

The association of high D-dimer level with high risk of ischemic stroke in nonvalvular atrial fibrillation patients

A retrospective study

Li-Rui You, MD^{a,b}, Mei Tang, MD^{a,*}

Abstract

This study aimed to explore the relationship of D-dimer level with the risk stratification of ischemic stroke, and determine whether high D-dimer levels could be used as a risk factor of ischemic stroke in patients with nonvalvular atrial fibrillation (NVAf).

This single-center, retrospective study recruited NVAf patients who did not undergo anticoagulant therapy. These patients were divided into 2 groups: ischemic stroke group and no-stroke group. The medical records of each patient were reviewed, demographic and clinical analyses were performed, and the laboratory results were summarized.

A total of 323 eligible in-patients with NVAf, who did not receive anticoagulant therapy, were recruited (206 male and 117 female patients, median age was 75.18 ± 10.46 years old). Among these patients, 78 patients suffered from acute ischemic stroke. D-dimer level increased with age, and was positively correlated with the risk stratification of stroke, CHADS₂ score ($r_s = 0.441$, $P < .001$), and CHA₂DS₂-VASc score ($r_s = 0.412$, $P < .001$), even after adjustment for age and gender ($r_s = 0.422$, $P < .001$). The difference in baseline D-dimer level between these 2 groups was not statistically significant (0.70 vs 0.66 mg/L, $P = .330$), but this significantly increased when patients suffered from stroke (1.34 vs 0.70 mg/L, $P < .001$). The D-dimer level after stroke (≥ 6 months) was also higher than the baseline (1.16 vs 0.68 mg/L, $P = .514$) in 6 months, and this level nearly returned to baseline level after one year (0.69 vs 0.68 mg/L, $P = .158$). However, logistic regression revealed that only the D-dimer level at stroke onset and OMI were independent risk factors for ischemic stroke ($P < .001$), while the increase from baseline D-dimer levels was not an independent risk factor ($P = .125$).

D-dimer level is positively correlated with the risk stratification of ischemic stroke, but has no predictive value on the occurrence of ischemic stroke in patients with NVAf.

Abbreviations: AD = aortic dissection, AF = atrial fibrillation, AMI = acute myocardial infarction, CAD = coronary artery disease, CHF = congestive heart failure, CRP = C-reactive protein, DBP = diastolic blood pressure, DM = diabetes mellitus, EF = ejection fraction, HC = hypercholesterolemia, HF = heart failure, HT = hypertension, LA = left atrial, LAE = Left atrial enlargement, MI = myocardial infarction, NVAf = nonvalvular atrial fibrillation, OGTT = oral glucose tolerance test, OMI = old myocardial infarction, PE = pulmonary embolism, ROC = receiver operator characteristic, SBP = systolic blood pressure, SD = standard deviation, TEE = transesophageal echocardiography, UA = uric acid.

Keywords: D-dimer, ischemic stroke, nonvalvular atrial fibrillation, risk factor, risk stratification

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1. Introduction

Atrial fibrillation (AF) is a common arrhythmia, and confers an independent increased risk of ischemic stroke and death.^[1] The majority of data on its epidemiology are available from studies in Western Europe and North America, and ranges from 0.5% to 2%.^[1,2] The prevalence of AF increases with age, and the number of patients is expected to increase due to the growing elderly population and the prevalence of AF in the elderly. Furthermore, it is encountered in 10% of patients who are ≥ 80 years old.^[3] Therefore, its management is important. Furthermore, as a major independent risk factor for ischemic stroke, the assessment of thromboembolic risk and appropriate thromboprophylaxis are important objectives of AF management, and the representative stratification systems presently being used include CHADS₂ and CHA₂DS₂-VASc scores.^[2,4,5] The CHADS₂ score has been widely used as a risk stratification scale. However, after considering additional risk factors such as vascular disease, gender and the age range of 65 to 74 years old, a more specific evaluation can be made. The scale that reflects these risk factors is the CHA₂DS₂-VASc score.

