

## RESEARCH ARTICLES

### **Relationship Between Elevated D-Dimer Levels And The Incidence Of Ischemic Stroke In Covid-19 Patients At Drs H. Amri Tambunan Regency, Deli Serdang Regency**

**Dinda Dwi Novani<sup>1</sup>, Anita Surya<sup>2</sup>, Hasanul Arifin<sup>3</sup>, Fani Ade Irma<sup>4</sup>**

<sup>1</sup>Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No. 53, Medan 20217, Indonesia

<sup>2,3</sup>Department of Neurology, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No. 53, Medan 20217, Indonesia

<sup>4</sup>Department of Clinical Pathology, Faculty of Medicine and Health Sciences, Universitas Muhammadiyah Sumatera Utara, Jalan Gedung Arca No. 53, Medan 20217, Indonesia

**Corresponding Email : dindaadwii1234@gmail.com**

**Abstract:** Acute ischemic stroke spreads from infected individuals, whether they are already showing symptoms or not. The initial symptom that often appears in infected individuals is fever, with a body temperature between 38.1 and 39°C. The mechanism of stroke in COVID-19 patients is caused by an increase in D-Dimer and fibrinogen, which are part of the coagulation pathway. Coagulation is related to the systemic inflammatory response caused by infection. The purpose of this study was to understand and further examine the relationship between increased D-Dimer levels in ischemic stroke patients infected with COVID-19 at Drs. H. Amri Tambunan Regional Hospital, Deli Serdang Regency. This research method is a retrospective descriptive study using a cross-sectional research design. This study used secondary data derived from medical records of COVID-19 patients with ischemic stroke events at Drs. H. Amri Tambunan Regional Hospital, Deli Serdang Regency. H. Amri Tambunan, Deli Serdang Regency, 2021. The results of the Chi-square test were 0.239 (P-value >0.05), which means there is no significant relationship between increased D-Dimer and the incidence of ischemic stroke and hemorrhagic stroke in COVID-19 patients. The conclusion obtained was that there was no significant relationship between increased D-Dimer and the risk of ischemic stroke in COVID-19 patients.

**Keywords:** Ischemic stroke, COVID – 19, D-dimer

#### **INTRODUCTION**

Acute ischemic stroke (AIS) has recently become a common cause of death and disability worldwide. Diagnosis of acute

ischemic stroke is difficult because computerized tomography (CT) results may appear normal in the early stages or in

patients with mild symptoms, and magnetic resonance imaging (MRI) is not always possible. Therefore, many eligible cases experience delays in receiving intravenous thrombolysis treatment.<sup>1</sup>

Coronavirus disease (COVID-19) is an infection caused by a virus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). This disease is spread by infected individuals, whether they are already showing symptoms or not. The most common initial symptom in infected individuals is fever, with body temperatures reaching between 38.1 and 39°C.<sup>2,3</sup>

In 2020, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern. During that year, more than 105 countries reported 114,253 cases of COVID-19 and 4,000 deaths. SARS-CoV-2 was first reported in bronchoalveolar lavage fluid samples from three patients at Jinyintan Hospital in Wuhan and was confirmed as the cause of COVID-19 on January 24, 2020.<sup>3</sup> Indonesia declared its first COVID-19 case on March 2, 2020, with both cases identified. Both cases were linked to contact with a Japanese citizen who was then living in Malaysia (Ratcliffe, 2020). Meanwhile, the first COVID-19 death in Indonesia was recorded on March 11, 2020 (Indonesian Ministry of Health, 2020).<sup>4</sup>

The mechanism of stroke in COVID-19 patients is caused by increased D-Dimer and fibrinogen levels, which are part of the coagulation pathway. Coagulation is related to the systemic inflammatory response

caused by infection. This is what causes arterial thrombosis and venous thrombosis with paradoxical embolism in stroke patients. Furthermore, excessive cytokine release in COVID-19 patients indicates uncontrolled immune system activation caused by SARS-CoV infection. Excessive cytokine release can lead to thrombosis, plaque rupture, and endothelial injury.<sup>5,7</sup>

According to previous research by Hilda (2020), of 109 patients analyzed, 14.68% (16 of 109) died within 30 days of COVID-19. Of these, 93.75% (15 of 16) patients had elevated D-Dimer levels greater than 0.63 µg/mL.<sup>6,8</sup>

