Stroke: Vascular and Interventional Neurology

ORIGINAL RESEARCH

D-Dimer Level After Endovascular Treatment Can Help Predict Outcome of Acute Ischemic Stroke

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BACKGROUND: D-Dimer level is a marker of hypercoagulability, which is associated with thrombus formation and resolution. We investigated the value of D-dimer levels in predicting outcomes of acute ischemic stroke in patients who underwent endovascular treatment (EVT).

METHODS: We analyzed data of patients who underwent only EVT from the SECRET (Selection Criteria in Endovascular Thrombectomy and Thrombolytic Therapy) registry. D-Dimer levels were routinely measured in 10 of 15 participating hospitals. Patients were grouped into tertiles (tertile 1, tertile 2, and tertile 3) according to D-dimer levels (lowest, moderate, and highest, respectively). We compared serial scores on the National Institutes of Health Stroke Scale at baseline, on day 1 of hospitalization, and at discharge; functional outcome 3 months after EVT; and rate of mortality within 6 months after EVT.

RESULTS: In the 170 patients, the median D-dimer level was 477 ng/mL (interquartile range, 249–988 ng/mL). In tertile 3, the National Institutes of Health Stroke Scale score was higher at discharge than on day 1 of hospitalization. Poor outcome 3 months after EVT (modified Rankin Scale score, ≥3) was more common with high D-dimer levels (26.3% of tertile 1, 57.1% of tertile 2, and 76.4% of tertile 3; $P<0.001$). Multivariable analysis showed that a high D-dimer level was independently associated with poor outcome 3 months after EVT (odds ratio [OR], 4.399 [95% CI, 1.594–12.135]). Kaplan–Meier survival analysis showed that a high D-dimer level was independently associated with death within 6 months after EVT (OR, 5.441 [95% CI, 1.560–18.978]; log-rank test, $P<0.001$). The D-dimer effect showed no heterogeneity across the subgroups for poor outcome 3 months after EVT or death within 6 months after EVT. The direction of effect was unfavorable for tertile 3 across all demographic strata.

CONCLUSIONS: High plasma D-dimer levels were predictive of early neurologic worsening, poor functional outcome 3 months after EVT, and death within 6 months after EVT.

REGISTRATION: URL: http://www.clinicaltrials.gov; Unique identifier: NCT02964052.

Key Words: D-dimer ■ endovascular treatment ■ prognosis ■ stroke

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Endovascular thrombectomy (EVT) is a proven and effective treatment of large vessel occlusion in patients with acute ischemic stroke. However, outcomes are still unsatisfactory in nearly half of treated patients.[1] Although many imaging markers are known to help predict outcomes after EVT,[2–5] blood markers for predicting outcomes after EVT have not been studied extensively.

D-Dimer is a biomarker of the formation and degradation of fibrin, which reflects activation of coagulation and fibrinolysis.[6] Plasma D-dimer has a long half-life (8 hours) and a relatively stable nature, which are favorable characteristics for measuring its levels. In addition, D-dimer measurement is simple, readily accessible, and inexpensive.[7] High D-dimer levels are associated with venous thromboembolism, coronary heart disease, atrial fibrillation, peripheral arterial disease, and stroke.[8–11] In cases of acute ischemic stroke, the blood D-dimer level is a well-known biomarker of initial stroke severity,[12] cardioembolic subtypes of stroke,[12–14] and cancer-related stroke[15] and is a predictor of large vessel occlusion.[16]

Reports about the value of D-dimer for predicting outcomes in patients with stroke have been inconsistent. Some studies showed that elevated plasma D-dimer levels were a predictor of severe neurological deficits, early stroke recurrence, poor functional outcome, and mortality.[6,13,17,18] However, other studies failed to show an association between D-dimer levels and recurrence of or mortality from ischemic stroke.[19,20] Furthermore, little information is available about the association between plasma D-dimer levels and outcomes in patients with EVT.[21]

We hypothesized that early elevation of D-dimer after EVT reflects initial stroke severity and near-term events because the fibrinolytic system responds quickly to the acute situation and measuring D-dimer level is stable because of a long half-life. In this study, we studied cases of acute ischemic stroke that were treated with EVT to investigate the association of plasma D-dimer levels with changes in neurological status during admission, functional outcome 3 months after EVT, and rates of mortality within 6 months after EVT.

Nonstandard Abbreviations and Acronyms

EVT	endovascular thrombectomy
NIHSS	National Institutes of Health Stroke Scale
SECRET	Selection Criteria in Endovascular Thrombectomy and Thrombolytic Therapy

CLINICAL PERSPECTIVE

- The use of blood markers to predict outcomes following endovascular thrombectomy has not been well researched.
- High D-dimer levels were associated with poor outcomes following endovascular thrombectomy, including deterioration of neurological status during hospitalization, poor outcomes at 3 months, and death within 6 months.
- Measuring D-dimer levels, which is a simple and inexpensive process, may aid in identifying patients at risk for poor outcomes following endovascular thrombectomy.

METHODS

Data are available from the corresponding author upon reasonable request.