D-dimer is a specific degradation product of cross-linked fibrin, and its presence in plasma is a biomarker that indicates the activation of coagulation and fibrinolysis.^[6] D-dimer level increases with age, and is elevated when AF has long been recognized.^[7–9] In recent years, a researcher also reported that D-dimer level has a positive relationship with BNP.^[9,10] Furthermore, some prospective studies have confirmed that D-dimer level can predict the occurrence of thromboembolic and cardiovascular events, such as acute myocardial infarction and acute aortic dissection, in atrial fibrillation patients, particularly patients complicated with clinical risk factors.^[11,12]

The aim of the present study was to identify the relationship between D-dimer level and the risk stratification of ischemic stroke in nonvalvular atrial fibrillation (NVAF) patients, and assess whether elevated D-dimer level could be proposed as a risk factor of ischemic stroke among patients with NVAF.

2. Design and method

2.1. Study patients

This single-center, retrospective study included patients with AF, who were admitted to Beijing Friendship Hospital, Capital Medical University, between January 2011 and June 2014. This study was conducted with approval from the Ethics Committee of Beijing Friendship Hospital. Written informed consent was obtained from all participants. Inclusion criteria: patients with pre-existing diagnosis or new-onset NVAF during admission (defined after undergoing an ECG/Holter recording and echocardiography), patients who were ≥ 50 years old, and patients who did not receive anticoagulation treatment (warfarin or new oral anticoagulants such as dabigatran or apixaban).

Exclusion criteria: patients with vein thrombosis, acute or chronic pulmonary embolism (PE), aortic dissection (AD), sepsis, severe pneumonia, heart failure (HF), acute myocardial infarction (AMI), and hepatic and renal insufficiency; patients who had surgery and trauma within 1 month; patients who have cancer, and received radiotherapy and chemotherapy; patients with hematologic disorders.

The ischemic stroke of patients was based on their diagnosis of acute ischemic stroke or recurrence of ischemic stroke (defined as a focal neurologic deficit of sudden onset diagnosed clinically by a neurologist and confirmed by CT or MRI).

2.2. Clinical variables

At baseline, demographic data (age and gender), medical history (hypertension [HT], diabetes mellitus [DM], congestive heart failure [CHF], and hyperlipidemia), and laboratory blood biomarkers (C-reactive protein [CRP], glucose, creatinine, uric acid [UA], and cholesterol) were obtained during admission. The stroke risk of these patients was assessed based on the CHADS₂ and CHA₂DS₂-VASc scores. In addition, the D-dimer level of stroke patients was recorded at different time phases. These were not only measured during admission, but also at baseline (at least one year before stroke onset), at stroke onset within 6 to 48 hours, and after stroke within 6 months and 1 year later.

2.3. Definitions

HF diagnosis was performed according to cardiac function level III-IV (NYHA classification) or ejection fraction (EF) $< 40\%$. HT was established through clinical records that indicated a systolic blood pressure (SBP) > 140 mm Hg and/or diastolic blood

pressure (DBP) > 90 mm Hg, or the use of antihypertensive agents. DM was defined as treatment with oral hypoglycemic agents or insulin, fasting glucose level ≥ 7.0 mmol/L, glycosylated hemoglobin A1c $\geq 6.5\%$, or an oral glucose tolerance test (OGTT) that revealed that glucose in 2 hours was ≥ 11.1 mmol/L. Old myocardial infarction (OMI) refers to myocardial infarction (MI) that occurred for at least more than 2 months. Elevated D-dimer level means that the level was > 1.0 mg/L. Left atrial enlargement (LAE) refers to a left atrial (LA) diameter of > 35 mm. Hypercholesterolemia (HC) was defined as a cholesterol level of > 5.20 mmol/L (normal range: 3.9–5.2 mmol/L). Hyperuricemia refers to a uric level of > 416 μ mol/L (normal range: 178–416 μ mol/L). Elevated CRP means a level > 5.0 mg/L (normal range: 0–5 mg/L).

