Journal of the American Heart Association

ORIGINAL RESEARCH

Association of Level and Increase in D-Dimer With All-Cause Death and Poor Functional Outcome After Ischemic Stroke or Transient Ischemic Attack

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BACKGROUND: D-dimer is involved in poor outcomes of stroke as a coagulation biomarker. We aimed to investigate the associations of the level and increase in D-dimer between baseline and 90 days with all-cause death or poor functional outcome in patients after ischemic stroke or transient ischemic attack.

METHODS AND RESULTS: We collected data from the CNSRIII (Third China National Stroke Registry) study. The present substudy included 10 518 patients within 7 days (baseline) of ischemic stroke or transient ischemic attack and 6268 patients at 90 days. Poor functional outcome at 1 year was assessed on the basis of the modified Rankin Scale (≥3). Multivariable Cox regression or logistic regression was used to assess the association of D-dimer levels with all-cause death or poor functional outcome. D-dimer levels at 90 days were lower than those at baseline (1.4 μg/mL versus 1.7 μg/mL; $P<0.001$). Higher baseline D-dimer level was associated with all-cause death (adjusted hazard ratio [HR], 1.77; 95% CI, 1.25–2.52; $P=0.001$) and poor functional outcome (adjusted odds ratio [OR], 1.49; 95% CI, 1.23–1.80; $P<0.001$) during 1-year follow-up. Higher D-dimer level at 90 days was also associated with poor outcomes independently. Furthermore, an increase in D-dimer levels between baseline and 90 days was associated with all-cause death (since 90 days to 1 year after index event) (adjusted HR, 1.99; 95% CI, 1.12–3.53; $P=0.019$) but not with poor functional outcome (adjusted OR, 1.08; 95% CI, 0.82–1.41).

CONCLUSIONS: Our study shows that high level and an increase in D-dimer between baseline and 90 days are associated with poor outcomes in patients after ischemic stroke or transient ischemic attack.

Key Words: D-dimer ■ outcome ■ risk factor ■ stroke ■ transient ischemic attack

Cerebrovascular disease is the leading cause of death and disability in China, with the majority of cases (69.6%–70.8%) involving ischemic stroke and transient ischemic attack (TIA).[1,2] Identifying potential risk factors of poor outcomes and developing targeted therapeutics are critical. In particular, we recently reported that lipid metabolism and inflammatory factors were associated with stroke outcomes.[3–5]

D-dimer, which is a fibrin degradation product, is a biomarker for coagulation and reflects increased thrombosis.[6,7] Although D-dimer level has been clearly confirmed to be associated with death in the general population in the long term,[8,9] only a few studies assessed the association of D-dimer with death[10–12] or poor functional outcome[13–15] in patients after stroke. However, a previous study reported that high D-dimer level was no longer associated with all-cause death after further adjustment for several variables in acute stroke.[16] Overall, the major findings indicated that high D-dimer levels may be associated

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CLINICAL PERSPECTIVE

What Is New?

- Baseline and 90-day D-dimer levels were associated with all-cause death and poor functional outcome in a large population with ischemic stroke or transient ischemic attack.
- An increase in D-dimer levels was associated with all-cause death after ischemic stroke or transient ischemic attack.

What Are the Clinical Implications?

- Dynamic measurements of D-dimer levels might be helpful for identifying patient with stroke or transient ischemic attack at a higher risk of recurrent events.
- It is uncertain if patients with stroke or transient ischemic attack and an elevated D-dimer may benefit from more aggressive antithrombotic or anticoagulant measures for secondary stroke prevention.

Nonstandard Abbreviations and Acronyms

CNSRIII	Third China National Stroke Registry
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
TOAST	Trial of Org 10172 in Acute Stroke Treatment

with poor outcomes in patients with stroke. However, these studies measured D-dimer at only a single time point and did not consider the different phases of recovery after stroke. Because D-dimer levels change during progression of stroke,[17,18] whether this relative change is associated with poor outcomes after stroke remains unclear.

We hypothesized that the level and an increase in D-dimer are associated with poor outcome. Using data from the CNSRIII (Third China National Stroke Registry) study, the present study aimed to examine the associations of the levels and changes in D-dimer between baseline and 90 days with poor outcomes followed up to 1 year.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Participants

The study design and methods for the CNSRIII were previously reported.[19] The CNSRIII is a nationwide prospective registry of patients presenting to hospitals with acute ischemic stroke or TIA within 7 days of symptom onset from 201 hospitals in China.[19] The present substudy enrolled 10 518 patients with D-dimer levels measured at admission (baseline), and 6268 patients with D-dimer levels measured at 90 days after ischemic stroke or TIA. The ethics committee of the study center approved the study protocol. Written informed consent was provided by all participants or their legal proxies.

The CNSRIII study was performed according to the principles expressed in the Declaration of Helsinki.

Measurement of Biomarkers

Fasting blood samples from CNSRIII patients were obtained within 24 hours of admission and at 90 days. EDTA plasma and serum samples were extracted and stored in cryotube at −80°C until use. No freezing or thawing circle occurred before testing. D-dimer and fibrinogen levels were measured using an OLYMPUS AU2700 analyzer (Beckman, Japan) and an immuno-turbidimetric assay (Kamiya Biomedical, Seattle, WA, USA), as previously reported.[6,11,20,21] Hs-CRP (high-sensitivity C-reactive protein) was tested on a Cobas c501 analyzer using a cardiac CRP (latex) high-sensitive assay (Roche, Basel, Switzerland). Measurements were performed in a core laboratory certified by the College of American Pathologists, with laboratory personnel blinded to the clinical data according to the manufacturers' recommendations.

Functional Outcomes and Follow-Up

The study outcomes included all-cause death or poor functional outcome at 1-year follow-up interview. Poor functional outcome was defined as a modified Rankin Scale of 3 to 6. Information on death was confirmed on a death certificate from the attended hospital or the local citizen registry. Patients with a modified Rankin Scale ranging from 0 to 5 were assessed at 1-year follow-up over the telephone by trained research coordinators.

