Journal of Stroke and Cerebrovascular Diseases 33 (2024) 107834

Contents lists available at ScienceDirect

Journal of Stroke and Cerebrovascular Diseases

journal homepage: www.elsevier.com/locate/jstroke

Factors impacting D-dimer levels in patients with acute ischemic cerebrovascular events

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ARTICLE INFO

Keywords:
Acute ischemic stroke
Transient ischemic attack
D-dimer levels
Symptom onset

ABSTRACT

Background and objectives: A better understanding of the factors influencing D-dimer levels in code stroke patients is needed to guide further investigations of concomitant thrombotic conditions. This study aimed to investigate the impact of time from symptom onset and other factors on D-dimer levels in patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA).

Methods: Data on consecutive AIS and TIA patients treated at our tertiary-care stroke center between January 2015 and December 2020 were retrospectively assessed. Patients with available D-dimer levels were evaluated for eligibility. Multivariable non-linear regression analyses were performed.

Results: In total, 2467 AIS patients and 708 TIA patients were included. The median D-dimer levels differed between the AIS and TIA groups (746 µg/L [interquartile range 381–1468] versus 442 µg/L [interquartile range 244–800], $p<0.001$). In AIS patients, an early increase in D-dimer levels was demonstrated within the first 6 h (standardized beta coefficient [β] 0.728; 95% confidence interval [CI] 0.324–1.121). This was followed by an immediate decrease (β −13.022; 95% CI −20.401 to −5.643) and then by a second, late increase after 35 h (β 11.750; 95% CI 4.71–18.791). No time-dependent fluctuation in D-dimer levels was observed in TIA patients.

Conclusion: The time from symptom onset may affect D-dimer levels in patients with AIS but not those with TIA. Further studies confirming these findings and validating time-specific variations are needed to enable D-dimer levels to be used efficiently as an acute stroke and thrombotic risk biomarker.

Introduction

D-dimer is a cleavage product of cross-linked fibrin, usually obtained from blood plasma.[1] Increased D-dimer levels are the result of thrombus degradation and therefore indirectly suggest prior thrombus formation.[1] D-dimer measurement is routinely used to rule out venous thromboembolism (VTE), such as deep venous thrombosis and pulmonary embolism.[2] In the context of acute ischemic stroke (AIS), physiological D-dimer levels have been shown to effectively rule out VTE.[3] However, elevated D-dimer levels are also often seen in AIS patients without VTE

Abbreviations: ABCD2 score, age, blood pressure, clinical features, duration, diabetes - Score; AIS, Acute ischemic stroke; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; IVT, intravenous thrombolysis; IQR, Interquartile range; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

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https://doi.org/10.1016/j.jstrokecerebrovasdis.2024.107834
Received 12 April 2024; Received in revised form 12 June 2024; Accepted 23 June 2024
Available online 26 June 2024

and can result from the AIS itself. This makes further management of AIS patients with elevated D-dimer levels challenging (i.e., potential search for VTE and underlying cancer).[3,4]

Our study aimed to investigate the influence of time from symptom onset to blood sample collection and other factors on D-dimer levels in patients with AIS. We hypothesized a time-dependent increase in D-dimer levels during the first hours and days after onset of AIS symptoms due to the degradation of occlusive thrombus in the hyperacute phase of AIS (<6 h after symptom onset) and the occurrence of cerebral thromboinflammation in the acute phase of AIS (between 6 and 48 h after symptom onset).[5,6] A group of patients with transient ischemic attack (TIA) formed a comparison group. We did not expect an increase in D-dimer levels in the TIA group over time because TIA is usually not associated with irreversible brain injury and, therefore, we assumed an absence of cerebral thromboinflammation.[7]

Material and methods

Study cohort

Consecutive patients diagnosed with AIS between January 1, 2015 and December 31, 2020 and consecutive patients diagnosed with TIA between January 1, 2015 and December 31, 2019 at our institution were assessed for eligibility. Patients with AIS were identified from the Swiss Stroke Registry, which includes prospective data recorded by qualified research personnel. Patients with TIA were retrospectively identified via a review of institutional electronic health records. The detailed definitions used to characterize patients with AIS and TIA are provided in the Supplementary Methods.