2.4. Blood samples and assays

Blood samples were collected from patients and controls at 6:00 AM of the next morning from the day of admission. All assays were performed in the laboratory of our institution within 2 hours of the blood sampling. The plasma D-dimer was assayed using the immunoturbidimetric method (Diagnostica Stago, Amercia, Nanopia D-dimer, Japan; normal limit ≤ 1.0 mg/L). A part of the blood samples were assayed in the Clinical Laboratory Center of the hospital, according to manufacturer's instructions.

2.5. Statistical analysis

All values were expressed as mean \pm standard deviation (SD). T-test was used for the comparison of continuous variables. Chi-square test or Fisher's exact test was utilized for the comparison of discontinuous variables. The relationship between D-dimer level and CHADS₂ scores were analyzed by Spearman's rank correlation, and the relationship with age and CRP were utilized by linear regression analysis. Multivariate analysis was performed by binary logistic regression analysis, which allows adjustment for the confounding factors of stroke. The optimal D-dimer cut-off point was evaluated through the receiver operator characteristic (ROC) curve. A *P*-value $< .05$ was considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics version 17.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline clinical characteristics on admission

A total of 323 consecutive in-patients with NVAF, who were ≥ 50 years old and did not receive anticoagulation treatment, were recruited into the present study. Among these patients, 78 patients had stroke. Furthermore, among these patients, 206 patients were male and 117 patients were female. Moreover, the median age of these patients was 75.18 ± 10.46 years old, and the difference in D-dimer level between these patients were not statistically significant (0.68 vs 0.64, *P* = .939). Clinical characteristics of patients at this inclusion are summarized in Table 1.

3.2. Correlation analysis

The stroke risk stratification of these patients was assessed by CHADS₂ and CHA₂DS₂-VASc scores, and the D-dimer levels of each point in these 2 schemes were listed in Table 2. As expected, these results revealed that baseline D-dimer level were positively correlated with CHADS₂ scores by Spearman's rank correlation

Table 1
Baseline clinical characteristics of patients with NVAf.

Clinical variables	Stroke	No stroke	P value
Number	78	245	—
Age	75.64 ± 5.26	75.03 ± 10.82	.018
Female (%)	41.02 (32)	34.69 (85)	.312
SBP, mm Hg	141.88 ± 19.07	133.42 ± 18.35	.794
DBP, mm Hg	81.12 ± 12.20	76.43 ± 11.85	.964
Cr, μmol/L	84.98 ± 29.62	94.55 ± 60.84	.149
GLU, mmol/L	5.70 ± 1.89	5.52 ± 1.71	.233
TC, mmol/L	4.11 ± 1.74	4.19 ± 0.95	.208
TG, mmol/L	1.31 ± 0.72	1.36 ± 0.88	.435
LDL-C, mmol/L	2.40 ± 0.81	2.32 ± 0.86	.241
HDL-C, mmol/L	1.08 ± 0.24	1.16 ± 0.38	.002
UA, mmol/L	303.03 ± 102.86	349.62 ± 101.08	.902
LA diameter, mm	42.42 ± 5.29	42.46 ± 6.32	.306
EF (%)	60.55 ± 8.79	64.12 ± 6.58	.115
HT (%)	80.76 (63)	84.90 (208)	.388
CHA2DS2-VASc	3.73 ± 1.48	2.91 ± 1.17	<.001
CHADS2	1.73 ± 0.85	2.31 ± 1.20	<.001
DM (%)	34.62 (27)	32.24 (79)	.698
OMI (%)	16.67 (13)	6.53 (16)	.006

DM=diabetes mellitus, DBP=diastolic blood pressure, EF=ejection fraction, GLU=glucose, HDL-C=high-density lipoprotein cholesterol, HT=hypertension, LA=left atrial, LDL-C=low density lipoprotein cholesterol, NVAf=nonvalvular atrial fibrillation, OMI=old myocardial infarction, SBP=systolic blood pressure, TC=total cholesterol, TG=triglyceride, UA=uric acid.

(rs=0.441, P<.001; Fig. 1A) and CHA2DS2-VASc scores (rs=0.412, P<.001; Fig. 1B). Furthermore, these results revealed that baseline D-dimer level increased with age (rs=0.533, P<0.001; Fig. 2). Meanwhile, it was also found that D-dimer level has positively correlated with CRP (rs=0.216, P<.001) by linear regression analysis (Fig. 3).

