Original Paper

Cerebrovascular Diseases

Cerebrovasc Dis 2013;35:64–72
DOI: 10.1159/000345336

Received: July 1, 2012
Accepted: October 22, 2012
Published online: February 14, 2013

# Relationship between Plasma D-Dimer Level and Cerebral Infarction Volume in Patients with Nonvalvular Atrial Fibrillation

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**Key Words**
Nonvalvular atrial fibrillation · D-Dimer · Anticoagulant · Infarct volume · Stroke severity

**Abstract**
***Background:*** Plasma D-dimer level may reflect the activity of thrombus formation in the left atrium of patients with nonvalvular atrial fibrillation (NVAF). Proper anticoagulation with warfarin dramatically decreases the rate of cerebral embolism, reduces stroke severity and subsequent risk of death, as well as the level of D-dimer in NVAF patients. However, the predictive value of D-dimer level on cerebral embolism severity has not been examined. Thus, the purpose of this study was to investigate the association between plasma D-dimer level at admission and infarct size in NVAF patients. ***Methods:*** We identified 124 patients with consecutive ischemic stroke and NVAF who were admitted within 48 h of symptom onset. We measured infarction volume from CT taken after 3 ± 1 days from the onset. Plasma D-dimer levels were measured at the time of admission. Relationships were analyzed between infarction volume and plasma D-dimer levels, cardiovascular risk factors, preadmission medications and admission conditions. We also assessed the influence of D-dimer level on functional outcome in patients with preadmission modified Rankin Scale (mRS) score of 0–1 and patients by tertile of D-dimer level (≤0.83, 0.83–2.16 and ≥2.16 μg/ml). ***Results:*** Infarction volume significantly correlated with D-dimer level ($r = 0.309$, $p < 0.001$), systolic blood pressure ($r = 0.201$, $p = 0.026$), diastolic blood pressure ($r = 0.283$, $p = 0.002$), National Institutes of Health Stroke Scale (NIHSS) score on admission ($r = 0.546$, $p < 0.001$) and mRS score at discharge ($r = 0.557$, $p < 0.001$). Multivariate regression analyses showed that the D-dimer level was significantly associated with infarction volume after adjusting for age, sex, current smoker or not, prothrombin time-international normalized ratio ≥1.6, diastolic blood pressure, $CHADS_2$ score and NIHSS score on admission. In patients with a preadmission mRS score of 0–1 ($n = 108$), D-dimer level was significantly associated with NIHSS score at admission ($r = 0.318$, $p < 0.001$) and mRS score at discharge ($r = 0.310$, $p = 0.001$). Patients in the highest D-dimer tertile group showed worse outcome than those in the middle ($p = 0.041$) and lowest ($p < 0.001$) tertiles. ***Conclusions:*** Plasma D-dimer level on admission is significantly related to infarction volume and functional outcome, following cardioembolic stroke in NVAF patients.



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1015–9770/13/0351–0064$38.00/0

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## Introduction

Nonvalvular atrial fibrillation (NVAF) affects 2–4% of 70-year-olds and its prevalence increases with age [1]. In the Framingham Study, NVAF was associated with a 5- to 6-fold increase in stroke incidence compared with an age-, sex- and blood pressure-matched control group without NVAF [2]. It is clear that cerebral embolism is one of the most common preventable events in NVAF patients [3]. D-Dimer, a product of fibrin degradation, is a reliable and sensitive index of fibrin deposition and stabilization [4]. An increased D-dimer level is hypothesized to be indicative of thrombus formation within the left atrium and is the key factor of cardiac embolism onset [5]. As expected, plasma D-dimer levels are higher in NVAF patients than in healthy controls [6]. More importantly, D-dimer level has been shown to predict the risk of incident thromboembolism in NVAF patients [7–9]. Proper anticoagulation with warfarin dramatically decreases the rate of cerebral embolism in NVAF patients [10]. Furthermore, warfarin treatment reduces stroke severity and subsequent risk of death [11–15], as well as the level of D-dimer in NVAF patients [16]. Although D-dimer level is associated with the clinical outcome of pulmonary embolism [17–19], the relationship between D-dimer level and cerebral embolism severity in NVAF patients remains unclear. Assessing the D-dimer level would facilitate stroke prevention, especially severe cerebral infarction in NVAF patients.