Standard protocol approvals, registrations, and patient consents

The ethics committee approved the study in accordance with Swiss law (reference ID: 2021-01031 and ID: 2022-01560, Kantonale Ethikkommission Bern). The study adheres to the STROBE checklist for cohort studies. As stated by decision of the ethics committee, a written consent from patients was not required for performance of this retrospective study.

Data availability statement

Data are available from the corresponding author upon reasonable request and after clearance by our institutional ethics committee.

Inclusion and exclusion criteria

Patients were excluded in case of 1) missing D-dimer measurement during the index event or a D-dimer measurement made more than 7 days after the time of symptom onset, 2) unknown symptom-onset time (missing data and wake-up symptoms), 3) in-hospital event with D-dimer measurement prior to documented symptom onset, 4) outliers with D-dimer values exceeding 30,000 µg/L, 5) administration of intravenous thrombolysis (IVT) before D-dimer measurement, 6) mechanical thrombectomy prior to D-dimer measurement, 7) documented active cancer at the time of the index event, and 8) VTE diagnosed within 30 days before and up to 7 days after the index event.

Active cancer was defined according to the criteria from the Haemostasis and Malignancy Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis.[8]

Data collection

D-dimer levels were obtained as part of a standardized blood sample panel, which is routinely measured in every patient with suspected AIS or TIA at our institution. The D-dimer value was measured using Innovance®.[9] For patients with multiple measurements, only the first D-dimer value was recorded.

The following data were extracted from the Swiss Stroke Registry or acquired through the review of electronic health records: 1) Epidemiological data including patients' age, sex, pre-stroke dependency defined as a modified Rankin Scale [mRS] ≥3, baseline imaging modality, use of anticoagulation and antiplatelet drugs before the event, and vascular risk factors including previous AIS, previous TIA, arterial hypertension, diabetes mellitus, hyperlipidemia, history of smoking, and atrial fibrillation; 2) event characteristics, such as time between symptom onset and D-dimer measurement at admission or during hospitalization for the index event, and AIS and TIA etiology at discharge according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. For AIS, the site of vessel occlusion was determined on admission imaging and categorized as: no vessel occlusion, intracranial carotid artery, M1 segment of middle cerebral artery (MCA), M2 segment of MCA, other occlusion in the anterior circulation, or occlusion in the posterior circulation. In patients with AIS, initial stroke severity was stratified according to the National Institutes of Health Stroke Scale (NIHSS), as follows: very minor (score 0), minor (score 1–4), moderate (score 5–14), severe (score 15–-24) and very severe (score >25). TIA patients were categorized according to the risk of subsequent AIS based on the ABCD2 score: low risk (score 0–3), medium risk (score 4–5), and high risk (score 6–7).[10] Besides plasma D-dimer, the following baseline blood parameters were recorded: C-reactive protein (CRP) in mg/L, glucose in mmol/L, fibrinogen in g/L and creatinine in µmol/L. The estimated glomerular filtration rate (eGFR) in mL/min/1.73 m^2 was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI 2021) formula.

Statistical analysis

Baseline characteristics were reported using median and interquartile range (IQR) for continuous variables and frequency (percentage) for categorical variables. Baseline differences were assessed for AIS and TIA patients combined. Differences between groups were assessed using Fisher's exact test for categorical variables and the Mann-Whitney U-test for continuous variables. Scatter plots were displayed to visualize the distribution of continuous D-dimer levels over time from symptom onset in the AIS and TIA groups separately. Pearson's correlation coefficient (r) and its corresponding p-values were used to assess the linearity of the correlations between D-dimer levels and time from symptom onset to D-dimer measurement. In the case of non-linearity of the correlations (r between -0.1 and +0.1),[11] non-linear models with restricted cubic splines were created using the Stata command mkspline2.[12] The restricted cubic spline was chosen as a non-linear model (instead of fractional polynomials, for example) because it behaved better in relation to the data and its interpretation was more intuitive. Multivariable non-linear regression analyses using standardized variables were performed and the resulting standardized coefficients of regression (β), their corresponding 95% confidence intervals (CI) and p-values were reported. Multivariable non-linear regression analyses using standardized variables were performed and the resulting standardized coefficients of regression (β), their corresponding 95% confidence intervals (CI) and *p*-values were reported. Multivariable analyses were adjusted for the following covariables: age, sex, pre-stroke dependency, vascular risk factors (arterial hypertension, history of smoking and hyperlipidemia), prior anticoagulant use, prior antiplatelet use, eGFR, etiology according to TOAST, stroke severity (NIHSS grades), site of vessel occlusion for AIS, and the risk for subsequent AIS in TIA patients (ABCD2 scores). Variables were selected based on previous literature and pathophysiological considerations.[4,13]

