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Predictive value of admission D-dimer levels in patient with acute ischaemic stroke and COVID-19: a second-wave prospective cohort study

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ABSTRACT

Objectives This study aimed to evaluate the predictive value of admission D-dimer levels for in-hospital mortality in patients with COVID-19 and acute ischaemic stroke.

Design Cohort (prospective).

Setting Tertiary referral hospital in the capital city of Indonesia conducted from June to December 2021.

Participants 60 patients with acute ischaemic stroke and COVID-19 were included. Patients were classified into D-dimer groups (low and high) according to a 2 110 ng/mL cut-off value, determined via receiver operating characteristic analysis.

Primary and secondary outcome measures The primary outcome was in-hospital mortality, with admission D-dimer levels as the major predictor. Secondary outcomes included associations between other demographic and clinical variables and the admission D-dimer value. Kaplan-Meier method was used to carry out survival analysis, with univariable and multivariable Cox regression performed to assess the association of D-dimer levels and other confounding variables (including demographic, clinical and laboratory parameters) with in-hospital mortality.

Results The findings demonstrated an association between elevated admission D-dimer levels (≥2 110 ng/mL) and an increased likelihood of death during hospitalisation. The adjusted HR was 14.054 (95% CI 1.710 to 115.519; p=0.014), demonstrating an increase in mortality risk after accounting for confounders such as age and diabetes history. Other significant predictors of mortality included a history of diabetes and increased white blood cell count.

Conclusions Admission D-dimer levels may be a useful predictive indicator for the likelihood of death during hospitalisation in individuals with COVID-19 and acute ischaemic stroke.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study employs a prospective observational design, assuring a time-bound and organised collection of patient data.
⇒ It is administered in a single tertiary facility, ensuring uniformity in treatment and diagnostic protocols.
⇒ Clear inclusion and exclusion criteria were established, with an emphasis on patients with confirmed diagnoses of acute ischaemic stroke and COVID-19.
⇒ The study concentrates particularly on the prognostic value of admission D-dimer levels, a crucial predictor that has not been studied extensively in this patient cohort.
⇒ As a single-centre study, it is possible that the results cannot be generalised to other contexts or populations.

INTRODUCTION

The COVID-19 pandemic has irrevocably altered the global health and disease landscape.[1] This disease has presented a multitude of complexities and challenges since its inception, not the least of which is its relationship with comorbid conditions and the complexities that ensue. Among these, the relationship between COVID-19 and acute ischaemic stroke has attracted increasing attention and grave concern.[2]

Acute ischaemic stroke is a prominent worldwide factor contributing to both disability and mortality.[3] As more information accumulates, it becomes more evident that COVID-19 has a substantial influence on the cerebrovascular system.[2] The hypercoagulable state induced by COVID-19 has been linked to an increased risk of stroke, particularly in patients with severe infection, according to previous research.[4 5] The prothrombotic condition linked to COVID-19 arises from widespread inflammation, damage to the inner lining of blood vessels and reduced blood flow.[6]

D-dimer, a fibrin degradation product that indicates persistent activation of haemostasis and fibrinolysis, is a potential biomarker for the hypercoagulable state.[7] Numerous studies have identified elevated D-dimer levels as a characteristic of patients with severe COVID-19. For instance, Zhang *et al*[8] found that higher D-dimer levels were linked to a greater likelihood of death in COVID-19 patients who

were admitted to the hospital. In addition, the prognostic value of D-dimer in acute ischaemic stroke has been observed. Zhang *et al* discovered that acute ischaemic stroke patients with elevated D-dimer levels on admission had poor functional outcomes and increased mortality.[9]