Therefore, the purpose of this study was to clarify the relationship between D-dimer level on admission and infarction volume and functional outcome following acute ischemic stroke in NVAF patients. These results will be applicable to prevent stroke, especially severe cerebral embolism, in the management of NVAF patients.

## Materials and Methods

*Patient Selection*

We retrospectively reviewed the records of all consecutive patients admitted to the Stroke Centers at Osaka University Hospital and Osaka National Hospital between January 2004 and August 2011, who were given diagnosis of acute ischemic stroke within 48 h of symptom onset and atrial fibrillation. We identified 259 patients as suitable candidates. We excluded 18 patients that did not have complete CT examination. Patients with a history of valve replacement (n = 17), implantation with a left ventricular assist device (n = 14), nonbacterial thrombotic endocarditis or cancer (n = 5), after cardiac catherization (n = 1), pacemaker insertion (n = 2), cardiac valvular disease (n = 4) or infective endocarditis (n = 4) were excluded from analysis in the NVAF group. Patients who received thrombolytic therapy (n = 46) were also excluded because thrombolysis treatment is likely to enhance recanalization and affect infarct size. Patients with moyamoya disease (n = 1) or carotid artery stenosis (n = 6) were excluded because of other possible causes of cerebral infarction. Patients without admission D-dimer measurements (n = 17) were also excluded.

*Clinical Variables*

Clinical, radiographic and clinical course data were retrospectively collected from medical records. Blood samples were obtained on admission. Admission blood pressure was defined as the first recorded blood pressure at the time of the initial emergency department or in-hospital evaluation for acute infarction. Diagnosis of atrial fibrillation was carried out with the prehospital medical record, ECG taken at admission, 24 h Holter ECG recording and 24 h ECG monitoring during the hospitalization. Hypertension was defined as blood pressure ≥140/90 mm Hg on measurements taken on at least 2 occasions, or use of antihypertensive medications. Diabetes was defined as fasting plasma glucose level ≥126 mg/dl, HbA1c level ≥6.5%, or use of antidiabetic therapy. Hyperlipidemia was defined as low-density lipoprotein cholesterol level ≥140 mg/dl, total cholesterol level ≥220 mg/dl, triglycerides level ≥150 mg/dl, high-density lipoprotein cholesterol level <40 mg/dl or use of cholesterol-lowering therapy. Smoking was classified as current or quit. Habitual alcohol intake was defined as alcohol drinking of >20 g/day. The $CHADS_2$ score was calculated by adding 1 point each for a history of congestive heart failure, hypertension, age ≥75 years or diabetes mellitus, and 2 points for a history of cerebral infarction or transient ischemic attack [20].

*Measurement of Plasma D-Dimer Level*

Blood was centrifuged at 3,000 rpm at 4°C for 15 min, and aliquots were stored at –80°C. Circulating plasma D-dimer was measured by the latex turbidimetric immunoassay with a sensitivity of 0.5 μg/dl (Mitsubishi Chemical Medience Inc.). The detection limit was 48 μg/ml. We diluted the plasma sample, assayed and calculated those exceeding the upper detection limit. The intra-assay variation was ±15% and corresponding interassay coefficients were <10%.