Statistical Analysis

Demographic and clinical characteristics were analyzed using quartiles of D-dimer levels with χ^2 statistics for categorical variables and the Kruskal–Wallis test for continuous variables. Absolute levels and the relative change in D-dimer were assessed as categorical variables. For categorical analyses, individuals were classified according to quartiles of the distribution of D-dimer levels as previously described.[22] Because

D-dimer levels were measured in different populations in the acute stage (baseline) and recovery stage (90 days), baseline cut points of <0.6, ≥0.6 to 1.0, ≥1.1 to 2.0, and >2.0 µg/mL and 90-day cut points of <0.5, ≥0.5 to 0.8, ≥0.9 to 1.5, and >1.5 µg/mL were used, respectively. The lowest quartile group was used as the reference group. To assess the association of a change (decrease, unchanged, and increase) in D-dimer levels between baseline and 90 days with poor outcomes, individuals were classified according to tertiles of the change and the tertile 2 group was used as the reference group.

The associations of the levels and changes in D-dimer with poor outcomes were assessed. For all-cause death, adjusted hazard ratios (HRs) with 95% CIs were assessed using a Cox regression model. The proportional hazards assumption was tested by adding a time-dependent covariate with interaction of D-dimer and a logarithmic function of survival time in the Cox model. For poor functional outcome, adjusted odds ratios (ORs) with their 95% CIs were assessed by a logistic regression model. Variables with a P value of <0.05 in the baseline characteristics were incorporated into the multiple linear models. Subsequently, variables with a P value of <0.1 were screened out by the backward method and then used as correction covariates in the multivariate models to investigate the associations of levels or changes in D-dimer with poor outcomes. We also evaluated the association between changes in D-dimer levels (continuous measures) and the risk of poor outcomes with restricted cubic splines that were adjusted for all potential covariates.

All statistical analyses were conducted by SAS software, version 9.4 (SAS Institute Inc, Cary, NC). All P values were 2-sided and $P<0.05$ was considered to be statistically significant.

RESULTS

Baseline Characteristics

Of 15 166 patients in the CNSRIII study, 10 518 patients at baseline and 6268 patients at 90 days provided plasma samples for D-dimer measurement. There were no differences in the baseline characteristics between the included and excluded patients, apart from a slightly higher proportion of history of dyslipidemia, atrial fibrillation, and ischemic stroke in the included patients with acute ischemic stroke or TIA, and a slightly lower proportion of history of atrial fibrillation in the included patients at 90 days after ischemic stroke or TIA (Tables S1 and S2). Of the 10 518 included patients, the mean age was 62.3±11.4 years and 3283 (31.21%) were female. The median D-dimer level was 1.1 (interquartile range, 0.6–2.1) µg/mL.

Patients with a high D-dimer level were older, had a higher proportion of females, had a higher baseline National Institutes of Health Stroke Scalescore, and had a history of atrial fibrillation. Table 1 shows the baseline characteristics of included patients within 7 days after stratification according to D-dimer quartiles. Of the 6268 included patients at 90 days, the mean age was 61.8±11.1 years and 1962 (31.30%) were female. The median D-dimer level was 0.9 (interquartile range, 0.5–1.5) µg/mL. Patients with high D-dimer level were older, had a higher proportion of females, and had a higher 90-day modified Rankin Scale. Table 2 shows the baseline characteristics of included patients at 90 days after stratification according to D-dimer quartiles. For patients with 2 measurements, the median change in the D-dimer levels was −0.2 µg/mL (interquartile range, −1.0 to 0.4 µg/mL). The baseline characteristics of patients with 2 measurements after stratification according to the tertiles of changes are shown in Table S3.

Baseline D-Dimer Levels and Poor Outcomes

The associations of absolute D-dimer levels with poor outcomes are shown in Table 3. Baseline D-dimer levels were strongly associated with all-cause death (P for trend <0.001) (Figure 1) and poor functional outcome (P for trend <0.001) in acute ischemic stroke or TIA. Of the 10 518 patients, 3.36% died (41.08% of whom died of cardiovascular causes, 32.01% of noncardiovascular cause, and 26.91% of unknown causes) and 13.03% had a poor functional outcome during 1-year follow-up.

According to the multiple linear regression analysis (Table S4), the potential confounding risk factors were adjusted. Baseline D-dimer level in quartile 4 was associated with an increased risk of all-cause death (adjusted HR, 1.87; 95% CI, 1.33–2.63; $P<0.001$) compared with quartile 1 in model 1. After further adjustment for baseline fibrinogen and hs-CRP levels, this association remained significant (adjusted HR, 1.77; 95% CI, 1.25–2.52; $P<0.001$) in model 2. Baseline D-dimer level in quartile 4 was associated with an increased risk of poor functional outcome (adjusted OR, 1.59; 95% CI, 1.32–1.91; $P<0.001$) compared with quartile 1 in model 1. After further adjustment for baseline fibrinogen and hs-CRP levels, this association remained significant (adjusted OR, 1.49; 95% CI, 1.23–1.80; $P<0.001$) in model 2.

D-Dimer Levels at 90 Days and Poor Outcomes

D-dimer levels at 90 days were strongly associated with all-cause death (P for trend <0.001) (Figure 1) and

Table 1. Characteristics of the Study Population (n=10 518) by D-Dimer Quartiles in Patients With Acute Ischemic Stroke or TIA

