalence of severe cases of COVID-19 in the Omicron variant.

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