*Imaging Data Collection*

Brain CT examinations were performed on a LightSpeed VCT, a Discovery CT 750HD (General Electric Medical Systems, Milwaukee, Wisc., USA) or an Aquilion ONE (Toshiba Medical Systems, Otawara, Japan) machine. The section thickness was 4 mm in the posterior fossa and 8 mm in superior brain regions (120 kV, 240 mAS). CT scans were performed 3 ± 1 days after stroke onset and were used to evaluate infarction volume [21]. All CT scans were retrospectively evaluated by 2 stroke neurologists (M.M. and S.O.) blinded to the patients' clinical information. We used ImageJ v. 1.43 software (National Institute of Health, Bethesda, Md., USA) on a desktop computer at a window level of 35 HU and a width of 60 HU for the tracing, manually traced each region of interest and calculated the ischemic lesion area in each slice. We multiplied the thickness of each slice and used integration to calculate the total infarction volume. We previously found that the inter-examiner reliability of this technique was high (intraclass correlation coefficient = 0.95) [15]. Differences in analysis were

**Table 1.** Baseline characteristics of participants (n = 124)

| | |
|---|---|
| Age, years | 76 ± 9 |
| Female | 52 (41.9) |
| Paroxysmal atrial fibrillation | 56 (45.0) |
| Current smoker | 35 (28.7) |
| Alcohol intake | 39 (32.0) |
| Hypertension | 89 (71.8) |
| Diabetes mellitus | 38 (32.2) |
| Dyslipidemia | 46 (38.0) |
| Chronic heart failure | 83 (66.9) |
| History of coronary artery disease | 14 (11.3) |
| Previous stroke or TIA | 41 (33.1) |
| Preadmission $CHADS_2$ score | 2.9 ± 1.4 |
| ACEI or ARB use | 47 (38.8) |
| Statin use | 19 (15.7) |
| Antiplatelet therapy | 41 (33.1) |
| Warfarin use | 36 (29.0) |
| PT-INR ≥1.6 | 19 (15.3) |
| Body temperature, °C | 36.5 (36.2–36.8) |
| Systolic blood pressure, mm Hg | 155 ± 29 |
| Diastolic blood pressure, mm Hg | 86 ± 19 |
| Serum glucose, mg/dl | 139 ± 49 |
| Infarction volume, ml | 45.5 (13.7–139.0) |
| D-Dimer, μg/ml | 1.37 (0.76–3.60) |
| Onset-to-admission time, hours | 11.0 ± 13.3 |
| NIHSS score on admission | 12 (4–19) |
| mRS score at discharge | 4 (1–5) |
| Duration of hospitalization, days | 26 (15–42) |

Data are presented as either mean ± SD, median with interquartile range in parentheses or number with percentage in parentheses. TIA = Transient ischemic attack; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type 1 receptor blocker.

resolved by consensus. Hemorrhagic transformation was diagnosed as a demarcated hyperdense area on CT together with neurological worsening involving a >2-point increase in the National Institutes of Health Stroke Scale (NIHSS) score compared with the NIHSS score at admission.

*Statistical Analyses*

Statistical analyses were performed using JMP (SAS Institute, Cary, N.C., USA). Relationships between categorical variables (infarction volume and baseline characteristics) were compared using Student's t tests. Continuous variables were characterized by slopes that were calculated with simple linear regression equations. Because distributions of admission D-dimer level appeared to be left-skewed, they were normalized by log transformation. Subsequently, multiple linear regression analyses were used to examine associations between admission D-dimer levels and infarction volume under the following conditions: (1) controlling for age and sex; (2) additionally controlling for traditional atherosclerotic risk factors that were associated at a significance level of $p < 0.10$ on univariate analysis [current smoker or not, prothrombin time-international normalized ratio (PT-INR) ≥1.6, diastolic blood pressure] and $CHADS_2$ score, and (3) further controlling for NIHSS score on admission. We compared the functional outcome as assessed by preadmission modified Rankin Scale (mRS) score 0–1 and patients by tertile of D-dimer level (≤0.83, 0.83–2.16 and ≥2.16 μg/ml). A p value <0.05 was considered statistically significant.