Characteristics	All (N=10 518)	Quartiles of D-Dimer at Baseline				P Value
		<0.6 µg/mL (N=2512)	0.6–1.0 µg/mL (N=2453)	1.1–2.0 µg/mL (N=2866)	>2.0 µg/mL (N=2687)	
Age, mean (SD), y	62.3±11.4	59.4±10.7	61.5±10.9	63.1±11.3	64.8±11.7	<0.001
Female, n (%)	3283 (31.2)	669 (26.6)	766 (31.2)	896 (31.3)	952 (35.4)	<0.001
Body mass index, median (IQR), kg/m^2	24.5 (22.5–26.5)	24.5 (22.7–26.5)	24.5 (22.8–26.6)	24.5 (22.6–26.7)	24.2 (22.1–26.2)	<0.001
Smoking, n (%)	3348 (31.8)	894 (35.6)	782 (31.9)	925 (32.3)	747 (27.8)	<0.001
Drinking, n (%)	1502 (14.3)	430 (17.1)	348 (14.2)	380 (13.3)	344 (12.8)	<0.001
Baseline National Institutes of Health Stroke Scale, n (%)						<0.001
≤3	5616 (53.4)	1423 (56.7)	1347 (54.9)	1540 (53.7)	1306 (48.6)	
>3	4902 (46.6)	1089 (43.4)	1106 (45.1)	1326 (46.3)	1381 (51.4)	
Fibrinogen, median (IQR), g/L	3.8 (3.2–4.5)	3.7 (3.1–4.4)	3.8 (3.2–4.5)	3.9 (3.2–4.6)	3.9 (3.1–4.7)	<0.001
High-sensitivity C-reactive protein, median (IQR), mg/L	1.8 (0.8–4.8)	1.3 (0.7–3.0)	1.6 (0.8–3.9)	2.0 (0.8–5.1)	2.8 (1.0–8.1)	<0.001
Time after event within 24 h, n (%)	7803 (74.2)	1832 (72.9)	1797 (73.3)	2116 (73.8)	2058 (76.6)	0.009
History of hypertension, n (%)	6573 (62.5)	1577 (62.8)	1545 (63.0)	1815 (63.3)	1636 (60.9)	0.245
History of diabetes mellitus, n (%)	2486 (23.6)	608 (24.2)	582 (23.7)	713 (24.9)	583 (21.7)	0.037
History of dyslipidemia, n (%)	898 (8.5)	231 (9.2)	207 (8.4)	246 (8.6)	214 (8.0)	0.464
History of atrial fibrillation, n (%)	763 (7.3)	107 (4.3)	124 (5.1)	214 (7.5)	318 (11.8)	<0.001
History of ischemic stroke, n (%)	2231 (21.2)	513 (20.4)	501 (20.4)	617 (21.5)	600 (22.3)	0.258
History of TIA, n (%)	316 (3.0)	81 (3.2)	78 (3.2)	89 (3.1)	68 (2.5)	0.416
History of myocardial infarction, n (%)	228 (2.2)	56 (2.2)	56 (2.3)	57 (2.0)	59 (2.2)	0.887
History of angina, n (%)	411 (3.9)	89 (3.5)	85 (3.5)	120 (4.2)	117 (4.4)	0.242
History of venous thrombus, n (%)	39 (0.4)	5 (0.2)	8 (0.3)	10 (0.4)	16 (0.6)	0.119
History of heart failure, n (%)	75 (0.7)	11 (0.4)	10 (0.4)	22 (0.8)	32 (1.2)	0.002
Complication during hospitalization, n (%)						
Pulmonary infection	582 (5.5)	68 (2.7)	117 (4.8)	144 (5.0)	253 (9.4)	<0.001
Urinary infection	156 (1.5)	28 (1.1)	27 (1.1)	40 (1.4)	61 (2.3)	0.001
Deep vein thrombosis	63 (0.6)	11 (0.4)	11 (0.5)	11 (0.4)	30 (1.1)	0.001
Trial of Org 10172 in Acute Stroke Treatment subtypes, n (%)						<0.001
Large artery atherosclerosis	2625 (25.0)	599 (23.9)	596 (24.3)	745 (26.0)	685 (25.49)	
Small artery occlusion	2184 (20.6)	580 (23.1)	552 (22.5)	581 (20.3)	471 (17.53)	
Cardioembolism	685 (6.5)	115 (4.6)	123 (5.0)	200 (7.0)	247 (9.2)	
Other/undetermined	116 (1.1)	22 (0.9)	22 (0.9)	32 (1.1)	40 (1.5)	
Undefined	4908 (46.7)	1196 (47.6)	1160 (47.3)	1308 (45.6)	1244 (46.3)	
Ischemic stroke, n (%)	9790 (93.1)	2326 (92.6)	2285 (93.2)	2664 (93.0)	2525 (93.6)	0.546
TIA, n (%)	728 (6.9)	186 (7.4)	168 (6.9)	202 (7.1)	172 (6.4)	

IQR indicates interquartile range; and TIA, transient ischemic attack.

poor functional outcome (*P* for trend <0.001). Of the 6268 patients, 1.29% died (34.57% of whom died of cardiovascular causes, 39.51% of noncardiovascular cause, and 25.93% of unknown causes 90 days to 1 year after the index event) and 3.36% had a poor functional outcome followed up to 1 year.

D-dimer levels at 90 days in quartile 2, quartile 3, and quartile 4 were associated with an increased risk of all-cause death (adjusted HR, 3.52; 95% CI, 1.18–10.47; *P*=0.024; adjusted HR, 3.45; 95% CI, 1.18–10.12; *P*=0.024; and adjusted HR, 4.79; 95% CI, 1.69–13.54; *P*=0.003) compared with quartile

Table 2. Characteristics of the Study Population (n=6268) by D-Dimer Quartiles at 90 Days After Ischemic Stroke or TIA