Sensitivity analysis compared the association between D-dimer levels and time from symptom onset in AIS patients with at least one symptomatic intracranial arterial occlusion versus AIS patients without symptomatic intracranial occlusion. Associations were deemed significant if their *p*-value was <0.05. No imputation was applied to

compensate for missing data. All statistical analyses were performed using Stata v16.

Results

Study population

Of 6371 patients assessed for eligibility (AIS n=5012 and TIA n=1359), 3175 (AIS n=2467 and TIA n=708) were included in this study (Fig. 1: Study Flowchart).

Baseline characteristics

The baseline differences between patients with AIS and TIA are summarized in eTable I. The time between symptom onset and D-dimer measurement was longer in AIS patients than in TIA patients (191 min [IQR 103–585] versus 161 min [IQR 106–286], $p<0.001$). The median D-dimer level differed between the AIS and TIA groups (746 µg/L [IQR 381–1468] versus 442 µg/L [IQR 244–800], $p<0.001$).

D-dimer levels in AIS patients

No linear correlation was found between D-dimer levels and time from symptom onset for AIS patients in this study (r= −0.06, P=0.003, Fig. 2). Based on visual review of the distribution of D-dimer levels in AIS patients (Fig. 2A) and pathophysiological considerations mentioned in the introduction, we set time-specific knots at 6 h and 35 h after symptom onset to create a non-linear model.[5,6] In the resulting multivariable non-linear regression analysis (Table 1), an early increase in D-dimer levels was observed in AIS patients within the first 6 h after symptom onset (β 0.773; 95% CI 0.370–1.176). Between 6 h and 35 h after symptom onset, a decrease of the D-dimer levels was demonstrated (β −13.022; 95% CI −20.401 to −5.643). A second, late increase of D-dimer levels starting from 35 h after symptom onset was also observed (β 12.334; 95% CI 5.294 – 19.374). An adjusted model of D-dimer levels over the time between symptom onset and D-dimer measurement is displayed in Fig. 2B. Lower D-dimer levels were associated with prior anticoagulation; other factors affecting D-dimer levels during AIS work-up are reported in Table 1.

Influence of intracranial occlusion in AIS patients

On baseline brain imaging, 1286 of the 2467 AIS patients (52%) were found to have an intracranial occlusion. The median D-dimer level differed between patients with and without intracranial occlusion (median 918 µg/L [IQR 474–1881] versus median 545 µg/L [IQR 326–1086], $p<0.001$). Patients with and without intracranial occlusion showed comparable time dynamics in the D-dimer values to those of the AIS group overall (eTable II and eFig. I).

D-dimer levels in TIA patients

The distribution of D-dimer levels over the time between symptom onset and D-dimer measurement in TIA patients is displayed in Fig. 3A. No linear correlation was found between D-dimer levels and time from symptom onset for TIA patients (r= −0.05, p=0.193). Using the same time-specific knots as for AIS patients (at 6 h and 35 h after symptom onset) for the non-linear regression analysis (Table 1 and Fig. 3B), no significant association between the time from symptom onset and increased D-dimer levels was observed within the first 6 h after symptom onset (β −0.019; 95% CI −0.837 to 0.800), between 6 and 35 h after symptom onset (β 0.380; 95% CI −21.413 to 22.173) or from 35 h after symptom onset (β 0.041; 95% CI −22.111 to 22.192).