Cohort

We analyzed the data from the SECRET (Selection Criteria in Endovascular Thrombectomy and Thrombolytic Therapy) registry. This nationwide registry included consecutive patients with hyperacute ischemic stroke who underwent intravenous thrombolysis or EVT. The aim of the SECRET registry was to determine the criteria for patient selection for reperfusion therapy, especially in relation to clots, core, collaterals, and comorbidities. The SECRET registry included both retrospective and prospective cohorts. Details of the registry protocol have been previously reported.[22]

The study is registered at Clinicaltrials.gov (NCT02964052). The study and registry were approved by the ethical review board of each participating site. For retrospectively enrolled patients, informed consent was waived by the institutional review board of Yonsei University, Severance Hospital, Seoul, Republic of Korea, because of the retrospective design. For prospectively enrolled patients, written informed consent was obtained from patients or their next of kin.

Outcomes

Among the assessed outcomes, successful recanalization was defined by a modified Thrombolysis in Cerebral

Infarction (mTICI) grade 2b or 3. Symptomatic intracerebral hemorrhage was defined in accordance with the European Cooperative Acute Stroke Study 3 criteria.[23] Poor functional outcome was defined by scores of 3 to 6 on the modified Rankin Scale 3 months after EVT. We also collected data about death within 6 months after EVT.

Inclusion and Exclusion Criteria

Of the patients in the SECRET registry, only those who underwent EVT were included in this study. We excluded patients who received plasminogen activators (tPA [tissue plasminogen activator] or urokinase) because those drugs could have affected D-dimer levels through degradation of cross-linked fibrin and formation of various fibrin fragments, including D-dimer.[13] Patients whose D-dimer levels were not measured were also excluded. The D-dimer levels were routinely measured in 10 of 15 participating hospitals. There are 2 different units of D-dimer measurements currently used in clinical laboratories; most samples in this study were measured in D-dimer units, and the remaining samples were measured in fibrinogen-equivalent units. Fibrinogen-equivalent units are based on the molecular weight of fibrinogen (340 kDa), whereas D-dimer units are based on the molecular weight of D-dimer itself (195 kDa), which is approximately half that of fibrinogen.[24] For data consistency, this study included only results that were measured in D-dimer units with the same type of equipment. Differences between patients who were included and excluded were provided in Supplemental Tables S5 and S6.

Measurements of Plasma d-Dimer Levels

Citrated blood was drawn before or within 1 day after EVT and, to separate platelet-poor plasma, centrifuged immediately at 1500*g* for 15 minutes at room temperature. The D-dimer levels were measured with the latex immunoturbidimetric method (HemosIL D-Dimer; Werfen, Bedford, MA) on an automated coagulometer (ACL-TOP750; Werfen). In this method, the latex particles are coated with F(ab′)2 of D-dimer–specific monoclonal antibody agglutinate as they bind D-dimers in plasma, which increases the turbidity of the reaction mixture. The D-dimer concentration is reported in nanograms per milliliter, which correspond to D-dimer units. The measurable range of the assay system was 150 to 69 000 ng/mL with the automatic onboard dilution of the coagulometer functioning. Normal D-dimer level was <243 ng/mL. The D-dimer levels were measured in 7 patients before EVT. The median D-dimer level measured before EVT was 599 ng/mL (interquartile range [IQR], 347.5–696.5 ng/mL), and that measured after EVT was 475 ng/mL (IQR, 249–970 ng/mL) ($P = 0.779$).

Statistical Analysis

Data were calculated as mean±SD, median and IQR, or frequencies and percentages as appropriate. To check variables for normality, we used the Kolmogorov–Smirnov test. We analyzed differences between the groups by using an independent-sample *t* test or the Mann–Whitney *U* test for continuous variables and the χ^2 test for categorical variables.

Patients were categorized into tertiles according to D-dimer levels: the tertile 1 (T1) group comprised patients with low D-dimer levels, the tertile 2 (T2) group comprised patients with moderate D-dimer levels, and the tertile 3 (T3) group comprised patients with high D-dimer levels. To evaluate the association between D-dimer tertiles and early worsening of neurological status after stroke, we compared National Institutes of Health Stroke Scale (NIHSS) scores at baseline, on day 1 of hospitalization, and at discharge. We used a linear repeated-measures mixed model with unstructured covariances within subjects. Fixed effects were D-dimer tertiles, time of assessment, and the interaction between D-dimer tertiles and time. In this model, we analyzed that interaction, adjusted for baseline NIHSS scores, because it indicates differential changes in NIHSS scores over time. In addition, we performed post hoc analyses to estimate the times when the D-dimer tertiles differed. We applied Bonferroni corrections for post hoc analysis. The receiver operating characteristic analyses were performed to identify the optimal D-dimer cutoff value of poor outcome 3 months and death within 6 months with the highest Youden index (sensitivity+specificity−1).

To assess independent factors associated with poor outcome 3 months after EVT, we performed logistic regression analysis. We used the Kaplan–Meier method to generate survival curves, which we compared by using the log-rank test. We also used Cox proportional hazards regression to analyze rates of death within 6 months after EVT. Along with age and sex, variables with *P* values <0.05 in univariable analysis were adjusted in multivariable analysis. To perform subgroup analyses of poor outcome 3 months after EVT and death within 6 months after EVT, we used logistic regression analysis and Cox proportional hazards regression analysis, respectively, testing the effect of high D-dimer levels. All *P* values were 2-sided; *P* values <0.05 were considered significant. To perform statistical analyses, we used IBM SPSS Statistics for Windows, version 26 (IBM Corporation, Armonk, NY).