Characteristics	All (N=6268)	Quartiles of D-Dimer at 90 d				P Value
		<0.5 µg/mL (N=1385)	0.5–0.8 µg/mL (N=1609)	0.9–1.5 µg/mL (N=1648)	>1.5 µg/mL (N=1626)	
Age, mean (SD), y	61.8±11.1	59.0±10.8	60.6±10.6	62.0±10.9	65.2±11.3	<0.001
Female, n (%)	1962 (31.3)	369 (26.6)	499 (31.0)	529 (32.1)	565 (34.8)	<0.001
Body mass index, median (IQR), kg/m²	24.5 (22.8–26.7)	24.7 (23.0–26.8)	24.5 (22.8–26.7)	24.7 (22.8–26.8)	24.2 (22.5–27.2)	<0.001
Smoking, n (%)	2021 (32.2)	489 (35.3)	564 (35.1)	529 (32.1)	439 (27.0)	<0.001
Drinking, n (%)	897 (14.3)	191 (13.8)	271 (16.8)	239 (14.5)	196 (12.1)	0.001
Baseline National Institutes of Health Stroke Scale, n (%)						0.009
≤3	3512 (56.0)	815 (58.8)	927 (57.6)	899 (54.6)	871 (53.6)	
>3	2756 (44.0)	570 (41.2)	682 (42.4)	749 (45.5)	755 (46.4)	
90-d modified Rankin Scale score, n (%)						<0.001
≤2	5604 (89.4)	1281 (92.6)	1486 (92.4)	1489 (90.4)	1348 (83.0)	
>2	662 (10.6)	103 (7.4)	123 (7.6)	159 (9.7)	277 (17.1)	
Fibrinogen, median (IQR), g/L	4.2 (3.5–5.0)	4.0 (3.4–4.8)	4.1 (3.4–4.9)	4.3 (3.5–5.0)	4.3 (3.5–5.3)	<0.001
High-sensitivity C-reactive protein, median (IQR), mg/L	1.2 (0.7–2.8)	1.1 (0.6–2.1)	1.1 (0.6–2.4)	1.2 (0.7–2.5)	2.7 (0.9–4.1)	<0.001
History of hypertension, n (%)	3936 (62.8)	847 (61.2)	991 (61.6)	1038 (63.0)	1060 (65.2)	0.085
History of diabetes mellitus, n (%)	1455 (23.2)	312 (22.5)	386 (24.0)	382 (23.2)	375 (23.1)	0.818
History of dyslipidemia, n (%)	511 (8.2)	117 (8.5)	138 (8.6)	123 (7.5)	133 (8.2)	0.661
History of atrial fibrillation, n (%)	362 (5.8)	69 (5.0)	82 (5.1)	93 (5.6)	118 (7.3)	0.023
History of ischemic stroke, n (%)	1333 (21.3)	291 (21.0)	335 (20.8)	334 (20.3)	373 (22.9)	0.267
History of TIA, n (%)	203 (3.2)	44 (3.2)	54 (3.4)	56 (3.4)	49 (3.0)	0.922
History of myocardial infarction, n (%)	109 (1.7)	21 (1.5)	28 (1.7)	20 (1.2)	40 (2.5)	0.046
History of angina, n (%)	262 (4.2)	59 (4.3)	64 (4.0)	66 (4.0)	73 (4.5)	0.873
History of venous thrombus, n (%)	28 (0.5)	4 (0.3)	12 (0.8)	5 (0.3)	7 (0.4)	0.188
History of heart failure, n (%)	28 (0.5)	9 (0.7)	5 (0.3)	4 (0.2)	10 (0.6)	0.210
Complication during hospitalization, n (%)						
Pulmonary infection	243 (3.9)	35 (2.5)	58 (3.6)	54 (3.3)	96 (5.9)	0.053
Urinary infection	73 (1.2)	9 (0.7)	18 (1.1)	18 (1.1)	28 (1.7)	<0.001
Deep vein thrombosis	34 (0.5)	4 (0.3)	5 (0.3)	9 (0.6)	16 (1.0)	0.028
Trial of Org 10172 in Acute Stroke Treatment subtypes, n (%)						0.008
Large artery atherosclerosis	1565 (25.0)	313 (22.6)	411 (25.5)	429 (26.0)	412 (25.3)	
Small artery occlusion	1475 (23.5)	347 (25.1)	411 (25.5)	375 (22.8)	342 (21.0)	
Cardioembolism	338 (5.4)	62 (4.5)	83 (5.2)	86 (5.2)	107 (6.6)	
Other/undetermined	68 (1.1)	17 (1.2)	20 (1.2)	20 (1.2)	11 (0.7)	
Undefined	2822 (45.0)	646 (46.6)	684 (42.5)	738 (44.8)	754 (46.4)	
Ischemic stroke, n (%)	5792 (92.4)	1261 (91.1)	1492 (92.8)	1530 (92.8)	1509 (92.8)	0.196
TIA, n (%)	476 (7.6)	124 (9.0)	117 (7.3)	118 (7.2)	117 (7.2)	

IQR indicates interquartile range; and TIA, transient ischemic attack.

1 in model 1. After further adjustment for 90-day fibrinogen and hs-CRP levels, this association remained significant (adjusted HR, 3.52; 95% CI, 1.18–10.50; *P*=0.024; adjusted HR, 3.50; 95% CI, 1.20–10.27; *P*=0.022; and adjusted HR, 4.62; 95% CI, 1.63–13.10; *P*=0.004) in model 2. D-dimer levels at 90 days in quartile 3 and quartile 4 were associated with an increased risk of poor functional outcome (adjusted OR, 1.46; 95% CI, 1.04–2.04; *P*=0.027 and adjusted OR, 1.75; 95% CI, 1.27–2.41; *P*=0.001) compared with quartile 1 in model 1. After further adjustment for 90-day fibrinogen and hs-CRP levels, this association remained significant (adjusted OR, 1.44; 95% CI, 1.03–2.01; *P*=0.035 and adjusted OR, 1.70; 95% CI, 1.23–2.35; *P*=0.001) in model 2.

