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Relationship between D-dimer levels and infarct pattern in acute ischemic stroke patients with non-valvular atrial fibrillation

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Abstract

Background: Cerebral embolism in patients with non-valvular atrial fibrillation (NVAF) is mainly caused by thrombus formation in the left atrial appendage. D-dimer is known to reflect the thrombogenic activity of the left atrium in NVAF patients. This study aimed to investigate the relationship between D-dimer levels and infarct pattern in ischemic stroke patients with NVAF. *Methods:* We enrolled 255 patients who developed cardioembolic stroke caused by NVAF and presented to the hospital within 7 days. We divided the infarct pattern into two groups: single lesions (SL) and multiple lesions (ML). The infarct pattern was also classified into two groups: ischemic lesions involving a single vascular territory (ST) and multiple vascular territories (MT). We analyzed the relationship between the infarct pattern and D-dimer levels. *Results:* Of the 255 patients, 79 (31.0%) and 176 (69.0%) were in the SL and ML groups, respectively. In addition, 207 (81.2%) and 48 (18.8%) patients were classified into the ST and MT groups, respectively. Compared with the SL group, a higher D-dimer level was observed in the ML group (p=0.006). Similarly, the MT group had higher D-dimer levels than the ST group (p=0.001). Logistic regression analysis showed that elevated D-dimer levels were significantly and independently associated with the presence of multiple ischemic lesions (p=0.021) and the involvement of multiple vascular territories (p=0.020).
Conclusions: This study showed that elevated D-dimer levels were independently associated with multiple ischemic lesions involving multiple vascular territories in ischemic stroke patients with NVAF.

Keywords: Ischemic stroke, atrial fibrillation, infarct pattern, D-dimer

INTRODUCTION

Non-valvular atrial fibrillation (NVAF), a common cardiac arrhythmia, is associated with an increased risk of embolic events such as ischemic stroke.[1] Cerebral embolism in patients with NVAF is attributed to the presence of thrombus in the left atrial appendage[2,3], and a hypercoagulable state is a well-recognized factor for thrombus formation in these patients.[4,5]

D-dimer is a fragment of fibrin degradation by the fibrinolytic system and is considered as a biomarker to quantify the hypercoagulable state.[6-8] Previous studies have shown a positive association between D-dimer levels and thrombus burden in several disease conditions, including pulmonary embolism and deep vein thrombosis.[9-11] In terms of NVAF, higher D-dimer levels on admission were correlated with increased lesion volume in patients with acute ischemic stroke.[12] We hypothesized that the infarct pattern, particularly the number and distribution of ischemic lesions, could differ according to D-dimer level because altered thrombus burden in the left atrium may affect the number of cerebral emboli in NVAF patients. However, there have been few considerations regarding this issue.

This study aimed to investigate the impact of D-dimer levels on the infarct pattern in patients with NVAF.

METHODS

Study population

We reviewed 2,412 patients with acute ischemic

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stroke who were admitted to the neurology department within 7 days of symptom onset and registered in a prospectively collected stroke registry from January 2015 to December 2019. A total of 526 NVAF patients with acute ischemic lesions demonstrated by diffusion-weighted imaging (DWI) were initially included in this study. We excluded patients who had stroke subtypes other than cardioembolism based on the Trial ORG 10172 in Acute Stroke Treatment (TOAST) classification system (n=95)[13], those who had a potential high-risk source of cardioembolism accompanied with NVAF (n=41), those who underwent DWI after acute reperfusion therapy (n=126), those who had hemorrhagic transformation on DWI (n=15), and those whose D-dimer tests were not performed (n=11). Finally, a total of 255 patients were included in this study. This study was approved by the hospital's institutional review board.

Clinical information

We collected data on baseline characteristics, prior medication history, and vascular risk factors such as hypertension, diabetes mellitus, hyperlipidemia, and cigarette smoking. Smoking status was categorized as current smoker or non-smoker. Data on the history of ischemic heart disease, ischemic stroke, and congestive heart failure were also obtained. Based on these data, we calculated the $CHADS_2$ scores before the index stroke.

Stroke severity was determined using the National Institutes of Health Stroke Scale (NIHSS) score at admission. Functional outcome was assessed according to the modified Rankin Scale (mRS) score, and an unfavorable outcome was defined as an mRS of 3–6 at 3 months after symptom onset.