Starting in July 2021, there was a rise in the occurrence of acute ischaemic stroke among COVID-19 patients who were admitted to the hospital, marking the beginning of the second phase of the pandemic and highlighting the need for more research into possible predictive variables to guide therapeutic care.[10] D-dimers have a potential predictive parameter due to the fundamental pathomechanism. When a blood clot dissolves in the body, D-dimer is produced.[4] Therefore, elevated D-dimer levels frequently indicate thrombosis or a degree of fibrinolysis.[4] This is particularly pertinent in the context of stroke. When a thrombus or embolus causes a stroke, the immediate response of the body is to initiate fibrinolysis to dissolve the clot.[11] Consequently, this procedure raises D-dimer concentrations. Thus, admission D-dimer levels of such patients are important. The comprehension of admission D-dimer levels in hospitalised patients with acute ischaemic stroke and COVID-19 remains limited. Therefore, it was necessary to conduct research to provide indications of their prognostic significance.

The objective of this research was to assess the prognostic significance of initial D-dimer levels on admission for predicting in-hospital mortality in patients diagnosed with acute ischaemic stroke and COVID-19. We hypothesise that elevated D-dimer levels on admission may serve as a useful prognostic indicator for disease progression and prognosis in this patient population. Through this study, we expect to provide more conclusive evidence on this subject, which may pave the way for improved risk stratification and patient management in these complex clinical scenarios. The results of this investigation may also contribute to the evolving comprehension of the interactions between COVID-19 and cerebrovascular disease, which may inform future therapeutic approaches.

METHODS

Study design

During the second phase of the COVID-19 pandemic, this prospective cohort study was conducted from June to December 2021 at the Cipto Mangunkusumo Indonesian National Referral Hospital. The protocol (917/UN2.F1/ETIK/PPM.00.02/2021) was approved by the Universitas Indonesia Institutional Review Board in May 2021. The research was carried out with written consent from each individual concerned or was represented by their family if the patient was unconscious. The investigation adheres to the World Medical Association's Code of Ethics (Declaration of Helsinki).[12] In writing this study report, the STROBE guideline has also been adapted.[13] In response to recent ethical concerns, the author confirms that there was no conflict of interest and that no artificial intelligence was used in the design or execution of this study.

Sample and eligibility criteria

Based on preliminary data indicating a significant difference in in-hospital mortality rates between patients with and without elevated D-dimer levels, the study's sample size was found to be 60 individuals. Using the formula for observational studies and assuming a 20% mortality rate in the lower D-dimer group and a 40% mortality rate in the higher D-dimer group,[14] with a power of 80% and alpha of 5%, the calculation of the sample size was performed. In addition, considering possible withdrawals and inconsistencies in the data, the sample size was rounded to 60.

This study included adult individuals, aged 18 years or older, who were diagnosed with COVID-19 by verified positive results from PCR swab tests. Additionally, patients who were diagnosed with acute stroke and had their diagnosis confirmed through radiological examination were also included. Importantly, the participation of all participants in this research requires approval from the individual concerned or is represented by their family if the patient is unconscious. In order to maintain the accuracy and reliability of the data, this research deliberately eliminated patients with missing information and those who had previously been diagnosed with ischaemic stroke before their COVID-19 diagnosis. To minimise confounding factors, subjects with a history of recent trauma or surgery, known coagulation disorders or active malignancy were excluded. If certain exclusions were not applied, we have acknowledged and accounted for them as limitations in our interpretation of results.

Study procedure and outcome

This research included gathering extensive data on the demographic, clinical and laboratory aspects of the individuals being investigated. The demographic and clinical variables encompassed essential information such as age, gender, smoking history, presence of diabetes, hypertension, high cholesterol and the duration of hospitalisation (referred to as hospital length of stay (LOS)). In terms of laboratory data, the parameters of interest included haemoglobin (Hb) levels, white blood cell (WBC) counts, platelet counts (PC), random blood glucose levels on admission (RBG), prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalised ratio (INR), fibrinogen levels and admission D-dimer levels.