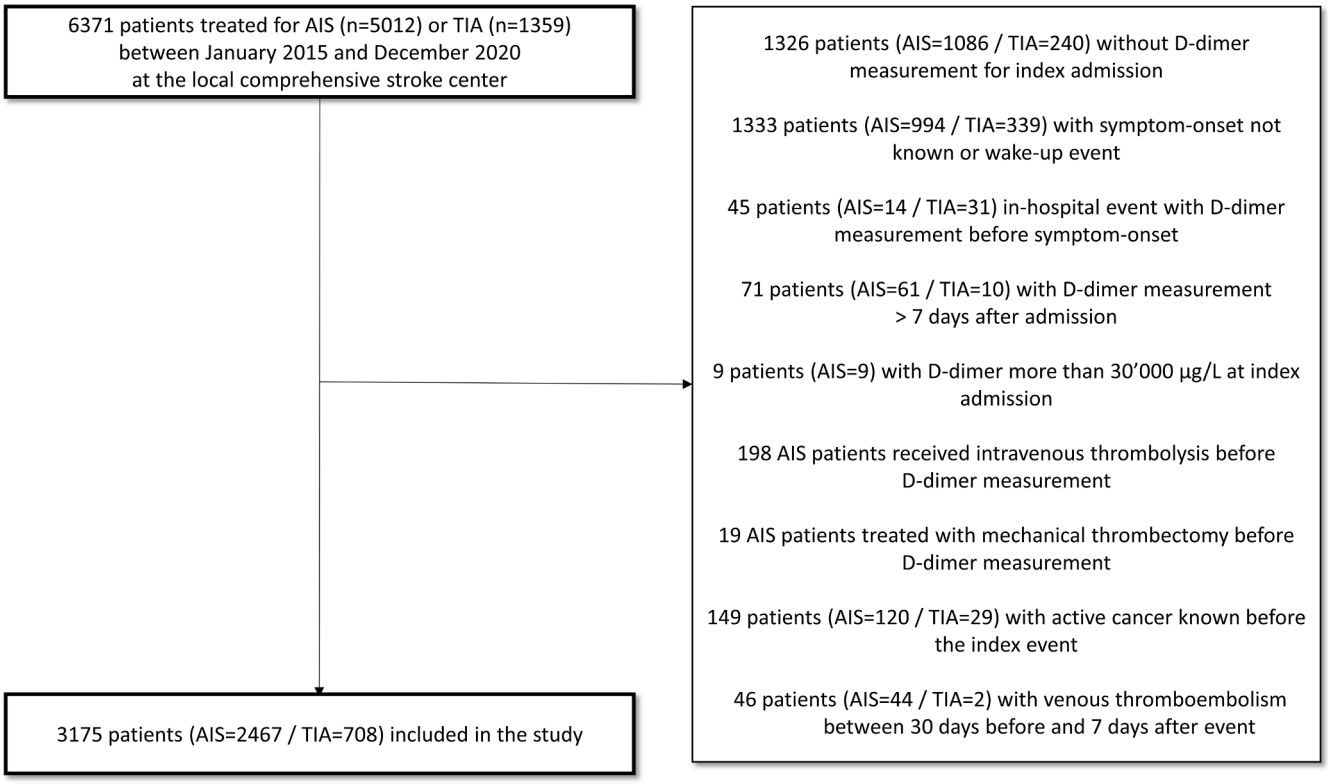

Fig. 1. Study Flowchart.
Inclusion and exclusion of study participants.
Abbreviations: AIS=acute ischemic stroke, TIA=transient ischemic attack.