We obtained the results of laboratory tests performed at admission, including complete blood counts, glucose, creatinine, prothrombin time, activated partial thromboplastin time, fibrinogen, D-dimer, C-reactive protein (CRP), and pro-B-type natriuretic peptide. The results for total and low-density lipoprotein cholesterol were collected from blood tests conducted in the morning after admission following an overnight fast. D-dimer was measured on Sysmex CS-5100 automatic blood coagulation analyzer (Siemens Healthcare Diagnostics, Erlangen, Germany) by utilizing a particle-enhanced immunoturbidimetric assay and the normal range was 0–2.74 nmol/L according to the manufacturer's reference.

Radiologic data

Ischemic lesion volume was measured on initial DWI using MIPAV software (version 10.0.0., http://mipav.cit.nih.gov). Two independent observers (H.-J.C. and S.-H.J.) manually outlined the boundary of hyperintense lesions, and the ischemic lesion volume was automatically calculated by multiplying the lesion area in each section by the slice thickness. The mean values of the measurements by the two observers were adopted in the analysis.

Regarding infarct patterns, we categorized the patients into those with single lesions (SL group) and those with multiple lesions (ML group) according to the number of ischemic lesions. Furthermore, we classified the patients into those with ischemic lesions confined to a single vascular territory (ST group) and those with ischemic lesions involving multiple vascular territories (MT group) based on the number of vascular territories involved. The vascular territories were divided into right anterior, left anterior, and posterior circulations. The anterior circulation included the territories of the anterior cerebral artery, middle cerebral artery, and anterior choroidal artery. The posterior circulation included the posterior cerebral artery, basilar artery, vertebral artery, superior cerebellar artery, anterior inferior cerebellar artery, and posterior inferior cerebellar artery territories. The infarct pattern for each patient was determined based on initial DWI and interpreted by two stroke neurologists (H.-J.C. and S.-H.J.). The discrepancies between two readers were resolved based on consensus.

Statistical analysis

Categorical variables were expressed as frequency (percentage) and were compared using the Pearson chi-square or Fisher exact test, where appropriate. Continuous variables were presented as median (interquartile range [IQR]) and were compared using the Mann-Whitney U test. Multivariable logistic regression analysis was performed to determine the independent variables associated with the infarct pattern, in which variables with p-value <0.05 on univariable analysis were included. The results are presented as odds ratios (ORs) and 95% confidence intervals (CIs). Statistical significance was set at $p<0.05$. All statistical analyses were conducted using SPSS for Windows (version 23.0; IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

The median age of the 255 patients included in this study was 74 years (IQR, 67–79), and 141 (55.3%) patients were males. The median time from symptom onset to hospital arrival and time from symptom onset to the acquisition of MRI was 9.2 h (IQR, 3.8–20) and 10.9 h (IQR, 5.0–22.2), respectively. The median NIHSS score was 5 (IQR, 2–15) on admission, and the median preadmission $CHADS_2$ score was 4 (IQR, 3–4). The median D-dimer value was 4.98 nmol/L (IQR, 2.85–10.62). Of the 255 patients, 79 (31.0%) were in the SL group and 176 (69.0%) in the ML group. In addition, 207 (81.2%) patients were classified into the ST group and 48 (18.8%) as the MT group.

Single vs. multiple ischemic lesions

Baseline characteristics, NIHSS score at admission, ischemic lesion volume, and vascular risk factors were not significantly different between the SL and ML groups. Compared to the SL group, lower hemoglobin level [8.4 (7.7–9.2) vs. 8.8 (8.1–9.4); p=0.017], higher platelet count [197.5 (163.3–237.5) vs. 182.5 (144.0–211.3); p=0.035], and higher D-dimer level [5.48 (3.07–12.92) vs. 3.89 (2.57–6.13); p=0.006] were observed in the ML group (Table 1). The incidence of unfavorable outcomes at 3 months did not differ between groups. In the multivariable logistic regression analysis, a higher D-dimer level (OR, 1.303; 95% CI 1.041–1.631; p=0.021) was a significant and independent predictor of the presence of multiple ischemic lesions (Table 2).

Single vs. multiple vascular territories

There were no statistically significant differences in age, sex, NIHSS score at admission, and ischemic lesion volume between the ST and MT groups. Higher $CHADS_2$ scores (4 [3–4] vs. 3 [3–4]; p=0.027) and a higher percentage of prior ischemic heart disease (31.3% vs. 15.0%; p=0.008) were observed in the MT group than in the ST group (Table 1). In the laboratory results, the MT group had lower hemoglobin level [7.9 (6.8–9.4) vs. 8.7 (7.9–9.3); p=0.038], higher admission glucose level [7.8 (6.4–9.1) vs. 6.8 (6.2–8.4); p=0.044], higher D-dimer level [7.83 (3.94–21.79) vs. 4.55 (2.68–8.76); p=0.001], and higher CRP level [3.5 (0.8–12.8) vs. 1.5 (0.6–4.2); p=0.005] compared to the ST group (Table 1). The incidence of unfavorable outcomes at 3 months was significantly higher in the MT group than in the ST group. Multivariable logistic regression analysis showed that a history of ischemic heart disease (OR, 2.213; 95% CI, 1.011–4.842; p=0.047) and higher D-dimer levels (OR, 1.165; 95% CI, 1.025–1.325; p=0.020) were significantly and independently associated with the involvement of multiple vascular territories (Table 2).