3.3. D-dimer level and stroke

From the above, it was noted that age can affect the D-dimer level. Hence, 73 stroke cases and 73 nonstroke patients were finally recruited after adjustment for age and gender. However, the overall baseline D-dimer level remained not significantly different between stroke (26 cases) and no-stroke (73 cases) patients (0.70 ± 0.34 vs 0.66 ± 0.30 mg/L, P=.330; Fig. 4). In patients who experienced stroke, the D-dimer level was significantly elevated, when compared with baseline D-dimer levels (1.34 ± 0.91 vs 0.70 ± 0.34 mg/L, P<.001). Furthermore, 16 cases had recurrence of stroke, and the baseline D-dimer level was 0.79 ± 0.45 mg/L, which was higher than that in the no-stroke group. However, the difference between these 2 groups was not statistically significant (P=.440), and there also no significant difference when

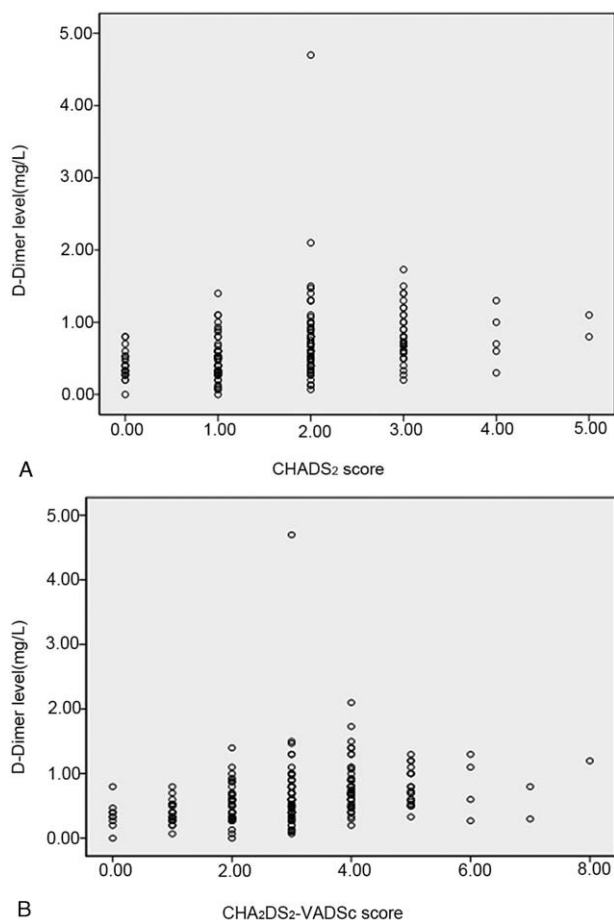


Figure 1. (A) The relationship between D-dimer level and CHADS₂ score: D-dimer level has positively correlated with the CHADS₂ score by Spearman's rank correlation (rs=0.441, P<.001). (B) The relationship between D-dimer level and CHA₂DS₂-VASc score: D-dimer level has positively correlated with CHA₂DS₂-VASc score by Spearman's rank correlation (rs=0.412, P<.001).

compared with the baseline D-dimer level in the stroke group (0.64 ± 0.29, P=.154). Furthermore, 7 cases had cardioembolic stroke. The baseline D-dimer level was 0.78 ± 0.26 mg/L, while the level for other stroke types was 0.67 ± 0.35 mg/L (P=.689). However, the D-dimer level at onset was higher than that for other types of stroke (1.68 ± 0.77 mg/L vs 1.15 ± 0.64 mg/L, P=.607). Moreover, the data we collected also revealed that D-dimer levels remained higher than the baseline (1.16 ± 0.41 mg/L vs 0.68 ± 0.33 mg/L, P=.514) in 6 months (10 cases), and nearly

Table 2
The D-dimer level of CHADS2 and CHADS2-VASc score.