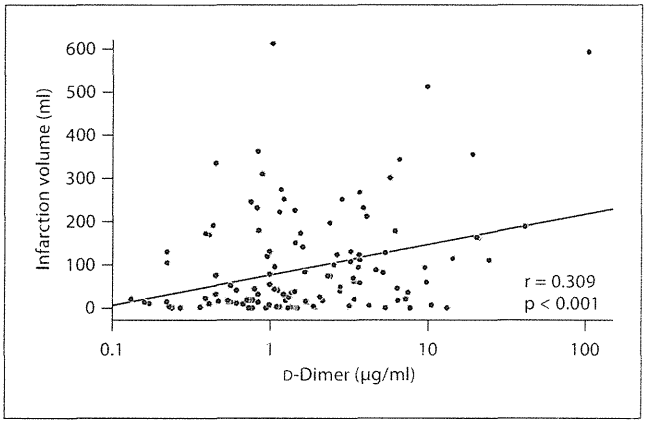


**Fig. 1.** Relationship between admission D-dimer level and infarction volume.

## Results

A total of 124 patients were included in the study and their characteristics are shown in table 1. Their mean age was 76 ± 9 years. The median values of infarction volume and D-dimer level were 45.5 ml and 1.37 μg/ml, respectively. The percentages of patients with previous stroke or transient ischemic attack, warfarin use and PT-INR ≥1.6, were 33.1, 36 and 15.3%, respectively. The mean preadmission $CHADS_2$ score was 2.9 ± 1.4 and the mean value of onset-to-admission time was 11.0 ± 13.3 h. CT imaging for defining infarct size was obtained on day 2 (n = 70), day 3 (n = 32) and day 4 (n = 22). Associations between infarction volume and risk factors are shown in table 2. Infarction volume was significantly correlated with log D-dimer level ($r = 0.309$, $p < 0.001$; fig. 1), systolic blood pressure ($r = 0.201$, $p = 0.026$), diastolic blood pressure ($r = 0.283$, $p = 0.002$), NIHSS score on admission ($r = 0.546$, $p < 0.001$) and mRS score at discharge ($r = 0.557$, $p < 0.001$). Associations of log D-dimer levels with risk factors and functional outcome are shown in table 3. D-Dimer levels were significantly correlated or associated with age ($r = 0.384$, $p < 0.001$), sex ($p = 0.024$), warfarin use ($p = 0.036$), PT-INR ≥1.6 ($p = 0.004$), sys-

**Table 2.** Associations of infarction volume with risk factors (n = 120)

| | | p |
|---|---|---|
| Age | r = 0.123 | 0.174 |
| Sex, men/women | 29.0 (10.6–117.0)/79.4 (18.3–173.0) | 0.151 |
| Paroxysmal/fixed atrial fibrillation | 43.0 (8.8–130.4)/53.5 (15.7–156.1) | 0.525 |
| Current smoker (yes/no) | 18.2 (5.8–111.4)/61.8 (17.9–160.9) | 0.100 |
| Alcohol intake (yes/no) | 61.8 (14.0–178.4)/42.1 (13.7–130.1) | 0.408 |
| Hypertension (yes/no) | 42.1 (14.4–156.2)/58.6 (12.9–130.5) | 0.581 |
| Diabetes mellitus (yes/no) | 36.3 (17.3–114.5)/51.3 (9.7–156.1) | 0.898 |
| Dyslipidemia (yes/no) | 34.5 (6.6–138.1)/58.6 (14.8–130.1) | 0.750 |
| Chronic heart failure (yes/no) | 58.6 (17.9–151.5)/29.6 (3.5–130.8) | 0.676 |
| History of cardiovascular disease (yes/no) | 28.7 (3.3–117.2)/51.3 (13.9–154.4) | 0.748 |
| Previous stroke or TIA (yes/no) | 60.4 (15.5–167.7)/42.1 (12.9–130.5) | 0.267 |
| ACEI or ARB use (yes/no) | 39.4 (14.0–169.3)/48.7 (13.9–130.6) | 0.939 |
| Statin use (yes/no) | 39.1 (12.9–188)/48.7 (13.9–130.6) | 0.851 |
| Antiplatelet therapy (yes/no) | 33.3 (7.14–152.3)/52.3 (14.0–130.5) | 0.741 |
| Warfarin use (yes/no) | 42.4 (12.1–138.9)/48.7 (13.7–146.4) | 0.465 |
| PT-INR ≥1.6 (yes/no) | 19.3 (4.9–106.1)/58.6 (15.6–161.9) | 0.084 |
| Body temperature ≥37.0 (yes/no) | 100.3 (15.9–176.4)/42.0 (14.0–129.3) | 0.146 |
| D-Dimer | r = 0.309 | <0.001 |
| Systolic blood pressure | r = 0.201 | 0.026 |
| Diastolic blood pressure | r = 0.283 | 0.002 |
| Serum glucose | r = 0.101 | 0.299 |
| Admission $CHADS_2$ score | r = 0.082 | 0.363 |
| Onset-to-admission time | r = –0.134 | 0.137 |
| NIHSS score on admission | r = 0.546 | <0.001 |
| mRS score at discharge | r = 0.557 | <0.001 |