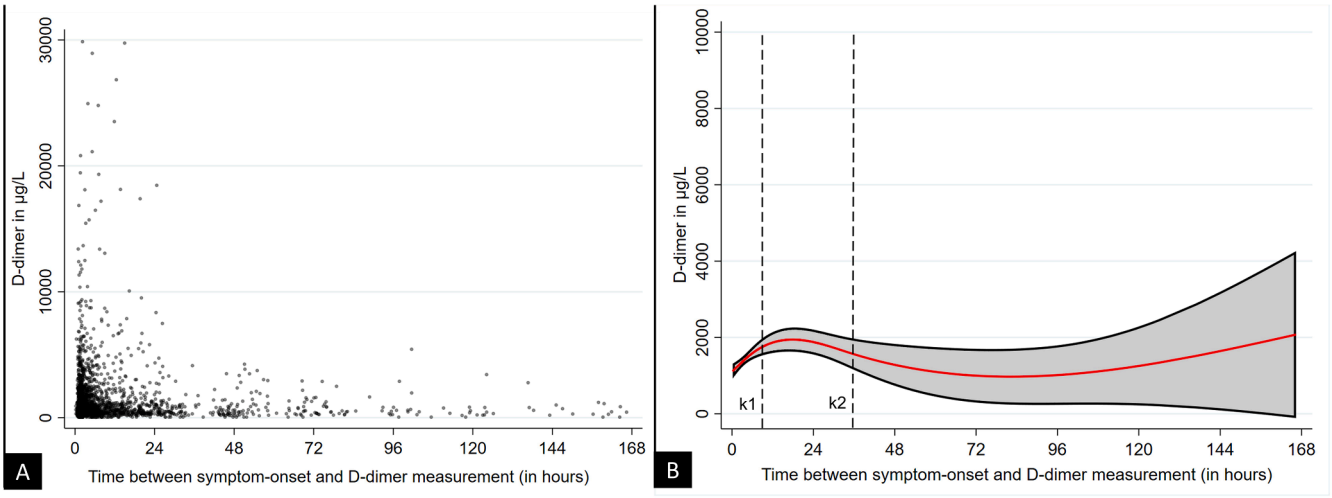

Fig. 2. Distribution (A) and Adjusted Model (B) of D-Dimer Levels Over Time from Symptom Onset to Blood Collection in Patients with AIS.
In Fig. 2A, gray dots represent individual D-dimer levels over time from symptom onset to blood collection for the index AIS (n = 2467). Fig. 2B displays the adjusted model with the restricted cubic spline regression line (red line) and its 95% CI (gray shading). The two knots at 6 h (k1) and 35 h (k2) after symptom onset are represented by the vertical black dashed lines. Abbreviations: AIS=acute ischemic stroke, CI=confidence interval.

Table 1
Predictors of Elevated D-Dimer Levels in Patients with Acute Ischemic Stroke (AIS) and Transient Ischemic Attack (TIA) Assessed in the Multiple Non-Linear Regression.

Multivariable non-linear regression model							
Predictive variables	**Patients with AIS**			**Predictive variables**	**Patients with TIA**		
	β	**95% CI**	***p* value**		**β**	**95% CI**	***p* value**
Symptom onset to D-dimer < 6h	0.773	0.370 – 1.176	<0.001*	Symptom onset to D-dimer < 6h	−0.019	−0.837 – 0.800	0.964
Symptom onset to D-dimer ≥ 6h and < 35h	−13.022	−20.401 – −5.643	0.001*	Symptom onset to D-dimer ≥ 6h and < 35h	0.380	−21.416 – 22.173	0.973
Symptom onset to D-dimer ≥ 35h	12.334	5.294 – 19.374	0.001*	Symptom onset to D-dimer ≥ 35h	0.041	−22.111 – 22.192	0.997
Age at admission	0.135	0.068 – 0.203	<0.001*	Age at admission	0.143	−0.064 – 0.150	0.427
Sex (male)	−0.034	−0.085 – 0.017	0.193	Sex (male)	−0.008	−0.088 – 0.073	0.848
Pre-stroke dependency (mRS ≥3)	0.314	0.157 – 0.471	<0.001*	Pre-stroke dependency (mRS ≥3)	0.091	0.024 – 0.157	0.008
Anticoagulation prior to event	−0.096	−0.154 – −0.038	0.001*	Anticoagulation prior to event	0.055	−0.030 – 0.141	0.203
Antiplatelet drugs prior to event	0.024	−0.031 – 0.078	0.392	Antiplatelet drugs prior to event	0.029	−0.059 – 0.117	0.511
Hypertension	−0.042	−0.099 – 0.015	0.148	Hypertension	−0.011	−0.101 – 0.080	0.816
Hyperlipidemia	−0.011	−0.062 – 0.040	0.664	Hyperlipidemia	0.027	−0.062 – 0.116	0.545
History of smoking	0.060	0.008 – 0.113	0.024*	History of smoking	−0.015	−0.097 –0.069	0.726
Lower eGFR	0.131	0.071 – 0.192	<0.001	Lower eGFR	0.065	−0.040 – 0.169	0.222
Stroke etiology	−0.032	−0.086 – 0.022	0.251	Stroke etiology	−0.014	−0.101 – 0.073	0.750
Stroke severity	0.125	0.071 – 0.179	<0.001*	Risk of AIS	0.001	−0.212 – 0.128	0.625
Site of vessel occlusion	0.010	−0.041 – 0.062	0.694	Site of vessel occlusion			