Point	CHADS ₂ score		CHA ₂ DS ₂ -VASc score	
	Number	D-dimer	Number	D-dimer
0	27	0.40 ± 0.18	10	0.35 ± 0.22
1	77	0.47 ± 0.26	25	0.39 ± 0.17
2	148	0.70 ± 0.46	54	0.52 ± 0.27
3	57	0.79 ± 0.32	117	0.64 ± 0.49
4	11	0.78 ± 0.38	78	0.79 ± 0.35
5	4	0.95 ± 0.21	28	0.78 ± 0.28
6			9	0.81 ± 0.49
7			2	0.55 ± 0.35
8				

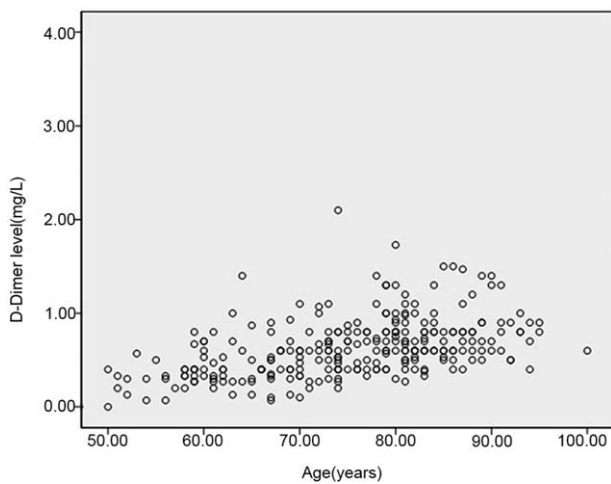


Figure 2. For the relationship between D-dimer level and age, Spearman analysis results revealed that D-dimer levels have a positive correlation with age ($r_s=0.533, P<.001$).

returned to baseline level after one year (19 cases) (0.69 ± 0.25 mg/L vs 0.68 ± 0.33 mg/L, $P=.158$). In addition, 36 cases diagnosed with pre-existing stroke (a history of at least 1 year) were collected. The D-Dimer level was 0.95 ± 0.37 mg/L, and this had no significant difference with baseline values in the no-stroke group ($P=.588$) and stroke group (0.95 vs $0.68, P=.639$).

3.4. Multivariate logistic regression for stroke

After adjustment for age and gender, the multivariate analysis of variance revealed that D-dimer level at stroke onset ($P<.001$) and OMI ($P=.011$) were independently related risk factors of stroke. However, DM ($P=.292$), HT ($P=.194$), and the baseline D-dimer level ($P=XXX$) were not. Furthermore, the investigators attempted to determine the cut off value for the D-dimer to predict stroke. However, they failed established the receiver operating characteristic (ROC) curve for D-dimer level and stroke.

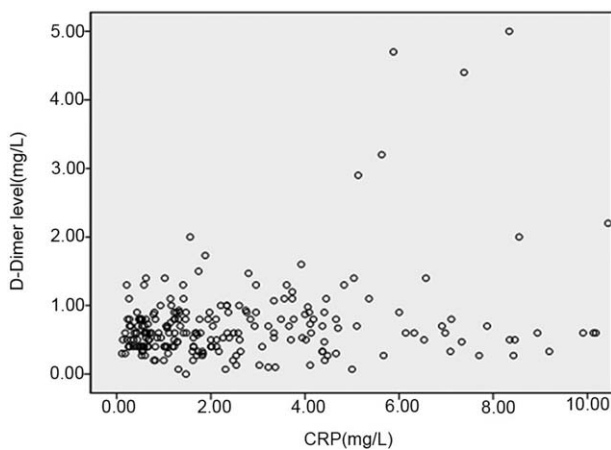


Figure 3. The relationship between D-dimer level and CRP: D-dimer level was positively correlated with CRP by linear regression analysis ($r_s=0.219, P=.000$). CRP=C-reactive protein