Data are presented as median with interquartile range in parentheses. D-Dimer level was analyzed as log-transformed values. TIA = Transient ischemic attack; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type 1 receptor blocker.

tolic blood pressure (r = 0.187, p = 0.038), diastolic blood pressure (r = 0.187, p = 0.039), serum glucose (r = 0.214, p = 0.027), preadmission $CHADS_2$ score (r = 0.239, p = 0.008), NIHSS score on admission (r = 0.340, p < 0.001) and mRS score at discharge (r = 0.310, p < 0.001). D-Dimer level was not related to onset-to-admission time. Multivariate regression analysis showed that log D-dimer level was significantly associated with infarction volume after adjustment for age and sex, and after additional adjustment for PT-INR ≥1.6, diastolic blood pressure, serum glucose, preadmission $CHADS_2$ score and NIHSS score on admission (table 4). In 108 patients who had a preadmission mRS score of 0 or 1, the D-dimer levels were significantly associated with NIHSS score at admission (r = 0.310, p < 0.001; fig. 2a). Figure 2b shows the mRS distribution by D-dimer tertiles (≤0.83, 0.83–2.16 and ≥2.16 μg/ml). Significant difference existed among tertiles (p = 0.003). Patients in the highest D-dimer tertile group showed worse outcome than those in the middle (p = 0.041) and lowest (p < 0.001) tertiles. No significant difference was found between the middle and lowest tertiles (p = 0.209).

## Discussion

Our results demonstrate that the plasma D-dimer level on admission is related to the infarct volume and functional outcome following acute cerebral embolism in NVAF patients. Our findings suggest that management of anticoagulation with plasma D-dimer level may be useful for prevention of severe cardioembolic stroke.

Although several reports have shown that D-dimer level is a predictive factor of outcome after cerebral infarction [22], it is highly likely that the D-dimer level could be influenced by the different causes of thrombosis