Additionally, a thorough assessment of coagulation variables was performed at the first admission or diagnosis of acute stroke. These assessments aimed to provide a thorough understanding of the patients' coagulation profiles. The outcomes of interest in this study revolved around two key factors: in-hospital mortality and survival/outpatient status. These measures allowed for an evaluation of the overall patient outcomes within the hospital setting, as well as their subsequent survival or transition to outpatient care.

Statistical analysis

The data collecting process included tabulating the data using Microsoft Excel (Microsoft, USA). The data presented in the tables were analysed and displayed using SPSS V.26.0 (IBM, USA). The classification of high and low admission D-dimer groups is based on cut-off analysis based on receiver operating characteristic (ROC). ROC analysis was performed on admission D-dimer values versus patient outcome (deceased or survived). Discriminatory ability is assessed from the area under the curve (AUC) score. The cut-off value was determined from the sensitivity and specificity analysis using the Youden index.[15]

In addition to the D-dimer admission value categorisation, each continuous confounder is categorised into two groups. The categorisation was carried out based on previous study references, namely for Hb (high (≥165 g/L) vs low (<165 g/L)),[16] WBC (high (>0.011 x 10^9/L) vs low (≤0.011 x 10^9/L)),[17] PC (high (>450 × 10^9/L) vs low (≤450 × 10^9/L)),[18] RBG (high (≥200 mg/dL) vs low (<200 mg/dL)),[19] PT (high (≥12.3 s) vs low (<12.3 s)),[20] INR (high (>1.1) vs low (≤1.1)),[21] aPTT (high (>40 s) vs low (≤40 s))[22] and fibrinogen (high (≥400 mg/dL) vs low (<400 mg/dL)).[23] All confounder categorisations above were based on the in-hospital mortality cut-off in each study. The means (SD) of all continuous variables were calculated and analysed using an independent t-test for univariable analysis. The frequency of all categorical variables was determined and analysed using a χ^2 test. A p value below 0.05 is deemed to be statistically significant. All missing data and loss to follow-up would be excluded.

The study used survival analysis, namely the Kaplan-Meier method, to assess the survival of patients depending on their admission D-dimer levels. In addition, a survival analysis also had been carried out based on each demographic, clinical and laboratory confounder). Univariable Cox regression was also performed on each variable. Variables that have p-values below 0.25 were included in the multivariable Cox regression analysis. The result with a p value of less than 0.05 on multivariable Cox regression is considered statistically significant. For this survival analysis, the assumptions of the Cox proportional-hazards model were assessed. This requires HR to remain constant over time. We confirmed this assumption by visually inspecting log-minus-log survival plots and considering the theoretical basis of the model. Additionally, we ensured the independence of observations, addressed multicollinearity, managed outliers and adhered to the assumption of no time-dependent covariates.

Patient and public involvement

Prior to formulating our research questions, we conducted focus groups with patients and members of the general public to determine their priorities, experiences and preferences concerning acute ischaemic stroke and COVID-19. Our formulation of research questions and selection of outcome measures were directly influenced by their invaluable feedback. Patients and public representatives collaborated with our team during the design phase of the study, contributing valuable insights that helped us refine our approach. In addition, they played a pivotal role in recruitment strategies, assisting with the development of messages that resonated authentically with potential participants. Prior to commencing the study, we engaged in consultations with these representatives to evaluate the extent of intervention and the time obligations expected from participants, ensuring that our research maintained a courteous and thoughtful approach towards their requirements. As we transition to the dissemination phase, our patient and public collaborators are actively assisting in strategising the optimal methods for sharing our results, ensuring that the information is relevant, timely and accessible to both the participant cohort and the larger community affected by these health challenges.

RESULTS

Of the total 156 patients evaluated for eligibility, 96 were excluded because they did not satisfy the requirements (figure 1). This study included a total of 60 eligible individuals, with 35 (58.3%) males and 46 (76.7%) aged above 50 years. The mean age of participants was 62.1±13.3 years. During hospitalisation, 19 patients (31.7%) died. The average follow-up duration, described by hospital length of stay, was 16.9±11.9 days. The total follow-up duration was 6 months. No participant had missing data.

