



D-DIMER SERUM LEVEL ASSOCIATION WITH MORTALITY IN ACUTE STROKE PATIENS WITH COVID-19

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ABSTRACT

Background: Since WHO declared COVID-19 a pandemic, Indonesia, including RSUD Gambiran Kediri, has experienced a sharp increase in morbidity and mortality. The global incidence of acute stroke in COVID-19 patients is 1.4%, with symptoms varying from mild to severe, including death. Elevated serum D-dimer in COVID-19 patients can be a biomarker to predict severe complications.

Objective: This study aims to determine the relationship between elevated serum D-dimer levels (mild, moderate, severe) with mortality in acute stroke patients with COVID-19.

Methods: Observational analytic study with a cross-sectional method using secondary data from medical records of patients admitted to RSUD Gambiran Kediri from March 2020 to June 2023. Patients were categorized based on serum D-dimer levels: normal (<0.5 mg/L), mild (<1 mg/L), moderate (1-2 mg/L), and severe (>2 mg/L).

Results: Of 101 acute stroke patients with COVID-19, 52.48% were male. A total of 90 patients had elevated D-dimer levels, with 44 patients dying. Spearman correlation test and Chi-square test showed no significant association between D-dimer levels and mortality ($p > 0.005$).

Conclusion: There is no association between elevated serum D-dimer levels and mortality in acute stroke patients with COVID-19.

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

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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 (WHO, 2020). 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 (Atmaja *et al.*, 2021; Akbar *et al.*, 2022). 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 (Weitz, Fredenburgh and Eikelboom, 2017). 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, and D-dimer $>1 \mu\text{g/ml}$ is one of the risk factors for mortality in adult in patients with COVID-19 (Yao *et al.*, 2020).

This study adds new insights into the role of D-dimer as a prognostic biomarker in acute stroke patients with COVID-19, specifically focusing on its relationship with mortality. While previous research has established that elevated D-dimer levels are associated with coagulopathy and worse outcomes in COVID-19 patients, the specific relationship between D-dimer levels and mortality in acute stroke patients with COVID-19 remains underexplored (Aditiansih *et al.*, 2023). Most studies have primarily focused on the general population or patients with other comorbidities, but this study targets a specific subset: those with both acute stroke and COVID-19 (Nannoni *et al.*, 2021; Gallo-Guerrero *et al.*, 2022). Previous studies reported that patients with CAD undergoing percutaneous coronary intervention having high D-dimer levels were associated with increased long-term mortality for all causes, heart, and cancer, with hazard ratios indicating a more than threefold risk for the highest D-dimer tertile (Kurosawa *et al.*, 2022). In addition, D-dimer has been correlated with coronary microvascular dysfunction, suggesting its role in ischemic heart disease, where patients with elevated levels show almost double the risk of microvascular problems (Lin *et al.*, 2022). Moreover, in individuals with type 2 diabetes, high D-dimer concentrations are associated with a significantly increased risk of cardiovascular events, reinforcing its potential usefulness in risk stratification (Xing *et al.*, 2021; Cheng *et al.*, 2022).

This research uniquely categorizes D-dimer levels into four groups (normal, mild, moderate, and severe elevation) to better understand its gradation and its direct correlation with mortality risk in this critical patient population. By utilizing a robust dataset from Kediri Gambiran General Hospital, covering a significant period from March 2020 to June 2023, this study contributes to a more nuanced understanding of the predictive value of D-dimer in acute stroke patients with COVID-19, addressing a critical gap in the literature. These findings may potentially inform clinical decision-making and risk stratification for managing this dual pathology, offering new insights for clinicians in similar resource-limited settings.

METHOD

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) (Yao *et al.*, 2020).

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 AND DISCUSSION

Table 1. D-dimer Levels in Relation to Gender

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

The subjects in this study consisted of 53 women (52.48%) and 48 men (47.52%). In this study, a p-value > 0.05 was obtained, namely 0.111, meaning that there was no significant relationship

between the variable serum D-dimer levels and gender. This shows that gender does not affect serum D-dimer levels in the detection of Covid-19 or stroke (Widjaja, Bw and Ks, 2019). Several studies indicate that while the overall D-dimer levels do not significantly differ between males and females in mild COVID-19 cases, there is a correlation between age and D-dimer levels in both genders (Khudhur *et al.*, 2024). In severe COVID-19 cases, a higher prevalence of male patients has been observed, with elevated D-dimer levels correlating with increased mortality (Faltehal and Hapsah, 2023). Additionally, in pneumonia patients, a higher percentage of females were noted, yet D-dimer levels were significantly elevated compared to COVID-19 patients (Anggraini *et al.*, 2023). Overall, while gender may influence the prevalence and outcomes of diseases associated with elevated D-dimer levels, the direct impact of gender on D-dimer values remains inconclusive (Eljamay, Younis and Elgebaily, 2022; Patil, Khule and Toshniwal, 2023).