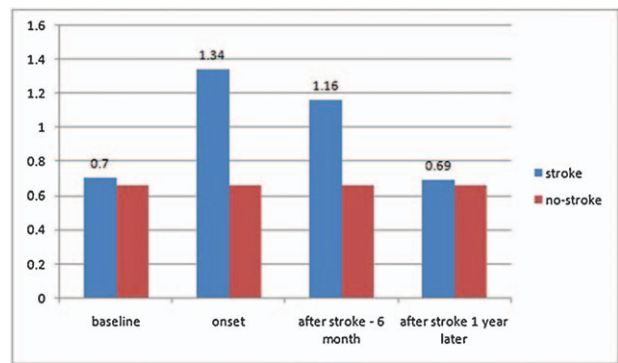


Figure 4. The baseline D-dimer level had no-significant difference between the stroke and no-stroke groups ($P=.330$). The D-dimer level of stroke on set, and post-stroke events in 6 months was significantly higher than that in the no-stroke group ($P<.001$). The difference in post-stroke D-dimer level after 1 year between the 2 groups was not statistically significant ($P=.365$).

4. Discussion

In the present study, the investigators failed to determine whether high D-dimer level was an independent risk factor of ischemic stroke in NVAF patients. However, to the best of our knowledge, the available study was able to assess the risk value of D-dimer level in patients with NVAF.

4.1. D-dimer levels in nonvalvular atrial fibrillation and stroke

D-dimer, a specific degradation product of cross-linked fibrin, is a sensitive biomarker for indicating the activation of coagulation and fibrinolysis, which remains stable over time in patients without any adverse event.^[13,14] D-dimer levels are usually used for the screening of pulmonary embolism and aortic dissection.^[15-17] Numerous studies had reported that D-dimer level is elevated during acute stroke, is associated with stroke subtypes and volume, and is significantly elevated in cardioembolic ischemic stroke.^[18-20] In the present study, the D-dimer level of cardioembolic stroke was higher than the other type, but the difference between these 2 was not statistically significant, which may be due to the small number of cases. In recent years, prospective studies have revealed that D-dimer levels were correlated to acute stroke, and can be a valuable and independent short-term prognostic marker for acute stroke.^[21,22] In the present study, it was also found that D-dimer levels were not correlated with stroke recurrence, and these results were similar with the report of Krarup et al.^[23] Reganon et al^[24] revealed that D-dimer remained elevated at 6 months in patients who have suffered from ischemic stroke. Hence, the results obtained in the present study were similar with above. Moreover, it was also found that D-dimer levels returned to baseline after one year. Indeed, more large clinical prospective studies are needed to confirm these findings.

4.2. D-dimer level with stroke risk stratification in NVAF patients

It is well known that AF confers a substantial risk of ischemic stroke and thromboembolism. As a major independent risk factor for ischemic stroke, the study conducted by Framingham was able to prove that the chance of ischemic stroke in NVAF patients was

5.6 to 7.0 times of the normal sinus rhythm.^[25] Therefore, it is necessary for anticoagulant therapy to prevent ischemic stroke in patients with AF, especially for high-risk patients. The CHADS2 score has been widely used as a risk stratification scale. Data has proven that warfarin can reduce the risk of ischemic stroke by 68% vs 33% in overall mortality.^[26] Furthermore, some studies have shown that warfarin decreases D-dimer levels.^[27] Furthermore, some studies have also shown that D-dimer levels in combination with clinical risk factors of ischemic stroke in NVAF patient were more higher and positive with BNP.^[2,9,10] In the present study, D-dimer levels were only affected by older age groups (≥ 75 years old), while this was not correlated with other risk factors in NVAF patients of ischemic stroke. These results revealed that D-dimer level were positively correlated with the CHADS2 score, even with the adjustment for age and gender. This proves that D-dimer levels are positively correlated with ischemic stroke risk stratification. It is noteworthy that in the present study, the D-dimer level was lower when compared between the CHA2DS2-VASc and CHADS2 score in same points. This proves that CHA2DS2-VASc scores are really more suitable for low-risk patients with AF for ischemic stroke screening, and this further confirms that D-dimer level is positively correlated with ischemic stroke risk stratification.