RESULTS

Demographic Characteristics

Of the 1359 patients, 1030 were excluded: 653 because they received intravenous tPA, 21 because they received intraarterial urokinase, and 356 because they received intravenous tPA and underwent mechanical thrombectomy. We excluded another 41 patients who did not have D-dimer measurements and 118 patients whose D-dimer levels were measured in fibrinogen-equivalent units. The final sample included 170 patients (Supplemental Figure S1). Their median age was 73 years (IQR, 66–80 years), and 96 patients (56.5%) were men. The median D-dimer level was 477 ng/mL (IQR, 249–988 ng/mL). The mean NIHSS score was 14.7±6.7 (Table 1).

Comparison of Clinical Variables According to d-Dimer Level

The median D-dimer level of T1 was 185 ng/mL (IQR, 123–252 ng/mL); that of T2, 481.5 ng/mL (IQR, 374–585 ng/mL); and that of T3, 1869.5 ng/mL (IQR, 1017–3112.5 ng/mL). Demographic characteristics of the 3 groups did not differ except for diabetes and active cancer (Table 1). Prestroke disability, measured by modified Rankin Scale, was more severe in patients with high D-dimer levels ($P = 0.026$). Initial NIHSS scores were higher in patients with higher D-dimer levels (11.9±6.2 in T1, 15.5±6.7 in T2, and 16.7±6.4 in T3; $P<0.001$). Fasting glucose, blood urea nitrogen, and triglyceride levels differed among the groups (Table 1). The groups did not differ with regard to time intervals from onset to EVT, Alberta stroke program early CT score, collateral score, or density and volume of thrombi (Supplemental Table S1). Patients under anticoagulation before stroke were different among the tertiles (lowest in the T2 group; T1, 20.7%; T2, 3.6%; and T3, 26.8% [$P = 0.003$]).

Early and Late Outcomes According to d-Dimer Tertiles

Recanalization rates in the 3 groups were similar ($P = 0.322$). No patients developed symptomatic intracranial hemorrhage. The rates of hemorrhagic transformation in the 3 groups were similar. Infarction volumes as measured on diffusion-weighted imaging were larger in T2 (15.0 cm^3 [IQR, 3.2–72.8 cm^3]) and T3 (22.1 cm^3 [IQR, 3.4–43.8 cm^3]) than in T1 (6.1 cm^3 [IQR, 2.0–17.7 cm^3]; $P<0.001$). Brain herniation was also more frequent in T2 (10.7%) and T3 (17.9%) than in T1 (0%; $P<0.001$; Table 2).

A linear mixed-model analysis demonstrated a significant difference in NIHSS scores over time ($P<0.001$). The interaction between the D-dimer tertiles and time was significant ($P = 0.004$), which also suggests that the changes in NIHSS scores over time among the 3 groups were significant. Patients in all groups showed significant decreases in NIHSS score between the initial admission and day 1 of hospitalization. NIHSS scores did not change between day 1 of hospitalization and discharge in T1 and T2, whereas they increased in T3 ($P = 0.027$; Figure 1A and Supplemental Table S2).

Functional outcomes 3 months after EVT differed among the groups. Poor outcomes (modified Rankin Scale score of ≥3) 3 months after EVT were more common among patients with high D-dimer levels (26.3% of T1, 57.1% of T2, and 76.4% of T3; Figure 1B). Death within 6 months after EVT was also more common among patients with high D-dimer levels (5.2% of T1, 17.9% of T2, and 37.5% of T3; $P<0.001$; Table 2).

Optimal Log_{10} (d-Dimer) Cutoff Value of Poor Outcome at 3 Months and Death Within 6 Months

The predictability of the log_{10} (D-dimer) level for poor outcome at 3 months showed an area under the curve of 0.764 (95% CI, 0.692–0.826 [$P<0.001$]). For death within 6 months, the predictability of the log_{10} (D-dimer) level showed an area under the curve of 0.783 (95% CI, 0.713–0.843 [$P<0.001$]). The cutoff value of poor outcome at 3 months by the Youden index was 2.658 (sensitivity, 72.7; specificity, 70.5) and that of death within 6 months was 2.932 (sensitivity, 63.6; specificity, 79.1) (Figure 2).

Factors Associated With Poor Outcome 3 Months After EVT

Univariable and multivariable logistic regression analyses showed that diabetes, previous modified Rankin Scale score, initial NIHSS score, recanalization failure, and D-dimer level were independent predictors of poor outcome 3 months after EVT. High D-dimer levels were independently associated with poorer outcome 3 months after EVT than were low D-dimer levels (odds ratio [OR], 4.456 [95% CI, 1.598–12.425]). A high log-transformed D-dimer level was also independently associated with poor outcome 3 months after EVT (OR, 5.466 [95% CI, 1.862–16.046]; Table 3).

Factors Associated With Mortality Within 6 Months After EVT

Kaplan–Meier survival analysis revealed that high D-dimer levels were associated with death within 6 months after EVT (log-rank test; $P<0.001$; Figure 1C). Univariable and multivariable Cox proportional hazards regression analyses revealed that diabetes, initial