AIS, acute ischemic stroke; TIA, transient ischemic attack; β, standardized regression coefficient; CI, confidence interval; eGFR, estimated glomerular filtration rate; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale.
* Independent predictor of elevated D-dimer level identified by multiple regression analyses

Discussion

The main findings of this study are: 1) An initial increase in D-dimer levels in AIS patients occurs during the first 6 h after symptom onset and a second increase after 35 h, with a decrease in between, 2), no time-dependent pattern of D-dimer levels was observed in TIA patients, 3) prior use of anticoagulants was associated with lower D-dimer levels.

Alongside its key role in exclusion of VTE, D-dimer is increasingly used in the evaluation of AIS.[14,15] Measuring D-dimer levels at hospital presentation for AIS or TIA could provide clues to patients' underlying cerebrovascular etiology as well as their risk of early neurological deterioration and recurrent stroke.[4,16] For instance, a very high D-dimer level in a patient with cryptogenic stroke could prompt an investigation for occult cancer or acute venous thromboembolism with corresponding paradoxical embolization.[3,17]

Further, a persistently elevated D-dimer value despite antiplatelet therapy in patient with cancer-related stroke could trigger the consideration of empiric anticoagulant therapy.

Among patients with AIS, elevated D-dimer levels have been most consistently associated with cardioembolic and large-artery atherosclerotic etiologies or comorbid cancer with associated hypercoagulability.[17,18] In addition, like previous reports,[19–22] our study found that intracranial occlusion, higher stroke severity, and increased age were associated with higher D-dimer levels. Until now, there were few data on the effect of time from symptom onset to blood collection and D-dimer levels in patients with AIS.[14] Retrospective studies had hypothesized an