4.3. D-dimer level predicted the stroke event in NVAF?

Over the last 2 decades, numerous studies have explored the predictive value of D-dimer levels in thromboembolic and cardiovascular events with AF.^[2,27-29] Some studies^[30,31] found that D-dimer can be used as a possible test to exclude left atrial thrombus. Transesophageal echocardiography (TEE) is the gold standard for left atrial thrombus. However, TEE is unable to diagnose thrombi with diameters of < 2 mm. D-dimer is a sensitive index. When a thrombus starts to manifest, the D-dimer level would appear to be elevated. Tayebjee and Lip^[30] considered that for a D-dimer level of < 600 ng/mL, atrial thrombus negative diagnostic sensitivity and specificity would be 89% and 89%, respectively.

In a prospective study, Mahé et al^[12] found that the baseline D-dimer level was not significantly different in patients who suffered from cardiovascular events during follow-ups, when compared with patients who did not have a cardiovascular event. However, the incidence of cardiovascular events was significantly elevated for patients with D-dimer levels of > 334 ng/mL. Furthermore, for patients who experienced an event, the D-dimer level would be significantly elevated, when compared with baseline and in patients who did not have the event. Sadanaga et al^[10] were also able to prove that high D-dimer levels (≥ 0.5 mg/L) might be useful markers for both thromboembolic and cardiovascular events in patients with AF, even during oral anticoagulant therapy. However, the study failed to obtain the correlation between baseline D-dimer levels and stroke incidence. Furthermore, the study was not able to obtain the optimum cut off of the D-dimer value for stroke, which may be due to the small sample size and retrospective design of the study. Previously, various studies used D-dimer cutoff values of 0.5 to 1.0 mg/L for excluding pulmonary embolism and acute aortic dissection.^[32,33] On the basis of these findings, the cutoff value of the D-dimer level for the present study was set at 0.5 mg/L. Mahé I et al^[12] found that the incidence of coronary artery disease (CAD) significantly increase in patients with D-dimer levels ≥ 334 ng/mL. Nozawa et al^[34] considered that a D-dimer level of ≥ 150 ng/mL would be the optimal discriminating value for predicting subsequent thromboembolic

events in patients with NVAF. However, the patients in these 2 studies were treated with warfarin.

4.4. D-dimer and other biomarkers

Coagulative markers of prothrombin fragment 1+2, D-dimer, platelet factor 4 and β -thromboglobulin were determined upon enrollment in the prospective study conducted by Nozawa et al.^[34,35] These results revealed that only D-dimer levels in combination with clinical risk factors could effectively predict subsequent thromboembolic events in patients with NVAF, even when treated with warfarin.

Histological and clinical studies support the possible association between inflammation, AF and thrombosis.^[36] CRP is a biomarker of inflammation. In the SPAF III study, CRP was correlated with ischemic stroke risk factors, vascular events and total mortality.^[37] The study conducted by Ederhy et al^[38] was able to prove that CRP can help to exclude the presence of TEE thrombus, particularly in patients who were classified with low or moderate risk of ischemic stroke. CRP was also found to be correlated to fibrinogen and plasma viscosity.^[39,40] In the present study, D-dimer level were positively correlated with CRP, which indicates that D-dimer level are correlated with the thrombus.

4.5. Limitations

The main limitations for the present study are as follows: First, there was gender selection bias, but males with AF were more often admitted to our hospital than women, and most of the valvular diseases were found in female patients. Thus, we might be underpowered for the detection of relevant associations between the female gender and ischemic stroke/TEE.

Second, this is a single-center, retrospective study. All recruited subjects were in-patients, and some data from preadmission were not available. Furthermore, patients were combined with other diseases. Therefore, there was no obvious contrast, and selection bias was the major concern. Moreover, HT and DM were not risk factors for ischemic stroke, because most of the patients were complicated with diseases.

Finally and most importantly, the number of patients and events in the present study was small. Therefore, further larger-scale, multicenter studies are needed to confirm these findings.

5. Conclusion

D-dimer levels increase with age and have a positive correlation with stroke risk satisfaction, but cannot predict the occurrence of ischemic stroke in NVAF patients.

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