Infarct pattern according to D-dimer levels

In tertile analysis, the prevalence of multiple ischemic lesions showed a stepwise increase from the lowest to the highest tertile of D-dimer levels (61.6% vs. 66.3% vs. 79.1%; p=0.038). Similarly, as the tertile of D-dimer increased, the percentage of multiple vascular territories also significantly increased (9.3% vs. 18.1% vs. 29.1%; p=0.004, Figure 1).

DISCUSSION

Our study demonstrated that NVAF patients with higher D-dimer levels on admission were more likely to have multiple ischemic lesions involving multiple vascular territories. D-dimer is the degradation product of cross-linked fibrin.[6,7] Therefore, elevated D-dimer levels may be a marker of a hypercoagulable state by reflecting the increased fibrinolytic activity.[8,14] The hypercoagulable state, one of Virchow's triad, is traditionally invoked to explain the pathophysiologic mechanism leading to thrombus formation.[4,5] Previous studies have shown that D-dimer levels in NVAF patients with left atrial thrombus were significantly higher than those without left atrial thrombus.[15,16] Higher D-dimer levels were also associated with an increased rate of ischemic stroke.[17-21] Furthermore, NVAF patients treated with anticoagulants had lower levels of D-dimer compared to those on aspirin or those who were not received any antithrombotic therapy.[22] Given these results, the previous researchers have suggested that the D-dimer levels might reflect the thrombogenic activity in the left atrium. Therefore, in our study, we speculate that the increased thrombus burden in the left atrium under the hypercoagulable state may be the underlying reason for multiple ischemic lesions affecting multiple vascular territories by causing multiple cerebral emboli originating from cardiac chambers in patients with NVAF.

In our study, ischemic lesions involving multiple vascular territories were frequently