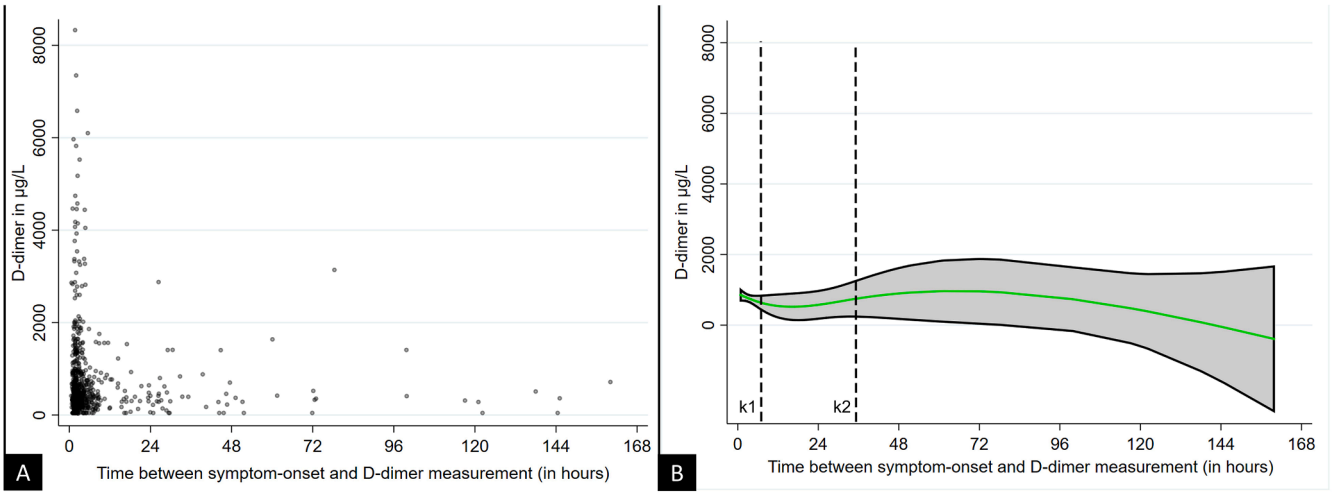

Fig. 3. Distribution (A) and Adjusted Model (B) of D-Dimer Levels Over Time from Symptom Onset to Blood Collection in Patients with TIA.
In Fig. 3A, gray dots represent individual D-dimer levels over time between symptom onset and blood collection for the index TIA (n = 708). Fig. 3B displays the adjusted model with the restricted cubic spline regression line (red line) and its 95% CI (gray shading). The two knots at 6 h (k1) and 35 h (k2) after symptom onset are represented by the vertical black dashed lines. Abbreviations: AIS=acute ischemic stroke, β=standardized regression coefficient, CI=confidence interval, TIA=transient ischemic attack.

initial rise in D-dimer levels within the first 24 h after symptom onset, followed by a gradual decline.[4,14,23] This is clinically relevant, as the timing of D-dimer measurements could lead to misinterpretation by treating physicians.

Pathophysiological mechanisms in the hyperacute phase of AIS (<6 h after symptom onset) determined by thrombus formation and subsequent resolution might explain the early rise in D-dimer levels.[5] Our finding of higher D-dimer levels in patients with intracranial vessel occlusions supports this hypothesis. The slight decrease in D-dimer levels between 6 and 35 h after symptom onset may be attributable to its rapid turnover resulting from a short half-life of 6 to 8 h.[24] A similar dynamic of decreasing D-dimer levels in the first hours after a thrombotic event has been reported in patients with VTE.[25] The second, later increase of D-dimer levels after 35 h may reflect the cerebral thromboinflammation process occurring in the late acute phase of AIS (6-48 h after symptom onset).[5,6] Although our study showed variations in D-dimer levels over time, further etiological investigations may be indicated if there is a clinical suspicion for venous thromboembolism with a D-dimer level ≥500 µg/L.[3] Furthermore, among patients with embolic stroke of undetermined source and concomitant cancer, emerging data indicate that D-dimer levels exceeding 2500 µg/L confer an increased risk for reS-current cerebrovascular events and other adverse outcomes.[26] For these reasons, and considering that the test is fairly inexpensive, it would be reasonable for hospital programs to integrate blood D-dimer measurements into their standard initial laboratory evaluations for patients presenting with AIS or TIA.

Overall, patients with TIA presented with lower D-dimer levels than patients with AIS.[27] This could be due to the lack of a persistent vessel occlusion and associated thrombus in TIA.[22] Furthermore, the fluctuation of D-dimer levels seen over time in AIS patients was not observed in TIA patients. A possible explanation could by the occurrence of initially smaller thrombi, their faster resolution and the absence of irreversible brain damage (resulting in cerebral thromboinflammation) in TIA patients. D-dimer may be a useful biomarker in patients with TIA, as it has been previously associated with confirmation of the underlying TIA diagnosis as well as the risk of subsequent AIS.[28,29] In AIS patients, anticoagulation was associated with consistently lower D-dimer levels (Table 1). This finding is in line with the current evidence from studies on VTE.[30,31] Studies in patients with cancer-related AIS have also demonstrated a reduction in D-dimer levels over time with anticoagulation.[32]