**Table 3.** Associations of log-transformed serum D-dimer levels with risk factors and functional outcome (n = 120)

| | | p |
|---|---|---|
| Age, years | r = 0.384 | <0.001 |
| Sex, men/women | 1.14 (0.64–2.60)/2.11 (0.82–5.28) | 0.024 |
| Paroxysmal/fixed atrial fibrillation | 1.31 (0.61–3.56)/1.41 (0.82–3.60) | 0.323 |
| Current smoker (yes/no) | 2.06 (0.75–5.30)/1.29 (0.73–3.30) | 0.214 |
| Alcohol intake (yes/no) | 1.03 (0.71–3.30)/1.54 (0.82–3.66) | 0.106 |
| Hypertension (yes/no) | 1.37 (0.70–3.76)/1.36 (0.93–2.52) | 0.827 |
| Diabetes mellitus (yes/no) | 1.26 (0.73–3.45)/1.31 (0.73–3.64) | 0.803 |
| Dyslipidemia (yes/no) | 1.11 (0.75–3.31)/1.40 (0.73–3.57) | 0.779 |
| Chronic heart failure (yes/no) | 1.41 (0.77–3.66)/1.20 (0.74–3.34) | 0.890 |
| History of cardiovascular disease (yes/no) | 1.25 (1.05–3.84)/1.41 (0.73–3.62) | 0.667 |
| Previous stroke or TIA (yes/no) | 1.54 (0.83–6.74)/1.28 (0.71–3.20) | 0.093 |
| ACEI or ARB use (yes/no) | 2.31 (0.84–4.19)/1.14 (0.69–3.23) | 0.252 |
| Statin use (yes/no) | 1.69 (0.92–4.12)/1.39 (0.75–3.62) | 0.915 |
| Antiplatelet therapy (yes/no) | 1.66 (0.88–4.19)/1.22 (0.56–3.35) | 0.115 |
| Warfarin use (yes/no) | 0.98 (0.45–1.51)/1.80 (0.84–3.66) | 0.036 |
| PT-INR ≥1.6 (yes/no) | 0.98 (0.27–1.41)/1.47 (0.81–3.76) | 0.004 |
| Body temperature ≥37.0 (yes/no) | 1.29 (0.92–3.79)/1.41 (0.73–3.53) | 0.288 |
| Systolic blood pressure | r = 0.187 | 0.038 |
| Diastolic blood pressure | r = 0.187 | 0.039 |
| Serum glucose | r = 0.214 | 0.027 |
| Preadmission $CHADS_2$ score | r = 0.239 | 0.008 |
| Onset-to-admission time | r = 0.061 | 0.500 |
| NIHSS score on admission | r = 0.340 | <0.001 |
| mRS score at discharge | r = 0.350 | <0.001 |

Data are presented as median with interquartile range in parentheses. D-Dimer level and duration of hospitalization were analyzed as log-transformed values. TIA = transient ischemic attack; ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type 1 receptor blocker.

formation [23]. Therefore, we only analyzed the relationship between D-dimer levels and ischemic severity in NVAF patients. To the best of our knowledge, this is the first study to demonstrate that plasma D-dimer level on admission is independently associated with infarction volume in NVAF patients.

Previous studies [24–26] have reported that heart failure, high systolic blood pressure, older age, diabetes mellitus and prior stroke were related to poor functional outcome after stroke. The $CHADS_2$ score is widely used for identifying high-risk patients who are eligible to use oral anticoagulants [20]. Recent studies have also shown that patients with higher $CHADS_2$ score are likely to develop severe stroke due to proximal location of arterial occlusion in NVAF patients after stroke presentation [27, 28]. These findings are reasonable considering the association between the prothrombotic/hypercoagulable state and $CHADS_2$ score. An association between plasma D-dimer levels and $CHADS_2$ score has also been reported [29], suggesting that the D-dimer levels could reflect stroke severity in NVAF patients. However, the association between D-dimer levels and stroke severity is controversial [30–35], probably because all stroke subtypes were included in the analysis. In this study, we clearly showed that D-dimer levels are associated with infarct volume in NVAF patients independent of their preadmission $CHADS_2$ score.

We have speculated some potential reasons for the association between D-dimer levels and cerebral infarct volume. First, D-dimer levels might reflect the size of thrombus within the left atrium. Although there are no reports of a relationship between cerebral emboli location and D-dimer levels in NVAF patients, D-dimer levels have shown a strong correlation to proximal emboli location for pulmonary embolism [17–19], suggesting that D-dimer levels reflect clot burden. In such cases, high D-dimer