Table 1. Demographics and Laboratory Findings According to D-Dimer Tertiles

	T1, n = 58	T2, n = 56	T3, n = 56	Total, N = 170	*P* value
Demographics					
Age, y	71.0 (60.0–79.0)	74.0 (69.0–80.0)	74.5 (67.5–81.0)	73.0 (66.0–80.0)	0.185
Sex					0.051
Men	39 (67.2)	32 (57.1)	25 (44.6)	96 (56.5)	
Women	19 (32.8)	24 (42.9)	31 (55.4)	74 (43.5)	
Hypertension	43 (74.1)	45 (80.4)	41 (73.2)	129 (75.9)	0.629
Diabetes	20 (34.5)	32 (57.1)	34 (60.7)	86 (50.6)	0.01
Hypercholesterolemia	22 (37.9)	19 (33.9)	29 (51.8)	70 (41.2)	0.131
Current smoking	10 (17.2)	8 (14.3)	7 (12.5)	25 (14.7)	0.77
Atrial fibrillation	28 (48.3)	33 (58.9)	31 (55.4)	92 (54.1)	0.508
Previous stroke	18 (31.0)	18 (32.1)	15 (26.8)	51 (30.0)	0.808
Coronary artery disease	14 (24.1)	19 (33.9)	18 (32.1)	51 (30.0)	0.476
Valvular heart disease	3 (5.2)	2 (3.6)	4 (7.1)	9 (5.3)	0.699
Congestive heart failure	3 (5.2)	5 (8.9)	6 (10.7)	14 (8.2)	0.546
Peripheral obstructive disease	3 (5.2)	2 (3.6)	2 (3.6)	7 (4.1)	0.883
Active cancer	3 (5.2)	3 (5.4)	12 (21.4)	18 (10.6)	0.006
Previous mRS score					0.026
0	54 (93.1)	43 (76.8)	40 (71.4)	137 (80.6)	
1	4 (6.9)	5 (8.9)	8 (14.3)	17 (10.0)	
2	0 (0.0)	1 (1.8)	5 (8.9)	6 (3.5)	
3	0 (0.0)	3 (5.4)	1 (1.8)	4 (2.4)	
4	0 (0.0)	2 (3.6)	2 (3.6)	4 (2.4)	
5	0 (0.0)	2 (3.6)	0 (0.0)	2 (1.2)	
Initial NIHSS score	11.9±6.2	15.5±6.7	16.7±6.4	14.7±6.7	<0.001
Occlusion site					
ICA	22 (37.9)	17 (30.4)	15 (26.8)	54 (31.8)	0.425
MCA	32 (55.2)	32 (57.1)	30 (53.6)	94 (55.3)	0.93
ACA	1 (1.7)	1 (1.8)	1 (1.8)	3 (1.8)	1
PCA	2 (3.4)	1 (1.8)	2 (3.6)	5 (2.9)	0.822
VBA	8 (13.8)	11 (19.6)	11 (19.6)	30 (17.6)	0.638
TOAST classification					0.802
Cardioembolism	26 (44.8)	31 (55.4)	34 (60.7)	91 (53.5)	
LAA	16 (27.6)	14 (25.0)	12 (21.4)	42 (24.7)	
LAC	3 (5.2)	1 (1.8)	2 (3.6)	6 (3.5)	
SOD	4 (6.9)	4 (7.1)	4 (7.1)	12 (7.1)	
UN	9 (15.5)	6 (10.7)	4 (7.1)	19 (11.2)	
UT	26 (44.8)	31 (55.4)	34 (60.7)	91 (53.5)	
Anticoagulant	12 (20.7)	2 (3.6)	15 (26.8)	29 (17.1)	0.003
Laboratory findings					
Hemoglobin, g/dL	14.3 (12.8–15.0)	13.4 (12.3–14.9)	13.6 (11.5–14.6)	13.7 (12.1–14.9)	0.14
Hematocrit, %	40.8±5.3	39.5±5.2	39.4±6.9	39.9±5.8	0.22
WBC, 103/μL	7.2 (6.0–9.3)	8.1 (6.8–9.8)	9.1 (6.7–11.2)	8.1 (6.2–10.1)	0.055
Platelet, 103/μL	228.7±59.5	218.7±63.2	203.2±75.7	217.0±66.9	0.042
PT, s	1.0 (0.9–1.0)	1.0 (0.9–1.0)	1.0 (0.9–1.1)	1.0 (0.9–1.1)	0.161
aPTT, s	29.3 (27.6–33.4)	30.0 (27.3–32.8)	29.6 (27.1–32.9)	29.6 (27.2–33.0)	0.975
BUN, mg/dL	15.4 (12.3–18.4)	18.2 (12.9–21.9)	17.9 (14.2–21.6)	17.2 (13.0–20.9)	0.032
Creatine, mg/dL	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.9 (0.7–1.1)	0.9 (0.7–1.0)	0.142
Glucose initial, mg/dL	117.5 (107.0–148.0)	131.5 (113.0–143.5)	124.5 (110.0–146.0)	122.5 (109.0–144.0)	0.364
Glucose fasting, mg/dL	107.5 (88.0–121.0)	121.0 (105.0–153.0)	131.0 (112.5–159.0)	119.0 (97.0–145.0)	<0.001
Total cholesterol, mg/dL	167.0 (137.0–188.0)	152.0 (127.0–184.5)	179.0 (138.5–198.5)	164.0 (133.0–188.0)	0.079
Triglyceride, mg/dL	84.5 (63.0–119.0)	80.5 (58.5–110.0)	104.0 (80.5–153.0)	90.0 (64.0–122.0)	0.007
HDL, mg/dL	43.1 (38.0–53.0)	41.0 (36.0–49.6)	41.5 (35.0–47.0)	42.0 (37.0–50.5)	0.325

(*Continued*)

Table 1. (Continued)

