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RESEARCH ARTICLE **OPEN ACCESS**

THE RELATIONSHIP BETWEEN LEVEL OF D-DIMER SERUM WITH MORTALITY IN ACUTE STROKE PATIENS WITH COVID-19

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ABSTRACT

Background: COVID-19 has significantly increased morbidity and mortality in Indonesia, particularly at Gambiran General Hospital in Kediri, East Java, following the WHO's pandemic declaration. The global incidence of acute stroke with COVID-19 is 1.4%, presenting varying clinical features from mild to severe outcomes, and even death. The identification of specific biomarkers, such as elevated D-dimer serum levels, is crucial for predicting severe complications in acute stroke patients with COVID-19.
Objective: This study aimed to explore the correlation between elevated levels of mild, moderate, and severe D-dimer serum and mortality in acute stroke patients with COVID-19.
Methods: Conducted as an observational analytical study using a cross-sectional approach, this research utilized secondary data from medical records at Kediri Gambiran General Hospital (March 2020 to June 2023). Inclusion and exclusion criteria were applied to hospitalized patients, categorized based on D-dimer levels: normal, mild, moderate, and severe. Statistical analyses, including the Spearman correlation test and Chi-square correlation test, were employed to assess the relationship between D-dimer levels and total mortality.
Results: Among the 101 enrolled patients, 53 were male (52.48%), with 90 exhibiting elevated D-dimer levels. Out of these, 44 patients died. The Spearman correlation test showed a non-significant value of 0.069 ($p>0.005$). The Chi-square correlation test for mild, moderate, and severe D-dimer levels on total mortality also yielded a non-significant value of 0.878.
Conclusion: This study found no significant relationship between elevated levels of mild, moderate, and severe D-dimer serum and mortality in acute stroke patients with COVID-19 at Gambiran General Hospital.

Keywords: acute stroke; COVID-19; D-dimer serum; mortality

Introduction

Morbidity and Mortality due to COVID-19 increased very sharp in Indonesia since the WHO declared the disease pandemic, including at the Gambiran General Hospital in Kediri East Java. The World Health Organization (WHO) reported that the risk of ischemic stroke in COVID-19 patients is approximately 5% (95% confidence interval [CI] 2.8-8.7) with a mortality rate 3.2-7.8 times higher (about

38%) than the stroke patients without COVID-19.[1,2] The COVID-19 infection increases the risk of ischemic stroke occurrence by several mechanisms, including, activation of coagulation and inflammatory factors reflected on the increased D-dimer level, erythrocyte sedimentation rate, and lactic acid dehydrogenase enzyme, and the decrease in lymphocyte.[1,3]

D-dimer is a biomarker of fibrin formation and degradation that can be measured in whole blood or in plasma. Healthy individuals have low levels of circulating D-dimer, whereas elevated levels are found in conditions associated with thrombosis.[4]

Coagulopathy was reported, and D-dimer elevations were seen in 3.75-68.0% of the COVID-19 patients. D-dimer levels is higher in severe cases and may be used as a prognostic biomarker.[5,6] However, the role of D-dimer in COVID-19 patients has not been fully investigated. The recent findings suggest association between elevated D-dimer level with disease severity and mortality only. Hidayat et al chose D-dimer was as a categorical variable: normal and increased level in his analysis.[1] We stratified elevated D-dimer level by mild, moderate, and severe in this study.

Methods

The research conducted is analytical observational. The design used is a cross-sectional method. The research subjects are all patients of stroke with COVID-19 undergoing inpatient treatment at Gambiran General Hospital, Kediri, East Java who meet the inclusion and exclusion criteria.

The participants in this study consists of all stroke patients with COVID-19 from March 2020 to June 2023. Whereas the sample of this study are acute stroke patients with COVID-19 undergoing inpatient treatment at Gambiran General Hospital, Kediri, East Java who meet the inclusion and exclusion criteria during the period from March 2020 to June 2023. The research sample collection was carried out in the COVID-19 isolation inpatient ward at Gambiran General Hospital, Kediri, East Java on admission. The examination of D-dimer levels was conducted at the clinical pathology laboratory of Gambiran General Hospital, Kediri, East Java on admission. Patients were grouped into D-dimer level of normal (< 0,5 mg/L), mild elevated (< 1 mg/L), moderate elevated (1-2 mg/L), and severe elevated (> 2 mg/L).[5]

Inclusion criteria of this research include stroke patients with COVID-19 who were diagnosed both neurological clinically and non-contrast head CT scan. They are also willing to participate in the study (informed consent). While the exclusion criteria are patients stroke with COVID-19 who did not undergo D-dimer level examination nor non-contrast head CT scan. The samples can be excluded from the study if patients leave the hospital against medical advice.