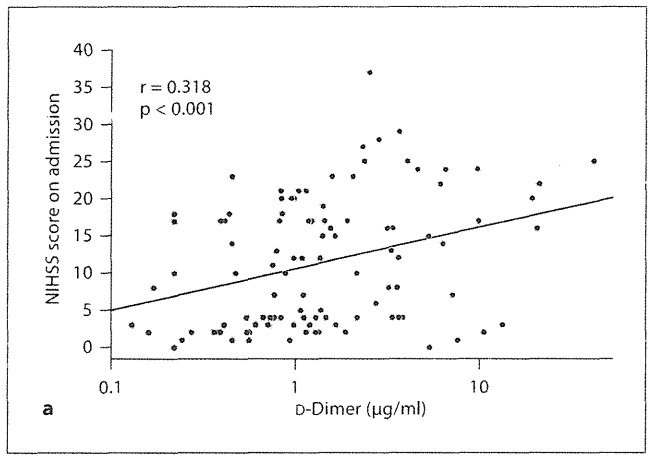


**Fig. 2.** Relationship between admission D-dimer level and stroke severity. **a** The D-dimer level at admission positively correlates with the NIHSS score on admission. **b** The mRS score distribution at discharge by D-dimer tertile group.

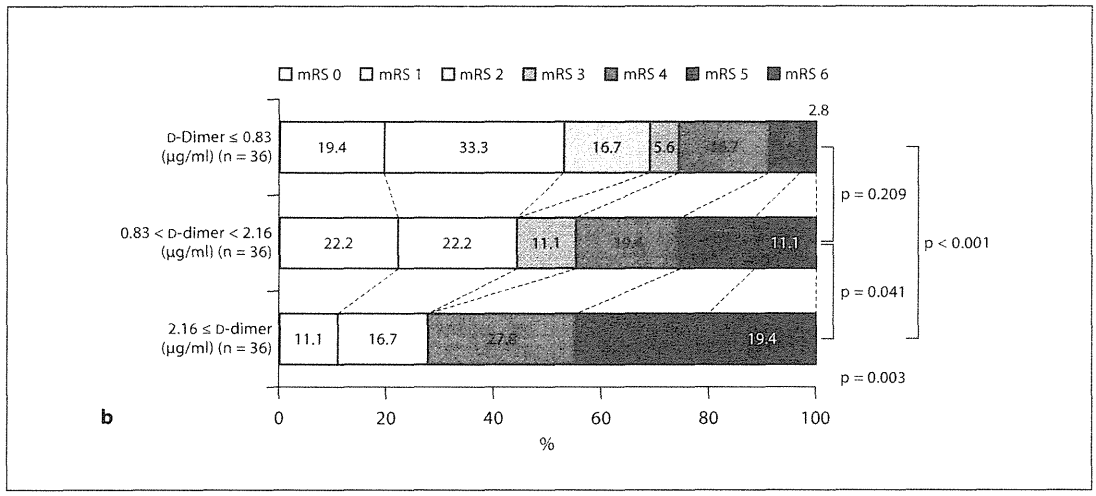


**Table 4.** Multivariate analyses of infarction volume

| Variables | Model 1 | | Model 2 | | Model 3 | |
|---|---|---|---|---|---|---|
| | β | p | β | p | β | p |
| D-Dimer, μg/ml | 0.30 | 0.001 | 0.28 | 0.003 | 0.19 | 0.043 |
| Age, years | −0.01 | 0.902 | −0.08 | 0.428 | −0.13 | 0.220 |
| Sex | 0.07 | 0.425 | 0.03 | 0.679 | −0.03 | 0.986 |
| Current smoker (yes/no) | | | 0.25 | 0.014 | 0.18 | 0.115 |
| PT-INR ≥1.6 (yes/no) | | | 0.07 | 0.438 | 0.09 | 0.228 |
| Diastolic blood pressure, mm Hg | | | 0.28 | <0.001 | 0.14 | 0.097 |
| NIHSS score on admission | | | | | 0.44 | 0.001 |

Levels of D-dimer were analyzed as log-transformed values.

levels may indicate the existence of a lodging clot in a major artery such as the internal carotid artery. Because internal carotid artery obstruction has been shown to predict poor clinical outcome after intravenous thrombolysis [36], acute ischemic stroke patients with high D-dimer levels may be refractory to intravenous thrombolysis. Furthermore, thrombi formed in hypercoagulable states such as high D-dimer levels may be resistant to the endogenous fibrinolytic system [37]. In addition to thrombus formation and stability, elevated systemic inflammation reflected by high D-dimer levels could also contribute to the stroke severity [38].