	T1, n = 58	T2, n = 56	T3, n = 56	Total, N = 170	*P* value
LDL, mg/dL	96.7±34.1	90.4±30.3	103.7±40.0	96.9±35.1	0.313
D-Dimer, ng/mL	185.0 (123.0–252.0)	481.5 (374.0–585.5)	1869.5 (1017.0–3112.5)	477.0 (249.0–988.0)	

Data are expressed as number (percentage), median (interquartile range), or mean±SD. ACA indicates anterior cerebral artery; aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen; HDL, high-density lipoprotein; ICA, internal carotid artery; LAA; larger artery atherosclerosis; LAC, lacunar infarction; LDL, low-density lipoprotein; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; PT, prothrombin time; SOD, stroke of other determined cause; T1, tertile 1; T2, tertile 2; T3, tertile 3; TOAST, Trial of Org 101072 in Acute Stroke Treatment; UN, undetermined negative cause; UT, undetermined ≥2 causes; VBA, vertebrobasilar artery; and WBC, white blood cell.

Table 2. Radiological and Clinical Outcomes According to D-Dimer Tertiles

	T1, n = 58	T2, n = 56	T3, n = 56	Total, N = 170	*P* value
Recanalization, mTICI grade ≥2b	49 (86.0)	42 (75.0)	42 (77.8)	133 (79.6)	0.322
Symptomatic ICH	0 (0)	0 (0)	0 (0)	0 (0)	>0.999
Hemorrhagic transformation					0.964
HI1	8 (36.4)	8 (30.8)	8 (25.8)	24 (30.4)	
HI2	5 (22.7)	7 (26.9)	11 (35.5)	23 (29.1)	
PH1	6 (27.3)	8 (30.8)	8 (25.8)	22 (27.8)	
PH2	3 (13.6)	3 (11.5)	4 (12.9)	10 (12.7)	
DWI volume, cm^3	6.1 (2.0–17.7)	15.0 (3.2–72.8)	22.1 (6.9–70.4)	11.4 (3.4–43.8)	<0.001
Brain herniation	0 (0.0)	6 (10.7)	10 (17.9)	16 (9.4)	0.004
NIHSS score 1 day	6.1±5.9	10.9±7.7	13.8±8.8	10.2±8.2	<0.001
NIHSS score at discharge	4.2±6.9	9.7±11.1	17.0±15.3	10.2±12.7	<0.001
Poor outcome at 3 mo, mRS scores 3 to 6	15 (26.3)	32 (57.1)	42 (76.4)	89 (53.0)	<0.001
Death within 6 mo	3 (5.2)	10 (17.9)	21 (37.5)	34 (20.0)	<0.001

Data are expressed as number (percentage), median (interquartile range), or mean±SD. DWI indicates diffusion weighted image; HI, hemorrhagic infarction; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PH, parenchymal hematoma; T1, tertile 1; T2, tertile 2; T3, and tertile 3.

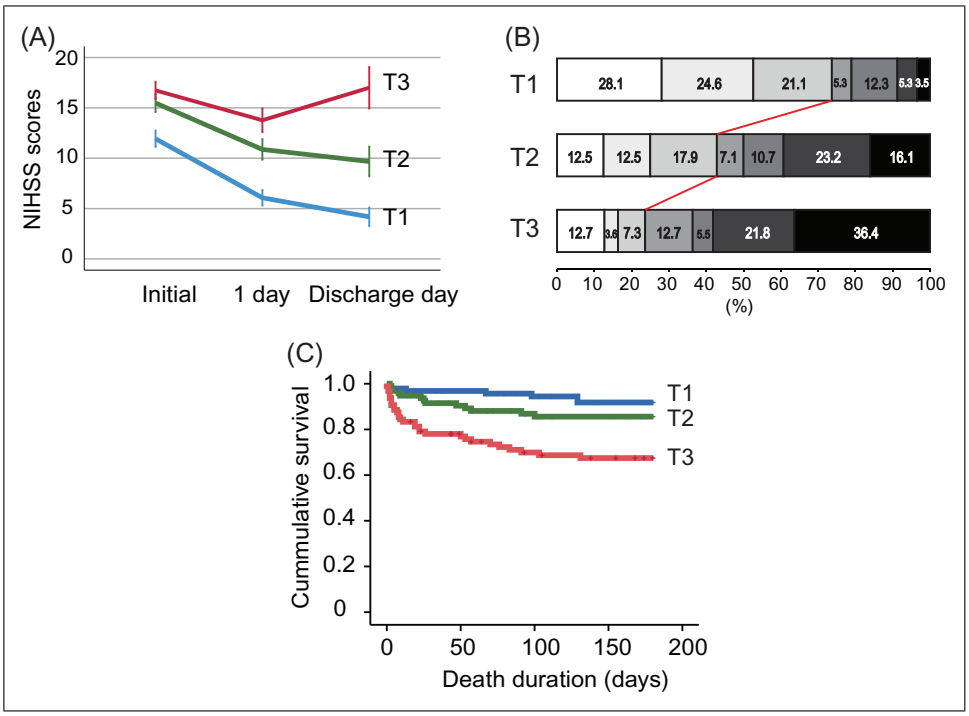

Figure 1. Changes in scores on the NIHSS from baseline to day 1 of hospitalization and discharge according to D-dimer tertiles (A), modified Rankin Scale score according to D-dimer tertiles in all patients (B; numbers indicate percentages of patients), and Kaplan–Meier survival curves within 6 months after endovascular treatment according to D-dimer tertiles (C). NIHSS indicates National Institutes of Health Stroke Scale; T1, tertile 1; T2, tertile 2; and T3, tertile 3.