Data is collected on data collection sheets. Subsequently, the collected data is processed using appropriate statistical tests with SPSS 25.0. The collected basic data was tested for normality using the Kolmogorov Smirnov test, further analyzed using the Spearman correlation test.

Results

The total number of research subjects was 101 individuals, consisting of 53 females (52.48%) and 48 males (47.52%).

Table 1. Characteristics of research subjects based on gender

Gender	Total	
	N	%
Female	53	52.48
Male	48	47.52
Total	101	100.0

The characteristics of research subjects based on blood pressure, 65 hypertensive (64.36%), 4 hypotensive (3.96%), and 32 normotensive (31.68%) participants (Table 1).

Table 2. Characteristics of research subjects based on blood pressure

Blood Pressure	Total	
	N	%
Hypertension	65	64.36
Hypotension	4	3.96
Normotension	32	31.68
Total	101	100.0

The characteristics of research subjects based on white blood cell count consisting of 56 subjects classified as leukocytosis (55.45%), 44 subjects as normal leukocyte count (43.56%), and 1 subject as leukopenia (0.99%) (Table 2).

Table 3. Characteristics of research subjects based on white blood cell count

Leukocyte	Total	
	N	%
Leukocytosis	56	55.45
Leukopenia	1	0.99
Normal	44	43.56
Total	101	100.0

The total number of research subjects was 101 individuals, consisting of 44 subjects who died

comprising 43.56% of the total sample, and 57 subjects who recovered, representing 56.44% of the overall population under study (Table 3).

Table 4. Characteristics of research subjects based on mortality

Morality	Total	
	N	%
Died	44	43.56
Recovered	57	56.44
Total	101	100.0

Based on D-dimer levels and mortality rates, the frequency of subjects who recovered with normal D-dimer levels was 7 individuals (6.94%), the frequency of subjects who died with normal D-dimer levels was 4 individuals (3.96%).

While the frequency of subjects who recovered with mild D-dimer elevation was 14 individuals (13.86%), and the frequency of subjects who died with mild D-dimer elevation was 8 individuals (7.92%).

The frequency of subjects who recovered with moderate D-dimer elevation was 7 individuals (6.93%) whereas the frequency of subjects who died with moderate D-dimer elevation was 6 individuals (5.94%).

The frequency of subjects who recovered with severe D-dimer elevation was 29 individuals (28.71%), and the frequency of subjects who died with severe D-dimer elevation was 26 individuals (25.74%) (Table 2).

Table 5. Details of research subject characteristics based on mortality

D-Dimer in relation to Morality	Total	
	N	%
D-Dimer normal Recovered	7	6.94
D-Dimer normal Diec	4	3.96
D-Dimer mild elevatio Recovered	14	13.86
D-Dimer mild elevatio Died	8	7.92
D-Dimer moderate elevation Recovered	7	6.93
D-Dimer moderate elevation Died	6	5.94
D-Dimer severe elevati Recovered	29	28.71
D-Dimer severe elevati Died	26	25.74
Total	101	100.0

In the correlation test between gender and D-dimer levels, a p-value greater than 0.05 was obtained, specifically 0.111. This result indicates that there is no significant relationship between gender and D-dimer levels. In other words, this finding suggests that gender does not have a meaningful influence on D-dimer levels in the population under study (Table 5).

Table 6. D-dimer Levels in Relation to Gender

D-Dimer Parameter	Gender				Total		p-value
	M		F				
	n	%	n	%	n	%	
Normal	7	6.93	5	4.95	12	11.88	
Mild Elevatio	6	5.94	16	15.84	22	21.78	
Moderate Elevation	5	4.95	8	7.92	13	12.87	0.111
Severe Elevation	30	29.70	24	23.76	54	53.47	
Total	48	47.52	53	52.48	101	100	

In the correlation test between D-dimer levels and blood pressure, a p-value > 0.05 was obtained, specifically 0.173, which means that there is no significant relationship between D-dimer levels and blood pressure (Table 6).

In the correlation test examining the relationship between D-dimer levels and leukocyte counts in patients with COVID-19 who have experienced a stroke, a p-value greater than 0.05 was obtained, specifically 0.460. This statistical result indicates that there is no significant relationship between D-dimer levels and leukocyte counts. In other words, variations in D-dimer levels do not correspond with changes in leukocyte counts among the studied patients.