Table 3.   Hazard Ratio/Odd Ratio of Poor Outcomes According to D-Dimer Quartile Categories

Outcomes	D-Dimer Levels	N	Events, n (%)	Crude OR/HR (95% CI)*	P Value	Adjusted Model 1† OR/HR (95% CI)*	P Value	Adjusted Model 2‡ OR/HR (95% CI)*	P Value	P for Trend
D-dimer level at baseline										
All-cause death	<0.6 µg/mL	2512	45 (1.79)	1 (Reference)	...	1 (Reference)	...	1 (Reference)	...	<0.001
	0.6–1.0 µg/mL	2453	61 (2.49)	1.39 (0.94–2.04)	0.097	1.17 (0.79–1.72)	0.431	1.19 (0.80–1.76)	0.390	
	1.1–2.0 µg/mL	2866	80 (2.79)	1.57 (1.09–2.25)	0.016	1.16 (0.80–1.67)	0.436	1.14 (0.791–1.67)	0.483	
	>2.0 µg/mL	2687	167 (6.22)	3.55 (2.55–4.93)	<0.001	1.87 (1.33–2.63)	<0.001	1.77 (1.25–2.52)	0.001	
Poor functional outcome§	<0.6 µg/mL	2443	215 (8.80)	1 (Reference)	...	1 (Reference)	...	1 (Reference)	...	<0.001
	0.6–1.0 µg/mL	2403	270 (11.24)	1.31 (1.09–1.58)	0.005	1.12 (0.92–1.37)	0.264	1.08 (0.88–1.32)	0.486	
	1.1–2.0 µg/mL	2788	371 (13.31)	1.59 (1.33–1.90)	<0.001	1.23 (1.02–1.49)	0.031	1.20 (0.99–1.46)	0.062	
	>2.0 µg/mL	2617	515 (19.68)	2.54 (2.14–3.01)	<0.001	1.59 (1.32–1.91)	<0.001	1.49 (1.23–1.80)	<0.001	
D-dimer level at 90 d										
All-cause death	<0.5 µg/mL	1385	4 (0.29)	1 (Reference)	...	1 (Reference)	...	1 (Reference)	...	<0.001
	0.5–0.8 µg/mL	1609	17 (1.06)	3.69 (1.21–10.96)	0.019	3.52 (1.18–10.47)	0.024	3.52 (1.18–10.50)	0.024	
	0.9–1.5 µg/mL	1648	20 (1.21)	4.21 (1.44–12.32)	0.009	3.45 (1.18–10.12)	0.024	3.50 (1.20–10.27)	0.022	
	>1.5 µg/mL	1626	40 (2.46)	8.64 (3.09–24.15)	<0.001	4.79 (1.69–13.54)	0.003	4.62 (1.63–13.10)	0.004	
Poor functional outcome§	<0.5 µg/mL	1375	80 (5.82)	1 (Reference)	...	1 (Reference)	...	1 (Reference)	...	<0.001
	0.5–0.8 µg/mL	1589	120 (7.55)	1.32 (0.99–1.77)	0.061	1.35 (0.95–1.91)	0.091	1.32 (0.94–1.88)	0.110	
	0.9–1.5 µg/mL	1634	154 (9.42)	1.68 (1.27–2.23)	<0.001	1.46 (1.04–2.04)	0.027	1.44 (1.03–2.01)	0.035	
	>1.5 µg/mL	1602	256 (15.98)	3.08 (2.37–4.00)	<0.001	1.75 (1.27–2.41)	0.001	1.70 (1.23–2.35)	0.001	

HR indicates hazard ratio; and OR, odd ratio.

*HR for all-cause death, and OR for poor functional outcome.

†Adjusted for age, sex, baseline National Institutes of Health Stroke Scale, body mass index, diabetes mellitus, atrial fibrillation, heart failure, pulmonary infection, deep vein thrombosis, and TOAST (Trial of Org 10172 in Acute Stroke Treatment) at baseline; adjusted for age, sex, baseline National Institutes of Health Stroke Scale, drinking, 90-day modified Rankin Scale score, myocardial infarction, pulmonary infection, and TOAST at 90 days.

‡Adjusted for the same risk factors as † plus fibrinogen and high-sensitivity C-reactive protein.

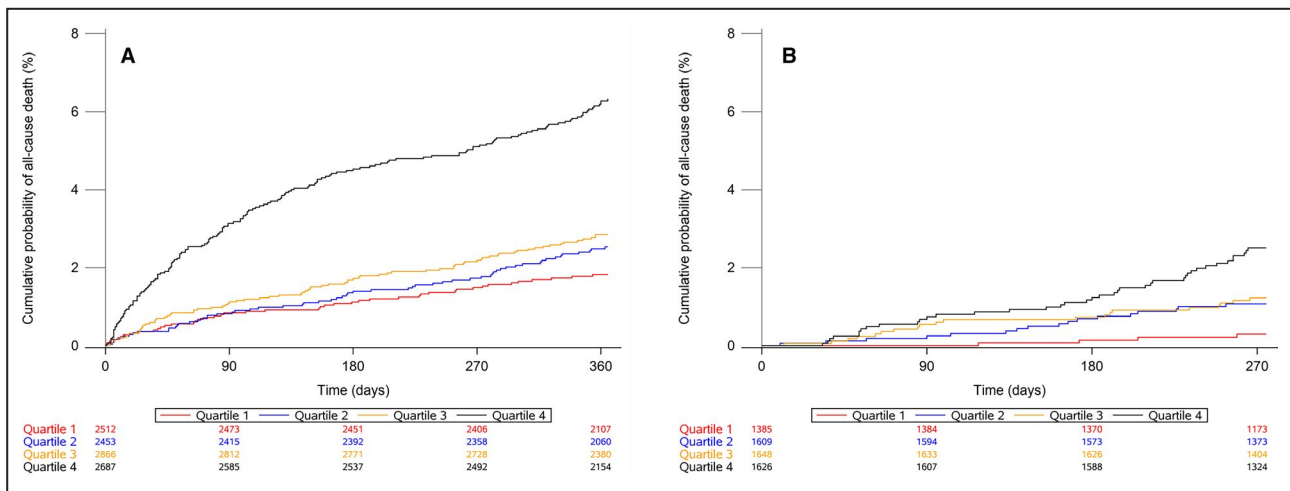§Poor functional outcome: modified Rankin scale score 3 to 6.

Figure 1.   Kaplan-Meier curves show the time to all-cause death according to D-dimer levels.
A, At baseline and (**B**) 90 days.