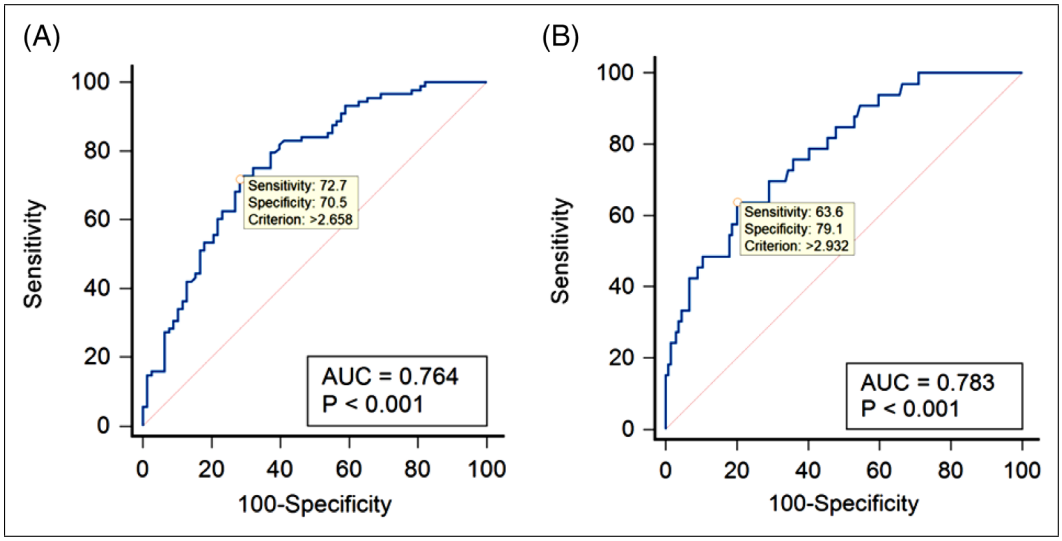

Figure 2. Receiver operating characteristic analyses to identify the optimal D-dimer cutoff value of poor outcome at 3 months (A) and death within 6 months (B). AUC indicates area under the curve.

NIHSS score, and low hemoglobin level were independent predictors of death within 6 months after EVT, as was high D-dimer level (OR, 5.441 [95% CI, 1.56–18.978]). High log-transformed D-dimer level was also independently associated with death within 6 months after EVT (OR, 4.454 [95% CI, 2.143–9.256]; Table 4).

Subgroup Analysis of Poor Outcome 3 Months After EVT and Death Within 6 Months After EVT

The effect of the highest D-dimer levels across the subgroups showed no heterogeneity with regard to poor outcome 3 months after EVT or death within 6 months after EVT. The direction of effect was unfavorable for T3 across all demographic strata (Figure 3).

Sensitivity Analysis of Poor Outcome 3 Months and Death Within 6 Months After EVT in Patients With Either the d-dimer units (DDU) or fibrinogen equivalent units (FEU) Method

Among 288 patients with either the DDU or FEU method, D-dimer level was an independent predictor of poor outcome at 3 months (T3 compared with T1; OR, 2.271 [95% CI, 1.080–4.778]; $P = 0.331$). That predictability was also seen in $\log_{10}$ (D-dimer) (2.598; OR, 2.598 [95% CI, 1.317–5.126]; $P = 0.006$) (Supplemental Table S3). Cox regression analysis also showed both D-dimer level and $\log_{10}$ (D-dimer) were independent predictors of death within 6 months (Supplemental Table S4).

DISCUSSION

In this study, we found that high plasma D-dimer levels were predictive of poor outcomes 3 months after EVT and death within 6 months after EVT. Higher D-dimer levels were also associated with in-hospital worsening of neurological status. Subgroup analysis showed that the highest D-dimer levels were consistently associated with poor functional outcome 3 months after EVT and mortality within 6 months after EVT.

We found that increased plasma D-dimer levels were associated with worsening of neurological status at discharge in patients who underwent EVT. The NIHSS scores decreased in T1 and T2 over time, whereas they were increased at discharge in T3. The fibrinolytic system responds quickly to the acute situation and is therefore a good predictor of early events.[10] Initial NIHSS score and infarction volume were higher in patients with high D-dimer levels. A previous study also showed that D-dimer levels were associated with initial stroke severity.[12] The initial burden of ischemic stroke might be a strong determinant of future outcome.[25] High D-dimer level was associated with early stroke recurrence and progressive stroke.[6,18,26] In our study, brain herniation was more frequent in patients with high D-dimer levels. This might also contribute to worsening of neurological status at discharge.

Table 3. Factors Associated With a Poor Outcome at 3 Months (mRS scores 3–6)