Previous research has shown that D-dimer levels increase in severe COVID-19 infection. This is likely due to the onset of cerebrovascular disease, including acute ischemic stroke, in COVID-19 patients (Dmytriw et al., 2022; Merkle et al., 2020). Furthermore, COVID-19 can trigger an overreaction of cytokines through increased receptor (ACE 2), leading to hypercoagulation and an increased incidence of vascular thrombosis in COVID-19 patients (Larson et al., 2020).<sup>8,9,10</sup>

Based on this description, it can be seen that several studies have different variables than my own. Therefore, I am interested in conducting this research further regarding the relationship between elevated D-Dimer and the incidence of ischemic stroke in COVID-19 patients with different variables in 2020 at the DRS H. Amri Tambunan Regional Hospital, Deli Serdang Regency.

## METHOD

This is a retrospective descriptive study using a cross-sectional design. It used secondary data from the medical records of COVID-19 patients. The aim was to determine the relationship between elevated D-Dimer levels and the incidence of ischemic stroke at DRS. H. Amri Tambunan Regional General Hospital, Deli Serdang Regency, in 2021.

This study was conducted from July 2023 to August 2024 at H. Amri Tambunan Regional General Hospital, Deli Serdang Regency. The study population consisted of data on elevated D-Dimer levels and the incidence of ischemic stroke in COVID-19 patients recorded in medical records. The study population consisted of confirmed COVID-19 patients treated at H. Amri Tambunan Regional General Hospital, Deli Serdang Regency, in 2021. The sample in this study was drawn using the total sampling method, meaning the sample size equals the patient population. The sample consisted of first-time patients diagnosed with COVID-19 at the H. Amri Tambunan Regional General Hospital, Deli Serdang Regency, in 2021.

This study used secondary data as the data collection technique. In this study, the secondary data used included medical records of COVID-19 patients in 2021 at the H. Amri Tambunan Regional General Hospital, Deli Serdang Regency. The collected data were analyzed in two stages: univariate analysis, which examined one variable at a time, and bivariate analysis, which assessed the relationship between two

variables using the Chi-Square ( $X^2$ ) test. The analysis process was conducted using SPSS. For categorical variables, the results were presented as frequencies and percentages, displayed in graphs and tables. A p-value of less than 0.05 was considered statistically significant, and hypothesis testing was performed to determine the presence of a correlation between variables.

## RESULT

The sample used in this study comprised all patients diagnosed with COVID-19 and complicated by ischemic stroke. The data used were medical records from the Neurology Polyclinic at Drs. H. Amri Tambunan Regional General Hospital, Deli Serdang Regency, from January 2021 to December 2021. A total of 1,669 patients were enrolled, but only 39 met the inclusion criteria.

This study used univariate analysis to analyze the characteristics of ischemic stroke patients at Drs. H. Amri Tambunan Regional General Hospital, Deli Serdang Regency, and bivariate analysis to determine the association between elevated D-Dimer levels and the incidence of ischemic stroke in COVID-19 patients at Drs. H. Amri Tambunan Regional General Hospital, Deli Serdang Regency, from January 2021 to December 2021.

**Table 1. Frequency Distribution of Patient Characteristics Based on Age**

Age (years)	Frequency (n)	Percentage (%)

20 – 30	2	5,1
31 – 40	1	2,6
41 – 50	2	5,1
51 – 60	12	30,8
61 – 70	9	23,1
71 – 80	13	33,3
<b>Total</b>	<b>39</b>	<b>100</b>

Based on table 1, it can be seen that of the 39 COVID-19 sufferers with ischemic stroke and hemorrhagic stroke, the characteristics based on the most age are 71-80 years old with a frequency of 13 sufferers (33.3%), followed by 51-60 years old with a frequency of 12 sufferers (30.8%) and 61-70 years old with a frequency of 9 sufferers (23.1%), followed by 20-30 years old with a frequency of 2 sufferers (5.1%), 41-50 years old with 2 sufferers (5.1%), and 31-40 years old with 1 sufferer (2.6%).