Table 2. D-dimer Levels in Relation to Blood Pressure

Parameter D-dimer	Tekanan Darah						Total		p-value
	Hypotension		Normotension		Hipertension		n	%	
	n	%	n	%	n	%			
Normal	0	0,00	1	0,99	11	10,89	12	11,88	0.173
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	
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	

In the data from blood pressure measurements, it was found that the average subject had hypertension. A total of 65 subjects experienced hypertension (64.36%), 4 subjects experienced hypotension (3.96%), and 32 subjects were normotensive (31.68%). This proves that hypertension is one of the main risk factors for stroke (Kurikaose, 2020). In this study, the p-value was > 0.05 , namely 0.173, meaning that there was no significant relationship between the variable serum d-dimer levels and blood pressure. This is not in accordance with Atmaja's research in 2021 which stated that patients with comorbid hypertension had a significant influence on the death of Covid-19 sufferers (Atmaja, 2021). D-dimer levels have been shown to correlate significantly with blood pressure and hypertension severity across various studies.

Higher D-dimer concentrations are associated with an increased risk of developing hypertension, with individuals in the top quartile of D-dimer levels exhibiting a 47% higher risk of incident hypertension compared to those in the lowest quartile (Mukaz *et al.*, 2023). Additionally, in hypertensive patients, D-dimer levels were found to rise with the severity of hypertension, indicating a potential role of hypercoagulability in the pathophysiology of hypertension-related complications (Chekol, 2020).

Table 3. 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
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

An increase in the number of leukocytes (leukocytosis) is one of the parameters for suspecting severity in Covid-19 patients. In this study, the results obtained were leukocytosis in patients, namely 56 subjects (55.45%), 1 subject leukopenia (0.99%), and 44 subjects normal (43.56%). In this study, the p-value was > 0.05 , namely 0.460, meaning that there was no significant relationship between the variable serum d-dimer levels and the number of increased leukocytes. This is not in line with research conducted by Mus, et al which states that the severity of Covid-19 symptoms is characterized by an increase in the number of leukocytes (Mus *et al.*, 2021; Tigner, Ibrahim and Murray, 2024).

In the context of COVID-19, a significant correlation was observed between neutrophil-to-lymphocyte ratio (NLR) and D-dimer levels, indicating that elevated D-dimer may reflect increased inflammation and disease severity (Suhesty *et al.*, 2023). Furthermore, in patients with inflammatory conditions, D-dimer levels positively correlated with white blood cell counts and inflammatory markers, while showing a negative correlation with lymphocyte counts (Bao *et al.*, 2017). This suggests that elevated D-dimer levels may serve as a marker of inflammation, potentially linked to leukocyte dynamics in various disease states (Nannoni *et al.*, 2021; Thachil, Favaloro and Lippi, 2022)

Table 4. Total Serum D-Dimer Levels on Mortality Rates for the Period March 2020-January 2024

	Fatality Rate				Total		p-value
	Recovered		Died		n	%	
	n	%	n	%			
D-dimer	57	56.43	44	43.57	101	100	0.450

Another parameter that can be seen in detecting the severity of Covid-19 is the serum D-dimer level, which is one of the parameters seen in detecting Covid-19. Based on serum D-dimer levels and mortality rates, 57 patients recovered (56.43%) and 44 patients died (43.57%). In the correlation test between serum D-dimer levels and mortality, it was found that the p-value was > 0.05 , namely 0.450, meaning that there was no significant relationship between the variable serum D-dimer levels and mortality.

Table 5. Serum D-Dimer Levels on Mortality Rates 2020-2024

D-dimer Parameter	Fatality Rate				Total		p-value
	Recovered		Died		n	%	
	n	%	n	%			
Normal	7	6,93	5	4,95	12	11,88	0.528
Mild Elevation	14	13,86	8	7,92	22	21,78	
Moderate Elevation	7	6,93	6	5,94	13	12,87	
Severe Elevation	29	28,71	25	24,75	54	53,47	
Total	57	56,43	44	43,57	101	100	

Elevated D-dimer levels correlate with increased mortality, particularly in patients experiencing acute ischemic stroke (AIS) related to COVID-19 (Mus *et al.*, 2021). A study indicated that patients with AIS had higher D-dimer levels at admission, with a peak level above 5.15 µg/ml FEU associated with nearly threefold increased mortality risk (Kim *et al.*, 2021; Toker *et al.*, 2022). Conversely, another study found no significant relationship between varying D-dimer levels and mortality in acute stroke patients, suggesting that while D-dimer is a critical marker, its predictive value may vary based on patient characteristics and the severity of the stroke (Tarmidi and Bahrudin, 2024).

High levels of serum D-dimer are associated with the incidence of stroke in subjects. Serum D-dimer levels that exceed normal can trigger hypercoagulation resulting in thrombus formation (Magoon, Jose and Choudhary, 2022). This can allow strokes to occur in Covid-19 sufferers or can allow symptoms to worsen in stroke subjects who are exacerbated by Covid-19 (Kuriakose and Xiao, 2020; Okuyan, 2021). After that, a correlation test was also carried out based on the increase in serum D-dimer levels which had been classified. In this study, the p-value was > 0.05, namely 0.528, meaning there was no significant relationship between the D-dimer level variable and the death rate.