Additionally, the study included an analysis of the frequency distribution of leukocyte counts among these patients. It was found that a majority of the patients, 56 individuals or 55.45%, were classified as having leukocytosis, which is characterized by an elevated leukocyte count. This suggests that more than half of the COVID-19 stroke patients had higher than normal leukocyte levels.

Conversely, 44 subjects, making up 43.56% of the total sample, had leukocyte counts that were within the normal range. This indicates that a substantial proportion of the patients did not exhibit abnormal leukocyte levels despite their condition.

Moreover, there was 1 subject, representing 0.99% of the total patient population, who was classified as having leukopenia, defined by a lower than normal leukocyte count. This small percentage reflects the rarity of leukopenia among the studied group of COVID-19 stroke patients (Table 7).

Table 7. D-dimer Levels in Relation to Blood Pressure

D-Dimer Parameter	Blood Pressure						Total		p-value
	Hypotension		Normotension		Hypertension				
	n	%	n	%	n	%	n	%	
Normal	0	0,00	1	0.99	11	10.89	12	11.88	
Mild Elevation	0	0,00	6	5.94	16	15.84	22	21.78	
Moderate Elevation	0	0,00	6	5.94	7	6.93	13	12.87	0.173
Severe Elevation	4	3.96	19	18.81	31	30.69	54	53.47	
Total	4	3.96	32	31.68	65	64.36	101	100	

Table 8. D-dimer Levels in Relation to Leukocytes

D-Dimer Parameter	Leukocyte						Total		p-value
	Leukopenia		Normal		Leukocytosis				
	n	%	n	%	n	%	n	%	
Normal	0	0,00	3	2.97	9	8.91	12	11.88	
Mild Elevation	0	0,00	13	12.87	9	8.91	22	21.78	
Moderate Elevation	0	0,00	4	3.96	9	8.91	13	12.87	0.460
Severe Elevation	1	0,99	24	23.76	29	28.71	54	53.47	
Total	1	0,99	44	43.56	56	55.45	101	100	

A normality test was conducted to determine the data distribution from the research results, whether the data distribution is normal or not. The method used to perform the normality test in this study is the Kolmogorov-Smirnov test (Table 8).

Table 9. Results of the normality test

	Kolmogorov-Smirnov		
	Statistic	df	Sig.
D-Dimer Levels	0.161	101	0.000
Morality	0.373	101	0.000

The results of the normality test using the Kolmogorov-Smirnov test have a sig. value <0.05, indicating that the data is not normally distributed. Therefore, the data was further analyzed using the Spearman correlation test (Table 9).

Table 10. Results of the Spearman correlation test

Variable	Sig.(2-Tailed)	Correlation Coefficient	Explanation
D-Dimer Levels Morality	0.069	0.182	Not Significant

In the correlation test between D-dimer levels and the mortality rate, a Sig. value > 0.05 was obtained, specifically 0.069, indicating that there is no significant relationship between D-dimer levels and mortality. Subsequently, a correlation test was also conducted based on the classified increase in D-dimer (Table 10).

Table 11. D-dimer Levels in Relation to Mortality

D-Dimer Parameter	Fatality Rate				Total		p-value
	Recovered		Died				
	n	%	n	%	n	%	
Normal	7	6.93	5	4.95	12	11.88	
Mild Elevatic	14	13.86	8	7.92	22	21.78	
Moderare Elevation	7	6.93	6	5.94	13	12.87	0.878
Severe Elevation	29	28.71	25	24.75	54	53.47	
Total	48	47.52	53	52.48	101	100	

The majority of deceased acute stroke patients with COVID-19 had significantly elevated D-dimer levels, with 25 patients (24.75%). The relationship between D-dimer levels and mortality in acute stroke patients with COVID-19 resulted in a p-value > 0.05, specifically 0.878, indicating that there is no significant relationship between normal D-dimer levels, mild elevation, moderate elevation, significant elevation, and mortality in acute stroke patients with COVID-19 (Table 11).

Discussion

This study is analytical observational research with consecutive sampling technique conducted on patients with acute stroke and COVID-19 admitted to the COVID-19 inpatient ward of Gambiran General Hospital, Kediri, East Java, who met the inclusion and exclusion criteria from March 2020 to June 2023.