**Table 2. Frequency of Stroke Sufferers Based on Gender**

Types of stroke	Ischemic Stroke		Hemorrhagic Stroke		Total	
	(n)	(%)	(n)	(%)		
Gender	Lk	21	65,6	3	42,9	24
	Pr	11	34,4	4	57,1	15
		<b>32</b>	<b>100</b>	<b>7</b>	<b>100</b>	<b>39</b>

Description: (n): Frequency ; (%): Percentage

Based on Table 2, it can be seen that of the 39 COVID-19 patients with ischemic and hemorrhagic strokes, the most common gender-specific characteristics of ischemic stroke patients were males, with a frequency of 21 (65.6%) and females, with a frequency of 11 (34.4%). Furthermore, hemorrhagic stroke patients were males, with a frequency of 3 (42.9%) and females, with a frequency of 4 (57.1%).

**Table 3. Frequency Distribution of Patient Characteristics Based on Gender**

Gender	Frequency (n)	Percentage(%)
Men	24	61,5
Woman	15	38,5
<b>Total</b>	<b>39</b>	<b>100</b>

Based on table 3, it can be seen that of the 39 COVID-19 sufferers with ischemic stroke and hemorrhagic stroke, the characteristics of sufferers based on gender were mostly male with a frequency of 24 sufferers (61.5%) and female with a frequency of 15 sufferers (38.5%).

**Table 4. Frequency Distribution of Patients Based on D-Dimer Category**

D-dimer	Frequency(n)	Percentage (%)
Normal	19	48,7

Increased	20	51,3
<b>Total</b>	<b>39</b>	<b>100</b>

Based on table 4, it can be seen that the characteristics of patients based on the D-Dimer category are the highest category with a frequency of 20 patients (51.3%) and followed by the normal category with a frequency of 19 patients (48.7%).

**Table 5. Frequency Distribution of Patients Based on the Incidence of Ischemic Stroke**

Stroke	Frequency (n)	Percentage(%)
Ischemic Stroke	32	82,1
Hemorrhagic Stroke	7	17,9
<b>Total</b>	<b>39</b>	<b>100</b>

Table 5 shows that the frequency of ischemic stroke was 32 (82.1%), and the frequency of hemorrhagic stroke was 7 (17.9%).

The study found a correlation between elevated D-Dimer and ischemic stroke in COVID-19 patients at Drs. H. Amri Tambunan Regional Hospital, Deli Serdang Regency, from January 2021 to December 2021, as follows.

**Table 6. The Relationship Between Increased D-Dimer and Ischemic Stroke**

Stroke	D-Dimer			P-value
	Normal	Increased	Total	
Ischemic Stroke	17	15	32	0,239

Hemorrhagic Stroke	2	5	7
<b>Total</b>	<b>19</b>	<b>20</b>	<b>39</b>

Based on table 6, it can be concluded that the Chi-square test result is 0.239 (P-value >0.05), which means that there is no significant relationship between increased D-Dimer and the incidence of ischemic stroke and hemorrhagic stroke in COVID-19 patients.

## DISCUSSION

Based on the results of this study, the number of COVID-19 patients at Drs. H. Amri Tambunan Regional Hospital, Deli Serdang Regency, was 1,669 from January 2021 to December 2021. The sample used in this study was 39 patients with complete medical records and who met the inclusion and exclusion criteria. Sample characteristics were assessed based on age, gender, complications from ischemic stroke, and elevated D-Dimer levels.

It should be noted that of the 39 COVID-19 patients with ischemic and hemorrhagic strokes, the most common gender characteristics were males (21 patients with ischemic stroke (65.6%), and females (11 patients with female stroke (34.4%). Furthermore, hemorrhagic stroke patients were males (3 patients with male stroke, 42.9%), and females (4 patients with female stroke, 57.1%).

It can be seen that of the 39 COVID-19 patients who experienced stroke, the most

common age group was 71-80 years old, with a frequency of 13 sufferers (33.3%). This is inconsistent with research conducted by Huang et al. (2020) which found that the average age of COVID-19 patients was 51 years. According to the Indonesian Ministry of Health, the 46-55 age group has entered the early elderly phase, where long-term health problems and a decline in the immune system are common with age. This makes it more difficult for the elderly to fight infections. Furthermore, the decreased elasticity of lung tissue over time makes respiratory diseases such as COVID-19 a major problem for the elderly.<sup>11 12</sup>

Based on gender characteristics, of the 39 COVID-19 patients who experienced stroke, the most common gender was male, with a frequency of 24 patients (61.5%). This finding aligns with a retrospective cohort study involving 191 patients, in which 59% of the patients who died were male. This is due to the protective effects of estrogen in women, which include increased production of anti-inflammatory cytokines, increased numbers of helper T cells and B cells, and inhibition of pro-inflammatory cytokine release. These abilities may provide women with additional protection from the effects of COVID-19 infection, resulting in a lower mortality rate compared to men.<sup>12 13</sup>

The distribution of patient characteristics by D-Dimer category in Table 4.3 shows that the most common D-Dimer category was the increased category, with a frequency of 20 patients (51.3%).