Figure 2 depicts the ROC curve analysis of the admission D-dimer value versus patient outcome. The AUC was 0.772 (95%CI 0.655 to 0.889). The Youden index was used to ascertain the most effective admission D-dimer threshold for predicting in-hospital mortality. The best cut-off value for this test was determined to be 2 110 ng/mL, with a sensitivity of 90% and specificity of 60%.

Patients were classified into high-admission D-dimer (>2 110 ng/mL) and low-admission D-dimer (<2 110 ng/mL) groups based on the cut-off value of 2 110 ng/mL. Online supplemental table S1 provides a concise overview of the patients' demographic and clinical features. There are no significant relationships between demographic and clinical variables and the admission D-dimer value. In addition, online supplemental table S2 also analyses the association between laboratory parameter characteristics and admission D-dimer values because it also plays a role in the coagulation process. WBC and PT values correlate significantly with admission D-dimer concentrations. On the other hand, the average admission D-dimer level among patients who survived was 4762.9±7026.5 ng/mL, whereas it was 10711.6±10 735.7 ng/mL among patients who died. This difference is statistically significant (p=0.013).

Online supplemental figure S1 depicts the Kaplan-Meier analysis of patients' survival based on admission D-dimer levels. In addition, a survival analysis was performed on confounding variables such as demographic and clinical characteristics (online supplemental figure S2) and