	Unadjusted OR (95% CI)	*P* value	Adjusted OR (95% CI)	*P* value
Age	1.022 (0.998–1.047)	0.072	1.020 (0.986–1.055)	0.256
Male sex	1.686 (0.909–3.128)	0.098	0.548 (0.217–1.383)	0.203
Hypertension	0.964 (0.476–1.953)	0.920		
Diabetes	3.244 (1.724–6.107)	<0.001	2.371 (1.030–5.454)	0.042
Hyperlipidemia	0.992 (0.536–1.834)	0.979		
Current smoking	0.540 (0.227–1.283)	0.163		
Atrial fibrillation	1.751 (0.948–3.234)	0.073		
Previous stroke	0.891 (0.461–1.722)	0.732		
Coronary artery disease	0.753 (0.388–1.460)	0.401		
Valvular heart disease	1.116 (0.289–4.310)	0.873		
Congestive heart failure	0.744 (0.239–2.314)	0.609		
Peripheral artery obstructive disease	2.292 (0.432–12.158)	0.330		
Active cancer	1.896 (0.676–5.316)	0.224		
Previous mRS score	3.924 (1.657–9.291)	0.002	2.707 (1.278–5.734)	0.009
Initial NIHSS score	1.159 (1.092–1.230)	<0.001	1.172 (1.084–1.268)	<0.001
Occlusion site				
ICA	0.841 (0.437–1.619)	0.605		
MCA	0.567 (0.306–1.052)	0.072		
ACA	6.428 (0.207–199.312)	0.288		
PCA	10.353 (0.428–250.654)	0.151		
VBA	2.000 (0.873–4.583)	0.101		
Recanalization, modified mTICI grade ≥2b	0.283 (0.119–0.674)	0.004	0.128 (0.037–0.441)	0.001
Symptomatic ICH	NA			
Pulmonary embolism	6.428 (0.207–199.312)	0.288		
Deep vein thrombosis	6.428 (0.207–199.312)	0.288		
Onset to door, min	1 (0.999–1.002)	0.807		
Hemoglobin, mg/dL	0.789 (0.672–0.927)	0.004	0.838 (0.664–1.057)	0.135
Initial glucose, mg/dL	1.003 (0.996–1.010)	0.424		
Initial systolic blood pressure, mm Hg	1.005 (0.995–1.015)	0.307		
D-dimer tertiles		<0.001		0.010
T1	Reference		Reference	
T2	3.733 (1.691–8.245)	0.001	1.312 (0.482–3.571)	0.595
T3	9.046 (3.839–21.314)	<0.001	4.456 (1.598–12.425)	0.004
Log_{10}, D-dimer	10.176 (4.154–24.929)	<0.001	5.466 (1.862–16.046)	0.002

ACA indicates anterior cerebral artery; ICA, internal carotid artery; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PCA, posterior cerebral artery; T1, tertile 1; T2, tertile 2; T3, tertile 3; and VBA, vertebrobasilar artery.

This study showed that increased plasma D-dimer levels were predictive of poor functional outcomes 3 months after EVT, which is consistent with the results of recent studies that showed an association between high D-dimer levels and poor functional outcomes at discharge or 3 months later in patients who underwent EVT with or without combined intravenous thrombolysis.[21,27] We further showed an association between D-dimer levels and functional outcome in patients who underwent only EVT. A previous meta-analysis showed that a high D-dimer level within 24 hours after stroke onset was associated with mortality 30 days later in unselected patients with stroke.[6] We found that a high D-dimer level was also associated with increased mortality within 6 months after EVT. Elevated D-dimer levels may reflect the ongoing thrombus formation in brain vessels, and D-dimer may be a marker of systemic hypercoagulability.[26] Moreover, D-dimer may activate the inflammatory process.[28]

This study had several limitations. First, plasma D-dimer level was measured after EVT in many patients. The optimal time to measure D-dimer levels for

Table 4. Cox Regression Analysis for Mortality Within 6 Months

	Unadjusted HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age	1.013 (0.985–1.042)	0.376	0.990 (0.962–1.019)	0.501
Male sex	1.479 (0.754–2.900)	0.255	0.506 (0.209–1.222)	0.130
Hypertension	0.687 (0.328–1.436)	0.318		
Diabetes	4.291 (1.867–9.863)	0.001	2.378 (0.949–5.959)	0.065
Hyperlipidemia	0.988 (0.499–1.957)	0.973		
Current smoking	0.335 (0.080–1.396)	0.133		
Atrial fibrillation	1.272 (0.642–2.520)	0.490		
Previous stroke	0.805 (0.376–1.725)	0.577		
Coronary artery disease	1.157 (0.572–2.339)	0.685		
Valvular heart disease	0.495 (0.068–3.618)	0.488		
Congestive heart failure	1.428 (0.503–4.055)	0.503		
Peripheral artery obstructive disease	1.487 (0.356–6.207)	0.205		
Active cancer	1.769 (0.732–4.273)	0.205		
Previous mRS score	1.453 (1.163–1.815)	0.001	1.263 (0.944–1.692)	0.116
Initial NIHSS score	1.112 (1.061–1.166)	<0.001	1.092 (1.033–1.155)	0.002
Occlusion site				
ICA	1.597 (0.806–3.162)	0.179		
MCA	0.588 (0.299–1.157)	0.124		
ACA	3.511 (0.840–14.682)	0.085		
PCA	0.047 (0–246.181)	0.485		
VBA	1.505 (0.682–3.325)	0.312		
Recanalization, modified mTICI grade ≥2b	0.481 (0.228–1.017)	0.055		
Symptomatic ICH	0.049 (0–3916.59)	0.6		
Onset to door, min	0.999 (0.998–1.001)	0.514		
Pulmonary embolism	1.256 (0.172–9.188)	0.822		
Deep vein thrombosis	2.260 (0.309–16.533)	0.422		
Hemoglobin, mg/dL	0.770 (0.663–0.895)	0.001	0.810 (0.685–0.957)	0.013
Initial glucose, mg/dL	1.007 (1.002–1.013)	0.009		
Initial systolic blood pressure, mm Hg	0.998 (0.987–1.010)	0.750		
D-Dimer tertiles		0.001		0.008
T1	Reference		Reference	
T2	3.667 (1.009–13.328)	0.48	2.266 (0.606–8.473)	0.224
T3	8.864 (2.642–29.739)	<0.001	5.441 (1.560–18.978)	0.008
Log_{10}, D-dimer	6.473 (3.403–12.314)	<0.001	4.454 (2.143–9.256)	<0.001