An association between D-dimer level and infarction volume is further supported by findings from NVAF patients treated with warfarin. Several previous studies have shown that functional outcome after cerebral infarction is better in NVAF patients who received warfarin treatment than in those who did not [11–15]. Therefore, it is evident that anticoagulation therapy with warfarin decreases D-dimer levels [16], prevents stroke occurrence and decreases stroke severity. These findings support the presently described association between D-dimer level and infarct volume in NVAF patients.

Anticoagulation with warfarin has been assessed using PT-INR as an index of coagulation. Although novel oral anticoagulants such as dabigatran, rivaroxaban and apixaban have recently been shown to be as effective as adjusted-dose warfarin for preventing stroke and systemic embolism in NVAF patients [39], there is no established biomarker to monitor their effects. Our results suggest the possibility of using D-dimer as an index for these novel anticoagulants.

There are some limitations to our study. First, we cannot exclude the possibility that D-dimer levels increased after stroke onset as acute phase reactants. However, we obtained all blood samples within 48 h and in most cases within 24 h after stroke onset. Other factors that can also elevate the D-dimer level, such as bacterial infection and venous thrombosis, usually occur after the first week of stroke onset [40]. On the other hand it has been recently shown that plasma D-dimer level remains almost the same during the first week after stroke onset [41]. In our study, we did not find a relationship between the onset-to-admission time and D-dimer level (table 3). Second, we cannot exclude the possibility that plasma D-dimer increased under immobile state such as aspiration pneumonia and venous thrombosis. However, we confirmed that 5 patients with a preadmission mRS score of 4 or 5 in this study had no evidence of aspiration pneumonia or leg edema on admission. Thus, immobile state before the onset of stroke does not seem to affect the level of plasma D-dimer in this study. Furthermore, as we have mentioned before, plasma D-dimer remains at almost the same level during the first week after stroke onset [41], which suggests that it is unlikely that plasma D-dimer level increased during the first week. Third, our small sample size did not allow us to analyze the association between D-dimer level and infarct volume in separate groups with and without warfarin treatment. The significance of D-dimer level could be different between these groups. Fourth, we were not able to use MRI data to measure the infarction volume instead of CT, because there were too many patients who did not receive MRI on admission. On the other hand, most patients received CT repeatedly. Fifth, because our study was retrospective, the time from stroke onset to CT imaging employed in this study varied from 2 to 4 days. Although all patients received the first CT imaging on admission, the second CT imaging was not systematically scheduled. Thus, we could not exclude the possibility that infarct size expanded from day 2 to 4 in each patient after stroke onset. Sixth, we excluded 46 patients who received thrombolytic therapy because this treatment might obscure the relationship between plasma D-dimer level and infarction size. Although the role of plasma D-dimer level on admission would be limited in the management of acute stroke patients, the significance of D-dimer level on the outcome after thrombolysis could be another important issue related to acute stroke treatment.

In conclusion, our study demonstrates a relationship between D-dimer level and cerebral infarction volume in NVAF patients. The significance of D-dimer levels on NVAF patient management should be further evaluated in a prospective study with a larger number of patients using warfarin or new anticoagulants.


## Acknowledgments

The authors thank Ms. C. Kurano and K. Nishiyama for their secretarial assistance. This study was supported in part by the research grant for cardiovascular disease from the Japanese Ministry of Health, Welfare and Labor.


## Disclosure Statement

None.

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