This is consistent with a previous study conducted by Ahmad et al. in 2020 in Pakistan, which found a higher prevalence of elevated D-dimer levels in stroke patients.<sup>14</sup> Coagulation disorders are a significant systemic effect of COVID-19, which can be caused by either direct viral infection or indirect effects on the endothelium, or by immunothrombosis. COVID-19 can alter coagulation pathways, causing an imbalance in the regulatory mechanisms of coagulation and fibrinolysis, altered platelet function, and hyperinflammation. D-dimer is one of the early coagulation biomarkers altered in COVID-19 and can predict mortality upon hospital admission. Furthermore, plasma fibrinogen levels appear to be associated with hyperinflammation and the severity of COVID-19 disease. Endothelial dysfunction also appears to persist after recovery from COVID-19 and is directly related to the severity of pulmonary impairment.<sup>15 16</sup>

The distribution of patient characteristics based on stroke incidence shows that the frequency of ischemic stroke in 32 patients (82.1%). This is consistent with a previous study conducted by Zhang et al. in 2018 in China. The results of this study showed that higher D-dimer levels were associated with an increased risk of stroke, especially ischemic stroke, while for hemorrhagic stroke, D-dimer did not appear to be a risk factor.<sup>17 19</sup>

The association between elevated D-Dimer and age in COVID-19 patients experiencing ischemic stroke was observed using the Chi-square test to assess the

relationship between variables. The association between elevated D-Dimer and ischemic and hemorrhagic stroke in COVID-19 patients was observed using the Chi-square test to assess the relationship between variables. The Chi-square test results showed a value of 0.239 (P-value >0.05), indicating no significant association between elevated D-Dimer and ischemic and hemorrhagic stroke in COVID-19 patients. Subgroup analysis showed that for prospective studies, D-dimer remained a significant risk factor for all types of stroke and ischemic stroke across various ethnicities, genders, measurement methods, and threshold values. However, for hemorrhagic stroke, this association was not significant. In case-control studies, results varied by ethnicity and gender, but the number of studies in each subgroup was still limited, so the results should be interpreted with caution. Further research is needed to confirm these findings. The mechanism behind the association between D-dimer levels and stroke risk is not yet fully understood. D-dimer may reflect systemic hypercoagulability that can lead to ischemic stroke or subclinical fibrin thrombus formation.<sup>12</sup> Research by Folsom et al. showed that high plasma D-dimer is a risk marker for ischemic stroke, particularly cardioembolic stroke. D-dimer may also reflect thrombotic and hemostatic disorders associated with stroke or the heritability of a prethrombotic state. For hemorrhagic stroke, high D-dimer levels may predict poor

functional outcome and short-term mortality.<sup>18 20</sup>

## CONCLUSION

1. No significant association was found between elevated D-Dimer levels and the risk of ischemic stroke in COVID-19 patients.
2. The most common age group was 51-60 years old, with a frequency of 15 patients (38.5%).
3. The most common gender group was male, with a frequency of 26 patients (66.7%).
4. The most common D-Dimer group was the elevated category, with a frequency of 21 patients (53.8%).
5. The most common patient group was ischemic stroke, with a frequency of 35 patients (89.7%), and post-ischemic stroke, with a frequency of 4 patients (10.3%).