Limitations

This study has limitations. Firstly, all biases associated with a retrospective and single-center design apply. For instance, selection bias is possible, particularly because, at our institution, patients with AIS and TIA initially evaluated by internal medicine physicians do not receive systematic D-dimer assessments. This could have led to the non-differential exclusion of some patients with ischemic cerebrovascular events. Information bias is also possible as some relevant data were missing from the electronic medical records. Secondly, the D-dimer levels were routinely measured only at presentation or during the index hospitalization at our institution. The absence of follow-up D-dimer measurements in our cohort made it impossible to assess the dynamics of D-dimer levels over time at an individual level. Thirdly, information on infarct volume, previously associated with higher D-dimer levels on admission, is not available in our database.[19] Site of vessel occlusion and NIHSS score reflecting stroke severity were used as covariates to compensate for this. Fourthly, D-dimer levels can be influenced by external factors, including infection, systemic inflammation, atrial fibrillation, pregnancy, and trauma.[4,33–35] These factors need to be considered by clinicians when interpreting D-dimer levels in patients with AIS or TIA.

Conclusion

Our study demonstrated that time from symptom onset to blood collection impacted D-dimer levels in patients with AIS but not those with TIA. We also found lower D-dimer levels in patients with AIS taking anticoagulants. A prospective study with sequential D-dimer measurements during the acute and subacute periods of ischemic cerebrovascular events (days 0-14) are needed to confirm these findings.

Funding

This work was supported by grants provided by the Department of Neurology, Inselspital, Bern University Hospital, and University of Bern (research grant diversity and excellence in clinical research 2022) and the University of Bern (UniBE Doc. Mobility grant).

Ethical approval

The ethics committee approved the study in accordance with Swiss law (reference ID: 2021-01031 and ID: 2022-01560, Kantonale Ethikkommission Bern). The study adheres to the STROBE checklist for cohort studies. As stated by decision of the ethics committee, a written consent from patients was not required for the inclusion in this retrospective study.

Informed consent

According to the ethics committee's decision, no informed consent was required for the inclusion of patients in the study.

Guarantor

Morin Beyeler & Philipp Bücke

CRediT authorship contribution statement

Recep-Ali Hacialioglu: Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Moritz Kielkopf:** Writing – original draft, Investigation, Data curation, Conceptualization. **Mattia Branca:** Supervision, Formal analysis, Data curation. **Leander Clenin:** Validation. **Anna Boronylo:** Writing – review & editing. **Norbert Silimon:** Writing – review & editing. **Martina B. Göldlin:** Writing – review & editing. **Adrian Scutelnic:** Writing – review & editing. **Johannes Kaesmacher:** Writing – review & editing, Conceptualization. **Adnan Mujanovic:** Writing – review & editing. **Thomas R. Meinel:** Writing – review & editing. **David J. Seiffge:** Writing – review & editing. **Mirjam R. Heldner:** Writing – review & editing. **Ava L. Liberman:** Writing – review & editing. **Babak B. Navi:** Writing – review & editing. **Urs Fischer:** Writing – review & editing. **Marcel Arnold:** Writing – review & editing. **Simon Jung:** Writing – review & editing, Supervision, Conceptualization. **Philipp Bücke:** Writing – review & editing, Supervision, Investigation, Conceptualization. **Morin Beyeler:** Writing – review & editing, Writing – original draft, Supervision, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

Dr. Arnold reports personal fees from Bayer, Bristol-Myers Squibb, Medtronic, Amgen, Daiichi Sankyo, Nestlé Health Sciences, Boehringer Ingelheim, and Covidien during the conduct of the study.

Dr. Jung reports grants from the Swiss National Science Foundation and the Swiss Heart Foundation.

Dr. Beyeler reports research support from the Department of Neurology, Inselspital, Bern University Hospital and the University of Bern, Switzerland.

None of the other authors report any conflicts of interest.

Acknowledgements

We gratefully acknowledge Susan Kaplan, MSc (University Hospital of Bern, Bern, Switzerland), for her uncompensated review of the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jstrokecerebrovasdis.2024.107834.

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