Table 1: Clinical and laboratory characteristics according to infarct patterns

	Number of ischemic lesions			Number of vascular territories		
	Single (n=79)	**Multiple (n=176)**	**p-value**	**Single (n=207)**	**Multiple (n=48)**	**p-value**
Male	47 (59.5)	94 (53.4)	0.366	119 (57.5)	22 (45.8)	0.143
Age, year	74.0 (66.0-79.0)	75.0 (67.0-80.0)	0.460	74.0 (66.0-79.0)	76.0 (68.0-81.0)	0.159
Time from onset to arrival, hour	9.2 (3.8-19.0)	9.1 (3.9-21.3)	0.862	10.4 (4.1-20.2)	7.7 (2.4-16.2)	0.065
NIHSS score at admission	5.0 (1.0-12.0)	5.0 (2.0-15.0)	0.245	5.0 (2.0-14.0)	5.5 (1.0-17.0)	0.551
Ischemic lesion volume, cm^3	10.2 (1.1-30.0)	8.5 (2.5-32.1)	0.610	8.8 (2.2-28.5)	10.1 (2.7-94.8)	0.159
$CHADS_2$ score	3.0 (2.0-4.0)	4.0 (3.0-4.0)	0.080	3.0 (3.0-4.0)	4.0 (3.0-4.0)	0.027*
Risk factors						
Hypertension	57 (72.2)	134 (76.1)	0.479	153 (73.9)	38 (79.2)	0.449
Diabetes	24 (30.4)	59 (33.5)	0.620	67 (32.4)	16 (33.3)	0.898
Hyperlipidemia	10 (12.7)	34 (19.3)	0.193	36 (17.4)	8 (16.7)	0.905
Cigarette smoking	10 (12.8)	25 (14.7)	0.692	29 (14.4)	6 (12.8)	0.768
Prior ischemic heart disease	12 (15.2)	34 (19.3)	0.428	31 (15.0)	15 (31.3)	0.008*
Prior ischemic stroke	20 (25.3)	43 (24.4)	0.880	46 (22.2)	17 (35.4)	0.056
Laboratory findings						
Hemoglobin, mmol/L	8.8 (8.1-9.4)	8.4 (7.7-9.2)	0.017*	8.7 (7.9-9.3)	7.9 (6.8-9.4)	0.038*
Platelet count, $10^3/\mu L$	182.5 (144.0-211.3)	197.5 (163.3-237.5)	0.035*	191.5 (158.8-227.0)	194.5 (143.8-249.0)	0.943
Admission glucose, mmol/L	7.3 (6.3-8.8)	7.1 (6.1-8.9)	0.404	6.8 (6.2-8.4)	7.8 (6.4-9.1)	0.044*
Total cholesterol, mmol/L	4.1 (3.6-4.9)	4.1 (3.5-4.8)	0.334	4.1 (3.6-4.8)	3.9 (3.0-5.0)	0.187
LDL cholesterol, mmol/L	2.6 (2.0-3.3)	2.5 (1.9-3.1)	0.207	2.6 (2.0-3.2)	2.4 (1.5-3.2)	0.075
Creatinine, μmol/L	80.5 (62.8-99.9)	78.7 (63.7-98.2)	0.961	77.8 (62.8-94.6)	84.9 (63.7-114.1)	0.083
PT INR	1.06 (1.02-1.15)	1.05 (0.99-1.12)	0.082	1.06 (1.00-1.13)	1.07 (0.97-1.12)	0.445
aPTT, second	31.2 (27.6-34.8)	31.6 (27.6-34.9)	0.956	31.6 (28.2-34.8)	30.9 (24.7-34.7)	0.260
Fibrinogen, g/L	8.39 (7.56-10.16)	8.83 (7.64-10.18)	0.423	8.60 (7.61-10.17)	8.86 (7.41-10.16)	0.830
D-dimer, nmol/L	3.89 (2.57-6.13)	5.48 (3.07-12.92)	0.006*	4.55 (2.68-8.76)	7.83 (3.94-21.79)	0.001*
CRP, mg/L	1.2 (0.6-3.3)	1.8 (0.7-6.0)	0.168	1.5 (0.6-4.2)	3.5 (0.8-12.8)	0.005*
Pro-BNP, pmol/L	29.3 (19.4-42.7)	28.4 (17.6-45.3)	0.964	28.4 (17.6-43.5)	34.9 (23.1-52.4)	0.100
Prior medication						
Antiplatelet agent	40 (50.6)	90 (51.1)	0.941	104 (50.2)	26 (54.2)	0.624
Anticoagulant	15 (19.0)	29 (16.5)	0.624	36 (17.4)	8 (16.7)	0.905
Statin	20 (25.3)	58 (33.0)	0.221	60 (29.0)	18 (37.5)	0.249
Unfavorable outcome at 3 months	27 (36.5)	80 (46.0)	0.167	77 (38.5)	30 (62.5)	0.003*

Values are number (column %) or median (interquartile range).

*p<0.05.

NIHSS, National Institutes of Health Stroke Scale; LDL, low-density lipoprotein; PT INR, prothrombin time international normalized ratio; aPTT, activated partial thromboplastin time; CRP, C-reactive protein; Pro-BNP, pro-B-type natriuretic peptide.

Table 2: Multivariable analysis of independent factors associated with infarct patterns

	Multiple ischemic lesions		Multiple vascular territories	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Male	1.107 (0.593-2.067)	0.750	0.876 (0.417-1.840)	0.726
Age, year	1.003 (0.970-1.037)	0.867	1.001 (0.956-1.047)	0.981
$CHADS_2$ score	–	–	1.170 (0.777-1.760)	0.453
Prior ischemic heart disease	–	–	2.213 (1.011-4.842)	0.047*
Hemoglobin	0.874 (0.752-1.016)	0.079	0.899 (0.764-1.059)	0.203
Platelet count	1.000 (1.000-1.000)	0.192	–	–
Admission glucose	–	–	1.001 (0.994-1.007)	0.834
D-dimer	1.303 (1.041-1.631)	0.021*	1.165 (1.025-1.325)	0.020*
CRP	–	–	1.163 (0.924-1.463)	0.199

*p<0.05.
OR, odds ratio; CI, confidence interval; CRP, C-reactive protein.

observed in patients with a history of ischemic heart disease. This finding may be supported by a previous study using transesophageal echocardiography, in which a history of ischemic heart disease was an independent predictor of reduced flow velocity in the left atrial appendage.[23] Such reduction in flow velocity is known to be associated with the presence of left atrial thrombus and high thromboembolic risk in patients with NVAF.[3,23] Therefore, increased thrombus burden in the left atrium caused by blood stasis in NVAF patients with prior ischemic heart disease may be a plausible mechanism of ischemic lesions involving multiple vascular territories. However, we did not address the possible impact of the left atrial flow velocity in this study. Further studies are warranted to determine the relationship between hemodynamic parameters in the left atrium and infarct pattern in NVAF patients with acute ischemic stroke.