Change in D-Dimer Levels With Poor Outcomes

The associations of changes in D-dimer levels between baseline and 90 days with poor outcomes followed up to 1 year are shown in Table 4. After adjustment for all potential confounding factors, an increase in D-dimer levels in tertile 3 was associated with an increased risk of all-cause death (adjusted HR, 1.99; 95% CI, 1.12–3.53; P=0.019) compared with a smaller change in D-dimer levels in tertile 2. However, an increase in D-dimer levels was not associated with poor functional outcome (adjusted OR, 1.08; 95% CI, 0.82–1.41; P=0.586).

By using a regression model with a restricted cubic spline, we found that the correlation between increase in D-dimer and 1-year all-cause death (Figure 2).

DISCUSSION

In the present study, we found that D-dimer levels at 90 days were significantly lower than those at baseline. Baseline and 90-day D-dimer levels were associated with all-cause death and poor functional outcome. Furthermore, an increase in D-dimer levels was associated with all-cause death after ischemic stroke or TIA.

High D-dimer reflects thrombus formation and hypercoagulation,[23] and it is associated with death in patients with coronary artery disease and cancer.[24,25] However, the evidence of association between D-dimer levels and death or poor functional outcome after stroke is limited and inconsistent. A meta-analysis that included 9 studies showed that high D-dimer levels within 24 hours of stroke onset were associated with death and poor functional outcome.[14] However, 4 studies showed that these associations were no longer significant in multivariate models.[14] Stroke severity[16] and stroke subtypes[26] were found to be associated with poor outcomes. However, some studies suggested that high D-dimer level was associated with an increased risk for death or poor functional outcome

Table 4.   Association of Change in D-Dimer With Poor Outcomes

Outcomes	Groups	Crude OR/HR (95% CI)*	P Value	Adjusted Model 1[†] OR/HR (95% CI)	P Value	Adjusted Model 2[‡] OR/HR (95% CI)	P Value
All-cause death	< −0.7 µg/mL	1.24 (0.65–2.37)	0.510	0.98 (0.51–1.89)	0.957	0.94 (0.48–1.81)	0.841
	−0.7 to 0.2 µg/mL	1 (Reference)	…	1 (Reference)	…	1 (Reference)	…
	>0.2 µg/mL	2.26 (1.27–4.00)	0.005	1.98 (1.11–3.51)	0.020	1.99 (1.12–3.53)	0.019
Poor functional outcome[§]	< −0.7 µg/mL	1.28 (1.02–1.60)	0.032	0.94 (0.72–1.24)	0.658	0.93 (0.71–1.23)	0.622
	−0.7 to 0.2 µg/mL	1 (Reference)	…	1 (Reference)	…	1 (Reference)	…
	>0.2 µg/mL	1.38 (1.11–1.72)	0.004	1.07 (0.82–1.40)	0.624	1.08 (0.82–1.41)	0.586

HR indicates hazard ratio; and OR, odd ratio.

*HR for all-cause death, and OR for poor functional outcome.

[†]Adjusted for baseline National Institutes of Health Stroke Scale, 90-day modified Rankin Scale score, atrial fibrillation, venous thrombus, and Trial of Org 10172 in Acute Stroke Treatment.

[‡]Adjusted for the same risk factors as † plus fibrinogen and high-sensitivity C-reactive protein at 90 days.

[§]Poor functional outcome: modified Rankin scale score 3 to 6.

and these associations were independent of stroke severity or stroke type in acute ischemic stroke.[10,11,27] In contrast, a prospective, single-center study showed that high D-dimer level was no longer associated with an increased risk of death during follow-up in a multivariate model,[16] which included some biomarkers in addition to clinical risk factors. D-dimer might act as a stimulant to the inflammatory process.[28] Therefore, more adjustment for potential inflammatory factors may eliminate the association of D-dimer levels with poor outcome.[16,29] Because hs-CRP and fibrinogen are the most common markers of inflammation or hypercoagulability, they show a moderate correlation with D-dimer.[30] Previous studies have suggested that when hs-CRP is taken into account, D-dimer was no longer associated with poor outcomes.[30,31] Additionally, early stroke-related deep vein thrombosis[32] and infection[33,34] have an increased risk of poor outcome. In our study, stroke-related pulmonary infection and deep venous thrombosis were adjusted in addition to stroke subtypes and stroke severity. Furthermore, hs-CRP and fibrinogen were further adjusted in an additional multivariate model in this study. We found that high D-dimer level was associated with poor outcomes independent of all of the aforementioned risk factors.

D-dimer levels are higher in acute stroke and change during progression of stroke.[17,35] Because of these sequential changes in D-dimer levels after stroke, measurements at different phases of recovery after stroke may be helpful for fully understanding the association of D-dimer levels with stroke. Consistent with previous study, we found that D-dimer levels were significantly decreased at 90 days compared with those at baseline.[36] To date, there have been no studies regarding D-dimer measurements at 2 points to identify its association with poor outcomes after stroke. In the present study, we also found that high D-dimer level at 90 days was an independent risk factor for poor outcomes.

Several mechanisms may explain the association of high D-dimer levels with poor outcomes. One explanation is that D-dimer may play an important role in coagulation activity, thrombin generation, and fibrin formation. High D-dimer level might be associated with progression of stroke.[28] This may subsequently aggravate the severity of stroke and lead to poor outcomes. There is also evidence that D-dimer is the most common risk factor of venous thrombosis events after stroke, which might reflect a prothrombotic state that increases susceptibility to a major thrombotic event.[22] Another potential explanation is that D-dimer might mediate the inflammatory response. Previous studies have suggested that D-dimer upregulates the interleukin-6 pathway,[37] which was confirmed to be associated with recurrent vascular diseases.[38] Because recurrent vascular disease is unfavorable, subsequent vascular events might lead to functional disability.[4]

We further evaluated the association of an increase in D-dimer levels between baseline and 90 days with poor outcomes. Although the association of an increase in D-dimer levels with the risk of death has been shown in patients with stable coronary heart disease,[22] its association with poor outcomes after stroke has not been defined. We found that an increase in D-dimer levels was associated with an increased risk of death. Because death is the poorest outcome, an increase in D-dimer levels might indicate occurrence of exacerbation of stroke or malignant diseases. Therefore, repeated measurements of D-dimer levels should be considered for patients after stroke. This study suggests that D-dimer might be a novel target for stroke treatment. Our finding suggests that appropriate anticoagulation might be applied for treating stroke to reduce the occurrence of poor outcomes in clinical practice.