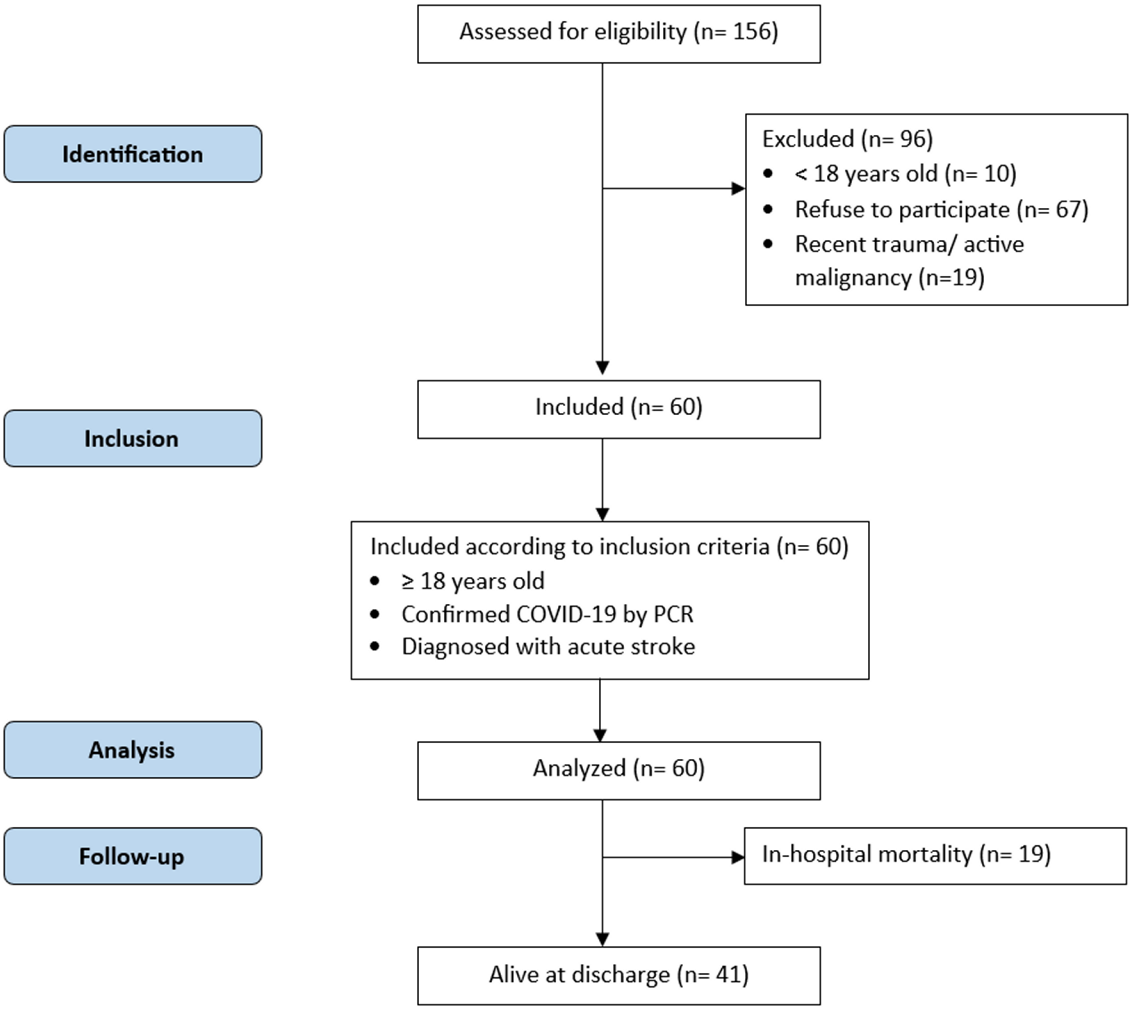

Figure 1 Strengthening the Reporting of Observational Studies in Epidemiology flowchart.

laboratory parameters (online supplemental figure S3). Table 1 displays the results of a univariable Cox regression analysis conducted on all variables. On independent analysis, admission D-dimer levels (p=0.019), history of diabetes (p=0.046) and WBC count (p=0.020) exhibited a significant HR. These predictors were then analysed using a multivariate Cox regression analysis for further analysis (table 2). Our Cox regression aligns with the assumptions for the Cox proportional-hazards model, which is detailed in the Methods section. After adjusting for age and diabetes history, the HR for high admission D-dimer levels was 14.054 (95% CI 1.710 to 115.519; p=0.014). This HR of 14.054 indicates a 14-fold higher risk of acute ischaemic stroke in patients with increased D-dimer levels on admission compared with those with lower D-dimer levels while considering other relevant factors. Practically speaking, this implies that those with higher levels of D-dimer in relation to COVID-19 are at a greatly increased risk of developing acute ischaemic stroke. Moreover, it is important to mention that the broad confidence range obtained in our findings has shown the level of uncertainty linked to our estimations. The wide range may indicate considerable ambiguity in the HR estimations, spanning from 1.71 to 115.52, which need to be interpreted with caution when applying these results to a wider population.

DISCUSSION

The results of our investigation indicate that admission D-dimer levels have a substantial predictive value for in-hospital mortality in patients with COVID-19 and acute ischaemic stroke. Our study revealed that the average admission D-dimer levels of those who died from their illness were substantially higher than those who survived. An ROC curve analysis further confirmed this observation with an AUC of 0.772, highlighting the robust discriminatory power of the admission D-dimer marker. Our study identified an optimal admission D-dimer cut-off value of 2 110 ng/mL, which, with a sensitivity of 90% and specificity of 60%, served as an effective mortality threshold. This cut-off is distinctively lower than what has been observed in COVID-19 patients without stroke,[24 25] highlighting the specific physiological responses in the patient cohort under our scrutiny.