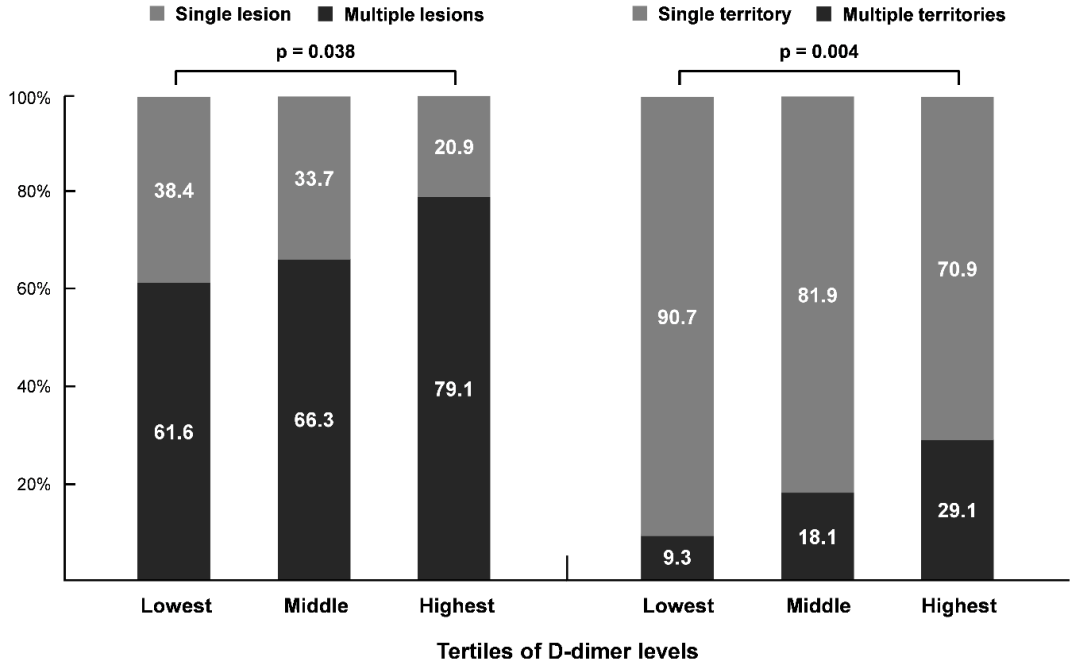

Figure 1. Tertile analysis for infarct patterns according to serum D-dimer levels.

Our study showed that patients with ischemic lesions involving multiple vascular territories were more prone to have unfavorable outcomes at 3 months than those with ischemic lesions within a single vascular territory. Our results may be in line with previous observations, which have shown that the presence of ischemic lesions located in multiple vascular territories was an independent factor for unfavorable outcomes in patients with ischemic stroke.[24,25] On the contrary, we could not find any significant difference in functional outcomes between patients with SL and those with ML. Therefore, from the viewpoint of infarct pattern, we suggest that functional outcomes in NVAF patients with acute ischemic stroke may be critically influenced by the number of affected vascular territories rather than by the number of ischemic lesions.

There are limitations to this study that should be considered. First, this was a single-center retrospective study with a relatively small sample size. Therefore, our findings need to be verified with a larger population since unrecognized biases might affect the interpretation of the results. Second, although several conditions, such as deep vein thrombosis, pulmonary embolism, cancer, infection, or recent surgery, are known to be associated with increased D-dimer levels, these factors were not fully considered and adjusted for in this study.[14] Finally, we included patients who presented within 7 days from symptom onset. This time window could be broad because the D-dimer level would be reduced over time. However, in this study, 205 (80.4%) patients presented to the hospital within 24 h and 242 (94.9%) within 72 h. In addition, a previous study showed no significant change in D-dimer levels over time during the first week after stroke onset.[26] These factors might reduce the potential bias caused by the time delay from symptom onset to hospital arrival.

In conclusion, our study showed that elevated D-dimer levels were associated with multiple ischemic lesions involving multiple vascular territories in patients with NVAF. We suggest that a larger thrombus burden in the left atrium implicated in a hypercoagulable state could affect the number and distribution of ischemic lesions, causing an increased number of cerebral emboli originating from the intracardiac thrombus.

DISCLOSURE

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Conflict of interest: None

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