There are some limitations of this study. First, a large number of patients did not provide blood samples at 90 days. The characteristics of patients with available blood samples at 90 days and those who were excluded were well balanced. However, some
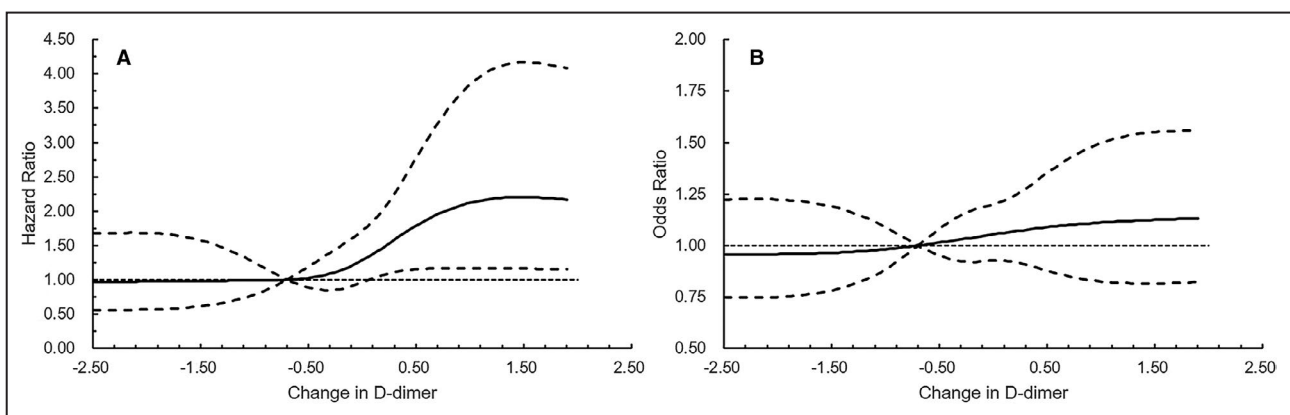

Figure 2. **Adjusted associations between changes in D-dimer and poor outcomes.**
A, All-cause death and (**B**) poor functional outcome.

deviation in the analysis of the associations between D-dimer levels and outcomes may have been present. Second, we measured D-dimer levels only at 2 recovery times. Dynamic detection at multiple time points may help to improve prediction of outcome after stroke and further understanding of the mechanism of injury. Third, we collected venous blood using vacuum tubes with EDTA as the anticoagulant, whereas sodium citrate is used as the anticoagulant in clinical practice. Furthermore, we used immunoturbidimetry to measure D-dimer levels,[6,11,39,40] which differs from common clinical practice. Nevertheless, our detection range was similar to that previously reported.[16] Therefore, these detection differences were unlikely to have affected the association of D-dimer stratification with poor outcomes in our study.

CONCLUSIONS

In conclusion, high D-dimer level was associated with all-cause death and poor functional outcome in patients with ischemic stroke or TIA. Furthermore, an increase in D-dimer levels between baseline and 90 days is associated with the poorest outcome.

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SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics between the study patients at baseline and those excluded.

	Patients excluded (N=4648)	Patients included (N=10518)
Age, mean (SD), y	62.1±11.2	62.3±11.4
Sex (female), n (%)	1519 (32.7)	3283 (31.2)
BMI, median (IQR)	24.5 (22.9-26.6)	24.5 (22.5-26.5)
Time after event within 24 hours, n (%)	3317 (71.4)	7803 (74.2)
Smoking, n (%)	1404 (30.2)	3348 (31.8)
Drinking, n (%)	624 (13.4)	1502 (14.3)
Baseline NIHSS, n (%)		
≤3	2644 (56.9)	5616 (53.4)
>3	2004 (43.1)	4902 (46.6)
History of hypertension, n (%)	2921 (62.8)	6573 (62.5)
History of diabetes mellitus, n (%)	1024 (22.0)	2486 (23.6)
History of dyslipidemia, n (%)	293 (6.30)	898 (8.54)
History of atrial fibrillation, n (%)	256 (5.51)	763 (7.25)
History of ischemic stroke, n (%)	918 (19.75)	2231 (21.21)
History of TIA, n (%)	100 (2.15)	316 (3.00)
History of myocardial infarction, n (%)	64 (1.38)	228 (2.17)
History of angina, n (%)	152 (3.27)	411 (3.91)
History of venous thrombus, n (%)	5 (0.11)	39 (0.37)
History of heart failure, n (%)	19 (0.41)	75 (0.71)

BMI indicates body mass index (the weight in kilograms divided by the square of the height in meters); IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

Table S2. Baseline characteristics between the study patients at 90 days and those excluded.

	Patients excluded (N=8898)	Patients included (N=6268)
Age, mean (SD), y	62.5±11.4	61.8±11.1
Sex (female), n (%)	2840 (31.9)	1962 (31.3)
BMI, median (IQR)	24.5 (22.5-26.4)	24.5 (22.8-26.7)
Smoking, n (%)	2731 (30.7)	2021 (32.2)
Drinking, n (%)	1229 (13.8)	897 (14.3)
Baseline NIHSS, n (%)		
≤3	4748(53.4)	3512(56.0)
>3	4150(46.6)	2756(44.0)
90-day mRS, n (%)		
≤2	7305 (83.8)	5604 (89.4)
>2	1413 (16.2)	662 (10.6)
History of hypertension, n (%)	5558 (62.5)	3936 (62.8)
History of diabetes mellitus, n (%)	2055 (23.1)	1455 (23.2)
History of dyslipidemia, n (%)	680 (7.6)	511 (8.2)
History of atrial fibrillation, n (%)	657 (7.4)	362 (5.8)
History of ischemic stroke, n. (%)	1816 (20.4)	1333 (21.3)
History of TIA, n (%)	213 (2.4)	203 (3.2)
History of myocardial infarction, n (%)	183 (2.1)	109 (1.7)
History of angina, n (%)	301 (3.4)	262 (4.2)
History of venous thrombus, n (%)	16 (0.2)	28 (0.5)
History of heart failure, n (%)	66 (0.7)	28 (0.5)

BMI indicates body mass index (the weight in kilograms divided by the square of the height in meters); IQR, interquartile range; mRS, modified Rankin Scale score; and TIA, transient ischemic attack.