When comparing our findings with other studies, it becomes evident that understanding the relevance of the reduced D-dimer cut-off levels in our cohort necessitates

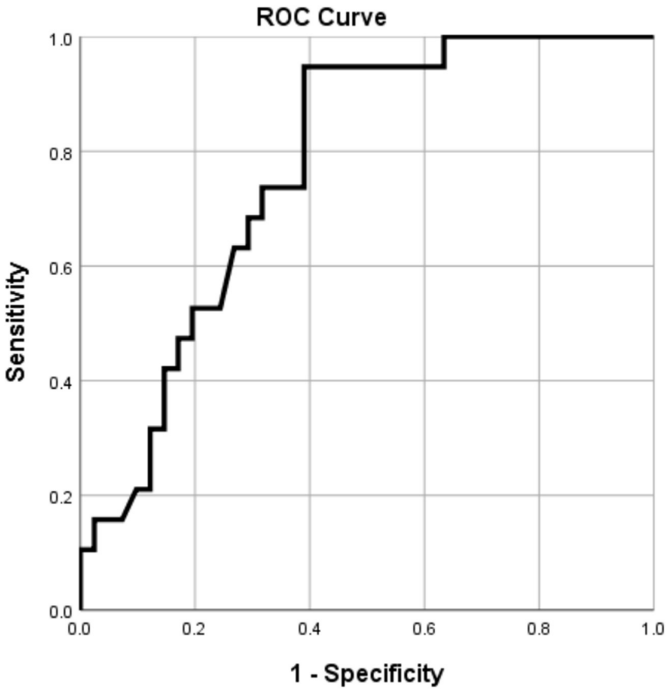

Figure 2 Receiver operating characteristic curve for admission D-dimer levels as a predictor of in-hospital mortality in COVID-19 patients with ischaemic stroke.

a closer look at the pathophysiology of acute ischaemic stroke and COVID-19. Ischaemic stroke induces a specific inflammatory reaction in a particular area, which then activates the coagulation process and causes an increase in D-dimer levels.[6 26] In COVID-19, the inflammatory response is systemic and fueled by the so-called 'cytokine storm', resulting in extensive activation of the coagulation cascade.[27] Hence, the combination of the systemic inflammatory response triggered by COVID-19 and the localised inflammation produced by stroke may explain the reduced D-dimer threshold found in our research, in contrast to COVID-19 patients without stroke.[26]

Intriguingly, our investigation discovered significant correlations between D-dimer levels and both WBC and PT. The positive association between WBC count and D-dimer levels suggests that an increased inflammatory response, as indicated by a high WBC count, may stimulate coagulation activation, thereby elevating D-dimer levels.[28] In addition, the correlation between D-dimer and PT may suggest a more severe impairment of the coagulation system in those with increased D-dimer levels.[29]

Other than the D-dimer admission, as the result of the univariable Cox regression survival analysis in our study, the presence of a medical background of diabetes and an elevated WBC count were identified as important factors that might predict the likelihood of death during a hospital stay. This discovery aligns with the existing literature, which indicates an increased susceptibility to catastrophic COVID-19 outcomes among individuals with diabetes.[30 31] Diabetes sometimes leads to an inflammatory condition that might worsen the 'cytokine storm'' seen in severe cases of COVID-19, therefore raising the chances of poor outcomes.[31] Similarly, a high WBC count, which indicates a robust systemic inflammatory response, may contribute to a poorer prognosis.[32]

The multivariable Cox regression survival analysis in our research showed that D-dimer levels on admission are a reliable indicator of mortality in hospitalised patients with COVID-19 and acute ischaemic stroke. After adjusting for age and diabetes history, our observations indicate that individuals who had high levels of D-dimer at hospital arrival had a risk of mortality that was more than 14 times higher.

D-dimer is a fibrinolysis and coagulation metabolite that can serve as a surrogate marker for these processes. Increased thrombosis and fibrinolysis may be indicative of a variety of clinical conditions, such as those associated with stroke and life-threatening infections such as COVID-19.[33] An overactive blood clotting mechanism, as seen by increased D-dimer levels in cases of acute ischaemic stroke, might worsen the pre-existing blockage in the blood vessels of the brain.[34] This exacerbation has a variety of causes. As the initial clot or embolus obstructs a blood vessel, the decreased blood flow can result in a hypoxic local environment.[35] This environment can stimulate platelet aggregation, leading to the growth of the obstructive thrombus.[35] More brain tissue is damaged, resulting in a more severe neurological deficiency and potentially a worse prognosis for the patient.[34]