ACA indicates anterior cerebral artery; HR, hazard ratio; ICA, internal carotid artery; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery; T1, tertile 1; T2, tertile 2; T3, tertile 3; and VBA, vertebrobasilar artery.

predicting long-term outcomes is uncertain. However, determination of post-EVT D-dimer levels may better reflect the potential effect of recanalization and post-procedural complications. Second, although D-dimer levels can be measured through several assay methods, we included patients who underwent a specific assay method with the same type of equipment. This was because plasma D-dimer measurements may vary widely among immunoassays.[24,29] Although we were able to obtain a homogeneous patient cohort by selecting patients on the basis of assay method, the number of included patients was low. It is uncertain whether our findings are reproducible when plasma D-dimer levels are measured with other assay methods. Third, we excluded patients who received tPA or urokinase along with EVT. Those drugs could have affected D-dimer levels by degrading cross-linked fibrin and forming various fibrin fragments. Exclusion of those patients may limit the study's generalizability. Fourth, the study registry included the patients who received intravenous tPA, urokinase, and/or EVT. Therefore, we cannot provide information on patients who did not receive tPA or were outside of the time frame. Lastly, data were obtained from a nationwide registry but in a single country with a single ethnicity; therefore, the generalizability of findings in this study is limited.

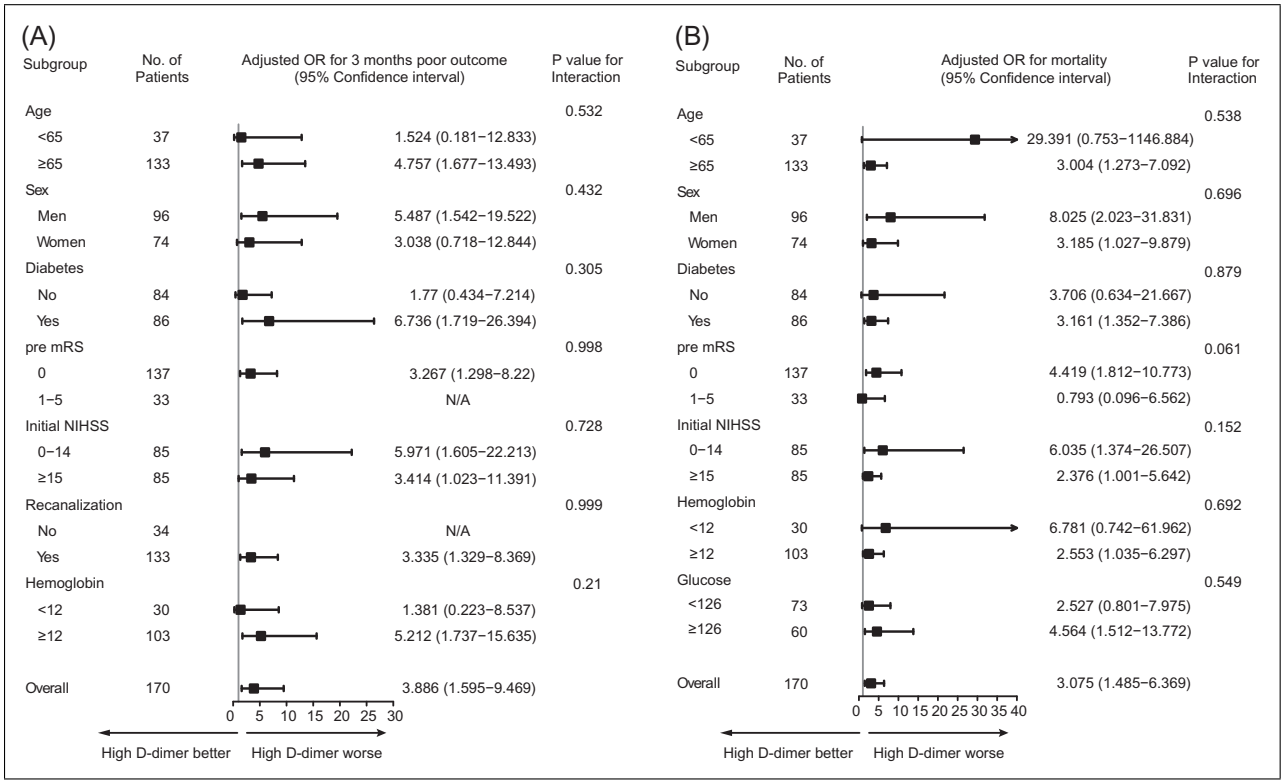

Figure 3. Subgroup analysis of poor outcome 3 months after endovascular treatment (A) and death within 6 months after endovascular treatment (B). mRS indicates modified Rankin Scale; NA, not applicable; NIHSS, National Institutes of Health Stroke Scale; and OR, odds ratio.

CONCLUSIONS

We found that D-dimer levels were predictive of early worsening of neurological status, poor functional outcome 3 months after EVT, and death within 6 months after EVT. Measurement of plasma D-dimer levels, which is simple, easily accessible, and inexpensive, may help identify patients with poor outcomes.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Materials

Supporting Material

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