Table S3. Characteristics of the study population by change in D-dimer level.

Characteristics	Change in D-dimer between baseline and 90 days			P Value
	<–0.7 µg/ml (N=1795)	–0.7–0.2 µg/ml (N=1892)	>0.2 µg/ml (N=1889)	
Age, mean (SD), y	62.5±11.3	60.9±11.0	62.2±11.1	<0.001
Female, n (%)	591 (32.9)	559 (29.6)	581 (30.8)	0.081
BMI, median (IQR)	24.5 (22.5-26.6)	24.5 (22.8-26.6)	24.5 (22.6-26.6)	0.918
Smoking, n (%)	549 (30.6)	649 (34.3)	608 (32.2)	0.053
Drinking, n (%)	248 (13.8)	287 (15.2)	267 (14.1)	0.469
Baseline NIHSS, n (%)				0.020
≤3	969 (54.0)	1108 (58.6)	1062 (56.2)	
>3	826 (46.0)	784 (41.4)	827 (43.8)	
Time after event within 24 hours, n (%)	1376 (76.7)	1410 (74.5)	1409 (74.6)	0.237
90-day mRS, n (%)				<0.001
≤2	1577 (8.9)	1743 (92.2)	1655 (87.6)	
>2	218 (12.1)	148 (7.8)	234 (12.4)	
Fibrinogen at 90 days, median (IQR), g/L	4.2 (3.5-5.1)	4.1 (3.5-4.9)	4.1 (3.4-5.0)	0.001
hsCRP at 90 days, median (IQR), mg/L	1.2 (0.7-2.9)	1.2 (0.7-2.4)	1.3 (0.7-3.0)	<0.001
History of hypertension, n (%)	1111 (61.9)	1178 (62.3)	1196 (63.3)	0.650
History of diabetes mellitus, n (%)	398 (22.2)	433 (22.9)	455 (24.1)	0.377
History of dyslipidemia, n (%)	150 (8.4)	153 (8.1)	173 (9.2)	0.472
History of atrial fibrillation, n (%)	146 (8.1)	85 (4.5)	95 (5.0)	<0.001
History of ischemic stroke, n (%)	401 (22.3)	399 (21.1)	414 (21.9)	0644
History of TIA, n (%)	61 (3.4)	65 (3.4)	65 (3.4)	0.997
History of myocardial infarction, n (%)	29 (1.6)	27 (1.4)	44 (2.3)	0.089
History of angina, n (%)	96 (5.4)	76 (4.0)	67 (3.6)	0.020
History of venous thrombus, n (%)	14 (0.8)	9 (0.5)	4 (0.2)	0.046
History of heart failure, n (%)	9 (0.5)	7 (0.4)	11 (0.6)	0.637
Ischemic stroke, n (%)	1659 (92.4)	1731 (91.5)	1748 (92.5)	0.425
TIA, n (%)	136 (7.6)	161 (8.5)	141 (7.5)	

BMI indicates body mass index (the weight in kilograms divided by the square of the height in meters); hsCRP, high-sensitive C-reactive protein; IQR, interquartile range; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

Table S4. Multiple linear regression analysis for D-dimer with the prespecified univariate.

Independent variable	At baseline β	SE	P value	At 90 days β	SE	P value	Change in D-dimer β	SE	P value
Age	0.016	0.002	<0.001	0.019	0.003	<0.001	-	-	-
Sex (female)	0.209	0.054	<0.001	0.143	0.071	0.042	-	-	-
Baseline NIHSS	0.202	0.050	<0.001	-0.122	0.066	0.062	-0.216	0.082	0.009
BMI	-0.015	0.007	0.040	-	-	-	-	-	-
History of diabetes mellitus	-0.133	0.058	0.022	-	-	-	-	-	-
History of atrial fibrillation	0.433	0.098	<0.001	-	-	-	-0.389	0.170	0.022
History of heart failure	0.489	0.292	0.094				-	-	-
Pulmonary infection	0.294	0.112	0.009	0.464	0.165	0.005	-	-	-
Deep vein thrombosis	2.018	0.324	<0.001	-	-	-	-	-	-
TOAST subtypes-small artery occlusion	-0.247	0.061	<0.001	-	-	-	0.194	0.110	0.078
TOAST subtypes-other/undetermined	0.622	0.233	0.008	-	-	-			
TOAST subtypes-undefined	-	-	-	0.167	0.063	0.008	0.181	0.092	0.050
Fibrinogen at bseline	-0.002	0.000	<0.001	-	-	-	-	-	-
hsCRP at baseline	0.017	0.001	<0.001	-	-	-	-	-	-
Drinking	-	-	-	-0.184	0.093	0.049	-	-	-
90-day mRS	-	-	-	0.628	0.107	<0.001	0.283	0.132	0.032
History of myocardial infarction	-	-	-	0.463	0.239	0.053	-	-	-
Fibrinogen at 90 days	-	-	-	-0.002	0.000	<0.001	-0.002	0.000	<0.001
hsCRP at 90 days	-	-	-	0.015	0.002	<0.001	0.004	0.002	0.057
History of venous thrombus	-	-	-	-	-	-	-0.946	0.562	0.093

BMI indicates body mass index (the weight in kilograms divided by the square of the height in meters); hsCRP, high-sensitive C-reactive protein; mRS, modified Rankin Scale score; NIHSS, National Institutes of Health Stroke Scale; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.