Table. 6 Serum D-Dimer Levels on Mortality Rates per Year

Year	D-dimer Parameter	Fatality Rate				Total		p-value
		Recovered		Died		n	%	
		n	%	n	%			
March - December 2020	Normal	1	5	0	0	1	5	0.196
	Mild Elevation	4	20	2	10	6	30	
	Moderate Elevation	1	5	2	10	3	15	
	Severe Elevation	4	20	6	30	10	50	
	Total	10	50	10	50	20	100	

January- December 2021	Normal	5	11,63	3	6,98	8	18,61	0.816
	Mild Elevation	7	16,28	4	9,30	11	25,58	
	Moderate Elevation	2	4,65	1	2,32	3	6,98	
	Severe Elevation	14	32,55	7	16,28	21	48,83	
	Total	18	65,11	25	34,89	43	100	
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January- December 2022	Normal	1	3,57	2	7,14	3	10,71	0.682
	Mild Elevation	2	7,14	1	3,57	3	10,71	
	Moderate Elevation	2	7,14	3	10,71	5	17,85	
	Severe Elevation	6	21,44	11	39,29	17	60,73	
	Total	11	39,28	17	60,72	28	100	
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January- December 2023	Normal	0	0	0	0	0	0	0.310
	Mild Elevation	0	0	1	14,28	1	14,28	
	Moderate Elevation	2	28,57	0	0	2	28,57	
	Severe Elevation	4	57,14	0	0	4	57,14	
	Total	6	85,71	1	14,28	7	100	
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January 2024	Normal	0	0	0	0	0	0	0.667
	Mild Elevation	1	33,33	0	0	1	33,33	
	Moderate Elevation	0	0	0	0	0	0	
	Severe Elevation	1	33,33	1	33,33	2	66,66	
	Total	2	66,66	1	33,33	3	100	
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This is not in line with research conducted by Akbar et al which said that D-dimer is a biomarker that can reduce the death rate of Covid-19 patients (Akbar *et al.*, 2022). Based on the data taken, the results of statistical analysis showed that there was no significance between mild, moderate

and severe serum D-dimer levels and the death rate of stroke patients with Covid-19 at Gambiran Regional Hospital. So, subjects were stratified on a yearly basis based on changes in basic therapy guidelines from year to year in line with growing knowledge about Covid-19 (Hayiroğlu *et al.*, 2021). The results of the statistical analysis test of the relationship between mild, moderate and high serum d-dimer levels on mortality rates in stroke patients with Covid-19 at Gambiran District Hospital showed p-values in 2020, 2021, 2022, 2023 and 2024 respectively. namely: 0.196, 0.816, 0.682, 0.310, 0.667. Statistically, if $p > 0.05$, it can be interpreted that there is no significant relationship between mild, moderate and severe serum d-dimer levels and mortality rates in stroke patients with Covid-19 at Gambiran Regional Hospital. The results of this study are new results and are not in accordance with research conducted by Akbar et al which reported that serum d-dimer is a biomarker that can reduce the death rate of Covid-19 patients (Akbar *et al.*, 2022).

The limitations of this study are first this research is observational analytic in nature that would be more meaningful if a prospective cohort study was carried out. Second, this research was only conducted in one hospital. Multicenter research needs to be carried out to obtain varied characteristics. Third, the population and sample size is limited, which affects the statistical analysis carried out. Forth, There are confounding factors in the form of comorbidities (diabetes mellitus, chronic kidney disease, congestive heart failure, hepatic cirrhosis, and so on) which were not taken into account in this study and influenced the subject's recovery and death. Fifth, Serum D-dimer levels in each subject were only checked once. Serial checks need to be carried out to obtain more valid data.

CONCLUSION

This study examined the relationship between elevated D-dimer levels and mortality in acute stroke patients with COVID-19, but found no significant correlation. Despite the established role of D-dimer as a biomarker for coagulopathy and its association with poor outcomes in COVID-19 patients, the results of this study suggest that D-dimer alone may not be a reliable predictor of mortality in this specific cohort. The lack of significant findings may be attributed to the complex interplay of multiple factors influencing the outcomes of acute stroke in COVID-19 patients, including the severity of the stroke, comorbidities, and the multifactorial nature of COVID-19-related complications.

While D-dimer remains a useful marker in assessing coagulation abnormalities, it is clear that a more nuanced approach is needed to identify high-risk patients. Future research could expand on the limitations of this study by including larger sample sizes across multiple hospitals or regions, which may increase the statistical power and offer more generalizable conclusions. Additionally, it would be valuable to conduct prospective cohort studies rather than relying on secondary data, as this could provide more controlled insights into the progression of COVID-19 in stroke patients and the dynamics of biomarkers over time. Given the complex pathophysiology of COVID-19 and its impact

on coagulation, a more comprehensive investigation involving a broader panel of biomarkers, such as C-reactive protein (CRP), ferritin, and interleukins, may yield better predictive accuracy for mortality and complications.

In summary, while this study did not find a significant link between D-dimer levels and mortality in acute stroke patients with COVID-19, the findings contribute to a broader understanding of the complexities involved in managing this dual pathology and highlight the necessity for further research in this area.

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