The unique interaction between acute ischaemic stroke and COVID-19 increases the predictive significance of D-dimer. COVID-19 has been linked to hypercoagulability,

Table 1 Univariable Cox regression of the variables

Variables	HR	95% CI		P value
		Lower	Upper	
D-dimer	11.267	1.496	84.881	0.019*
Age	0.463	0.174	1.232	0.123
Gender	0.900	0.346	2.339	0.828
Smoking	1.524	0.601	3.864	0.375
Diabetes	3.109	1.021	9.466	0.046*
Hypertension	0.507	0.199	1.290	0.154
Cholesterol	0.953	0.217	4.185	0.949
Hb	1.953	0.558	6.843	0.295
WBC	5.762	1.312	25.302	0.020*
PC	0.046	0.001	127 786.165	0.631
RBG	0.821	0.316	2.128	0.684
PT	1.527	0.501	4.652	0.457
INR	0.638	0.146	2.796	0.551
aPTT	1.143	0.407	3.210	0.800
Fibrinogen	2.422	0.908	6.460	0.077

*P value of less than 0.05 is considered statistically significant.
aPTT, activated partial thromboplastin clotting time; Hb, haemoglobin; INR, international normalised ratio; PC, platelet count; PT, prothrombin time; RBG, random blood glucose; WBC, white blood cell.

Table 2 Multivariable Cox regression of the predictors

Predictors	B	SE	Wald	DF	P value	HR	95% CI	
							Lower	Upper
D-dimer	2.643	1.075	6.046	1	0.014*	14.054	1.710	115.519
Age	−1.740	0.678	6.584	1	0.010*	0.176	0.047	0.663
Diabetes	1.638	0.626	6.851	1	0.009*	5.147	1.509	17.554

*P value of less than 0.05 is considered statistically significant.
DF, degree of freedom; SE, standard error.

also known as COVID-19-associated coagulopathy, which can manifest as disseminated intravascular coagulation, venous thromboembolism or arterial thrombosis.[36 37] Elevated D-dimer levels indicate activation of the coagulation cascade in these patients, which is linked to a higher likelihood of thrombotic events that might impact prognosis.[36]

D-dimer has been demonstrated to be a reliable predictor of unfavourable outcomes, as demonstrated by comparisons to the current body of literature. Other important investigations have produced similar findings. A study conducted by Zhang *et al* revealed that elevated D-dimer levels were a strong and independent indicator of death in COVID-19 patients who were admitted to the hospital, with an HR of 51.5.[8] In addition, a study by Si *et al* highlighted the significance of D-dimer levels in predicting the likelihood of recurrence in patients with venous thromboembolism,[38] thereby bolstering D-dimer's standing as a valid prognostic indicator.

The complex interaction between acute ischaemic stroke and COVID-19, both of which are associated with prothrombotic predispositions, distinguishes our patient sample from others. Patients with severe COVID-19 were found to be susceptible to acute ischaemic events due to a hypercoagulable condition, a phenomenon termed 'COVID-19-associated acute ischaemic stroke' in a 2020 study by Beyrouti *et al*.[39] However, this research did not examine the prognostic significance of D-dimer levels in this particular group of patients.

Our results show that D-dimer may be used to provide prognostic assessments for patients with COVID-19 and acute ischaemic stroke. Our investigation is the first to investigate the prognostic value of D-dimer in the context of acute ischaemic stroke with COVID-19. Due to the peculiar pathophysiological reaction that occurs when two severe conditions interact, D-dimer's ability to predict outcomes in this population of patients has not been extensively studied. Thus, our findings add a novel perspective to the growing body of knowledge regarding the prognostic indicators for individuals with both acute ischaemic stroke and COVID-19.