## REFERENCES

1. H. Buck B, Akhtar N, Alrohim A, Khan K, Shuaib A. Stroke mimics: incidence, aetiology, clinical features and treatment. *Annals of Medicine*. 2021;53(1):420-436. doi:10.1080/07853890.2021.1890205
2. Minggu RB, Rumbajan JM, Turalaki GLA. Struktur Genom Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). *Jurnal Biomedik (Jbm)*. 2021;13(2):233. doi:10.35790/jbm.13.2.2021.31996

3. Hu Y, Sun J, Dai Z, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . 2020;(January).
4. Gabriela. Analisa Jumlah Kasus Covid Di Indonesia Periode Maret-Desember 2020. 2021;10:6.
5. Markus HS, Martins S. COVID-19 and stroke—Understanding the relationship and adapting services. A global World Stroke Organisation perspective. *International Journal of Stroke*. 2021;16(3):241-247. doi:10.1177/17474930211005373
6. Ardiani S, Tursinawati Y, Wahab Z. Hubungan D-Dimer dengan Ketahanan Hidup Pasien Covid-19 Derajat Berat - Kritis di RSUD Tugurejo Semarang. *Health and Medical Journal*. 2022;5(1):44-49. doi:10.33854/heme.v5i1.1137
7. Amelia. D-Dimer Perbedaan Peningkatan Kadar D-Dimer Pada Dewasa Dan Lansia Yang Terkonfirmasi Covid-19 Di Rs Swasta Bintaro. *Journal Of Research And Education Chemistry*. 2022;4(1):1. Doi:10.25299/Jrec.2022.Vol4(1).9315
8. Syahrul, Imran VKM. Faktor Risiko, Gangguan Hemorheologi dan Outcome pada Pasien Stroke Iskemik Pasca Pandemi Corona Virus Disease (COVID-19) di RSUD dr. Zainoel Abidin Banda Aceh. *Journal of Medical Science*. 2023;4(1):31-38. doi:10.55572/jms.v4i1.95
9. Larson AS, Savastano L, Kadirvel R, Kallmes DF, Hassan AE, Brinjikji W. Coronavirus disease 2019 and the cerebrovascular-cardiovascular systems: What do we know so far? *Journal of the American Heart Association*. 2020;9(13). doi:10.1161/JAHA.120.016793
10. Kurniawan ID, Suryani Y, Kusumorini A, Akbar RTM. Analisis Potensi Kelelawar (Chiroptera) sebagai Reservoir Alami SARS-COV-2 Penyebab Covid-19. *Uinsgsg*. 2020;no. 4(Covid-19):1-10.
11. 38. Huang Y, Lyu X, Li D, et al. A cohort study of 676 patients indicates Ddimer is a critical risk factor for the mortality of COVID-19. *PLoS One*. 2020;15(11 November). doi:10.1371/journal.pone.0242045
12. Zhang J, Song Y, Shan B, et al. Elevated level of D-dimer increases the risk of stroke. *Oncotarget*. Published online 2017. www.impactjournals.com/oncotarget
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in

- Wuhan, China: a retrospective cohort study. *The* 2020;395(10229):1054-1062
14. Ahmad A, Islam Z, Manzoor Ahmad S, et al. The correlation of D dimer to stroke diagnosis within 24 hours: A meta-analysis. *J Clin Lab Anal.* 2022;36(3). doi:10.1002/jcla.24271
15. Battaglini D, Lopes-Pacheco M, Castro-Faria-Neto HC, Pelosi P, Rocco PRM. Laboratory Biomarkers for Diagnosis and Prognosis in COVID-19. *Front Immunol.* 2022;13. doi:10.3389/fimmu.2022.857573
16. Kojih
17. Folsom AR, Gottesman RF, Appiah D, Shahar E, Mosley TH. Plasma d-dimer and incident ischemic stroke and coronary heart disease: The atherosclerosis communities study. *risk in Stroke.* 2016;47(1):18-23. doi:10.1161/STROKEAHA.115.011035
18. Zakai NA, McClure LA, Judd SE, et al. D-dimer and the risk of stroke and coronary heart disease the REasons for geographic and racial differences in stroke (REGARDS) study. *Thromb Haemost.* 2017;117(3):618-624. doi:10.1160/TH16-07-0519
19. Yohana Y, Rahayu C, Destriana BS. Hubungan Nilai D-Dimer Dan LDL Kolesterol Pada Penderita Stroke Iskemik. *Open Journal System (OJS): journal.thamrin.ac.id.* 2020;6(2). <http://journal.thamrin.ac.id/index.php/anakes/issue/view/36>
20. Pertiwi I, Sudarsono T, Wardani D, Rahaju M. Hubungan Kadar D Dimer dengan Tingkat Keparahan Pasien Covid-19. *Jurnal Surya Medika.* 2023;9(2):273-280.