In this study, a total of 111 subjects were obtained. Among them, 10 subjects did not meet the inclusion

criteria for the study and were thus included in the exclusion criteria and dropout criteria, consisting of: 7 subjects excluded due to acute stroke patients with COVID-19 who did not undergo D-dimer level examination, and 2 subjects excluded for acute stroke patients with COVID-19 who did not undergo head CT scan without contrast, and 1 subject dropped out due to involuntary discharge. Statistical analysis was conducted using the SPSS 25.0 program. Basic data collected underwent univariate analysis to observe the frequency distribution of each demographic data. Subsequently, chi-square correlation tests were performed as the data were categorical. The subjects in this study consisted of 53 females (52.48%) and 48 males (47.52%). In this study, a p-value of > 0.05 was obtained, i.e., 0.111, indicating no significant relationship between D-dimer levels and gender. This indicates that gender does not affect D-dimer levels in detecting COVID-19 or stroke.[7]

Regarding blood pressure measurement results, the subjects had an average of hypertension. Out of 101 subjects, 65 experienced hypertension (64.36%), 4 subjects experienced hypotension (3.96%), and 32 subjects had normal blood pressure (31.68%). This proves that hypertension is one of the main risk factors in stroke incidence.[8] In this study, a p-value of > 0.05 was obtained, i.e., 0.173, indicating no significant relationship between D-dimer levels and blood pressure. This contradicts Atmaja's 2021 study stating that patients with comorbid hypertension significantly affect the mortality of COVID-19 patients.[9]

An increase in leukocyte count (leukocytosis) is one of the suspicious parameters for severity in COVID-19 patients. In this study, leukocytosis was found in 56 subjects (55.45%), leukopenia in 1 subject (0.99%), and normal leukocyte count in 44 subjects (43.56%). In this study, a p-value of > 0.05 was obtained, i.e., 0.460, indicating no significant relationship between D-dimer levels and leukocyte count increase. This is not in line with the study by Mus et al., which stated that the severity of COVID-19 symptoms is marked by an increase in the leukocyte count.[10] Sabatundung et al. stated that leucocyte count (WBC) the predominance in normal and the amount of leukocytosis is greater than leucopenia.[11]

The study by Another parameter to assess the severity of COVID-19 is the plasma D-dimer level, one of the parameters observed in detecting COVID-19. Based on the D-dimer levels and fatality rates, 57 patients recovered (56.43%), and 44 patients died (43.57%). Before conducting the correlation test, a normality test of the data was performed. The method used to test the data's normality in this study was the Kolmogorov-Smirnov test. The results of the normality test using Kolmogorov-Smirnov had a significant value <0.05, indicating that the data were not normally distributed. Therefore, the data were further analyzed using the Spearman correlation test. In the correlation test between D-dimer levels and mortality rate, a Sig. > 0.05 was obtained, i.e., 0.069, indicating no significant relationship between D-dimer levels and the mortality rate.

Furthermore, a correlation test was also conducted based on the classified D-dimer increase. Based on the D-dimer increase levels and fatality rates, the frequency of deceased subjects with normal D-dimer levels was 4 individuals (3.96%), the frequency of deceased subjects with a slight increase in D-dimer levels was 8 individuals (7.92%), the frequency of recovered subjects with a slight increase in D-dimer levels was 14 individuals (13.86%), the frequency of deceased subjects with a moderate increase in D-dimer levels was 6 individuals (5.94%), the frequency of recovered subjects with a moderate increase in D-dimer levels was 7 individuals (6.93%), the frequency of deceased subjects with a severe increase in D-dimer levels was 26 individuals (25.74%), and the frequency of recovered subjects with a severe increase in D-dimer levels was 29 individuals (28.71%). The high plasma D-dimer levels are related to stroke incidence in subjects. D-dimer levels exceeding normal can trigger hypercoagulation and thrombus formation. This possibility can lead to stroke in COVID-19 patients or worsen symptoms in stroke subjects exacerbated by COVID-19.[12] In this study, a p-value of > 0.05 was obtained, i.e., 0.878, indicating no significant relationship between D-dimer levels and mortality rate. This contradicts the study by Akbar et al., stating that D-dimer is one of the biomarkers that can reduce the mortality rate of COVID-19 patients.[13]

Fridman and his colleagues stated that comorbidity plays an important role in determining the mortality of stroke patients with COVID-19 infection.[14] This was in line with a meta-analysis research conducted by Zheng regarding risk factors related to mortality in COVID-19 patients found several risk factors: age over 65 years, comorbidities such as diabetes, hypertension, cardiovascular disease and respiratory tract disease that significantly influenced mortality in COVID-19 patients.[15] However, we did not assess these factors which could have influenced the results of this study.

The limitations of this study are first, it was done in the single center. Second, this study is retrospective in nature. Third, the patients included were not systematically assessed severity of COVID-19, comorbid, and vaccination status. Fourth, we did not asses the value of serial D-dimer monitoring.

Conclusion

No significant relationship was found between elevated level of mild, moderate and severe D-dimer serum with mortality in acute stroke patients with COVID-19.

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