Strengths and limitations

While our research provides insights into the predictive importance of initial D-dimer levels in patients with acute ischaemic stroke and COVID-19, it is important to acknowledge its limitations. As a single-centre study, this one is subject to the limitations that come with it. Our findings may not be applicable to the larger population of individuals with COVID-19 and acute ischaemic stroke, as the demographic and clinical characteristics of our patient cohort may not be representative of that population. Due to their impact on patient outcomes, hospital-specific procedures cannot be neglected when treating acute stroke and COVID-19. Furthermore, D-dimer levels were only evaluated on admission. With repeated measurements of D-dimer during the hospital stay, dynamic variations in coagulation activity and their relationship to disease progression and prognosis may be better understood.

The association between D-dimer levels and patient outcomes may have been influenced by factors beyond our control, such as anticoagulant therapy, patient adherence to medication and other coexisting disorders. While the research primarily focused on the prognostic value of admission D-dimer levels, factors such as preexisting risk factors, specific treatments administered, comorbidities and other clinical variables may also have influenced the results. These variables may cause an overestimation or underestimation of the effects attributable to D-dimer levels alone. Future research may benefit from a more comprehensive multivariable analysis that integrates these variables to provide a comprehensive understanding of their combined impact on in-hospital mortality in COVID-19 patients who have suffered an acute ischaemic stroke.

Although our research was intentionally constructed with a sample size of 60, determined by a priori power analysis, we recognise that this sample size may be seen as somewhat small for a model including many variables. We recognise the significance of the sample size in generating dependable estimates and express our interest in conducting additional research using larger cohorts to validate and enhance our preliminary results. The fact that our research was carried out in a developing country with constrained resources is significant since it created difficulties for patient recruitment and data gathering during the COVID-19 pandemic's second wave. Nevertheless, it is important to highlight that in the subject we examined, the association between admission D-dimer levels, acute ischaemic stroke and COVID-19 continues to have a great beneficial significance, particularly in settings with limited resources. Although our work has limits, it

provides useful preliminary insights into this crucial field, which should serve as a basis for future studies with larger sample numbers.

Particularly for certain covariates analysed (eg, D-dimer, diabetes, cholesterol, Hb, WBC, PC, PT and fibrinogen), the reasonably limited sample size in our cohort study might have resulted in broad CIs. When evaluating the significance of the observed associations, it is prudent to consider the substantial uncertainty that these CIs signify regarding our estimates. Additionally, the notable width was observed in the CIs for HR in table 2, which accounted for age and diabetes adjustments. Such a broad range (eg, 1.71–115.52) indicates that the HR estimates are subject to considerable uncertainty. The considerable uncertainty surrounding the applicability of these results should be borne in mind, even though our findings suggest an HR of 14.054.

Despite these limitations, this study sets the foundation for larger, multicentre investigations to confirm the potential predictive value of D-dimers in patients with COVID-19 who have suffered an acute ischaemic stroke.

Conclusion

There is an association between high levels of D-dimer in patients who have both acute ischaemic stroke and COVID-19 and a greater likelihood of dying while in the hospital. This emphasises the significance of D-dimer levels as a prognostic indicator in this particular group of patients. Tracking these levels may provide useful insights into patient outcomes and guide customised treatment interventions.

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Contributors Conceptualization, AR, SH, MK, TM and RH; methodology, AR, SH and MK; software, AR and EW; validation, AR and SH; formal analysis, AR, SH, MK, TM and RH; investigation, AR and EW; resources, AR and SH; data curation, EW; writing – original draft preparation, AR and EW; writing – review and editing, all authors; visualization, EW; supervision, AR and SH; project administration, EW; funding acquisition, AR; guarantor, AR. All authors have read and agreed to the published version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Ethics approval The University of Indonesia Institutional Review Board approved the report protocols, with protocol number 917/UN2.F1/ETIK/PPM.00.02/2021, in May 2021. The research was conducted with the knowledge and written consent of each individual concerned or was represented by their family if the patient was unconscious.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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