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Abstract

Background: Left atrial thrombus (LAT) often complicates with atrial fibrillation (AF). The evidence whether fibrin D-dimer levels could be used as a predictive biomarker for LAT is contradictory. This study firstly investigated the relationship between 'normal range' D-dimer and prevalent LAT. Second, we explored factors contributing to normal D-dimer levels in the presence of LAT. **Methods:** We studied 244 AF patients with LAT (mean age: 59.9 years, SD:11.7; 53.3% female): of these, 103 (42.2%) had normal D-dimer, 25 (10.2%) had atrial thrombus exclusion score (ATE score) of 0 19 (16.7%) males had CHA_2DS_2-VASc score of 0, 21(16.2%) females had CHA_2DS_2-VASc score of 1 and 16 had overlapped ATE score of 0 and CHA_2DS_2-VASc score of 0 (N = 8 if male) or CHA_2DS_2-VASc score of 1(N = 8 if female). Using multivariate binary analysis, larger left atrial diameter (LAD; adjusted OR: 1.06, 1.03−1.10, p = 0.001) were associated with increased D-dimer. Patients with high body mass index (BMI), hypertension history and previous anticoagulation were more likely to show normal range D-dimer levels in the presence of LAT. **Conclusions:** A high prevalence (42.2%) of 'normal range' D-dimer levels was found in AF patients with LAT, especially in those with hypertension, high BMI and prior anticoagulation. D-dimer levels of those patients with larger LAD were more likely to be increased.

Keywords

atrial fibrillation, left atrial thrombus, d-dimer, left atrial diameter

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Key Messages:

What is already known about this subject:

There are contradictory opinions on whether D-dimer could be considered as a biomarker for the existence of left atrial thrombus (LAT).

What this study adds:

A high prevalence (42.2%) of 'normal range' D-dimer levels was found in AF patients with LAT, especially in those with hypertension, high BMI and prior anticoagulation. D-dimer levels of those patients with larger LAD were more likely to be increased.

How might this impact clinical practice:

LAT is common in AF patients showing normal D-dimer. Larger LAD were associated with increased D-dimer while hypertension history, higher BMI and previous

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anticoagulation were associated with normal D-dimer with existing LAT.

Introduction

Atrial fibrillation (AF) is a common arrhythmia, leading to stroke and systemic embolism,[1, 2] with thromboembolism arising from the left atrial thrombus (LAT). Although transesophageal echocardiography (TEE) is often used to exclude LAT in patients scheduled for radiofrequency ablation,[3] they are sometimes impractical for urgent cardioversion. Therefore, an efficient biomarker is necessary for excluding LAT in AF patients. Unfortunately, no such biomarker is currently recommended for predicting the existence of LAT.

Some studies found normal fibrin D-dimer (an index of fibrin turnover and a biomarker of thrombogenesis[4]) to be useful for excluding LAT in AF patients,[5] which is contradictory to our clinical experience and another study.[6]

Therefore, understanding the possible factors associated with normal range of D-dimer in the existence of LAT would be clinically helpful. This study firstly investigated the relationship between 'normal range' D-dimer and prevalent LAT confirmed by TEE. Second, we explored factors contributing to normal D-dimer levels in the presence of LAT.

Methods

Patients' medical records with the diagnoses of AF and LAT between September 2008 and April 2021 were retrospectively reviewed to obtain detailed information on demographics, comorbidities and laboratory examinations. We included patients with both AF and LAT confirmed by TEE. Patients would be excluded if there was any of the following items: (i) No results of D-dimer and TEE test with the interval of less than 24 h could be obtained during the period of hospitalization; (ii) Contemporarily diagnosed with deep venous thrombosis (DVT) and/or pulmonary embolism (PE); and (iii) With stroke or systemic embolism related with LAT, and (iv) Patients with intra-atrial spontaneous echo-contrast or slow blood flow. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by clinical research ethics committee of our centers and individual consent for this retrospective analysis was waived.

TEE Tests

Instruct the patient to lie on his side facing the doctor, remove the foreign body in the patient's mouth, and give ECG and blood pressure monitoring. In the local anesthesia state, the dental pad is placed first, and the probe is gently delivered from the patient's dental pad to the posterior pharyngeal wall by holding the front 1/3 of the probe body. When the probe is placed in the middle of the esophagus, the depth of the ultrasound image is 14 cm, and the rotation Angle is 0°−10°, four heart chambers, namely left and right atria and left ventricles, can be seen. When the probe reached a depth of 32−40 cm, the left atrial appendage and pulmonary vein income of the patient were completely displayed by retreating to the back of the left atrium and adjusting the section angle. In the diagnosis of left atrial thrombosis, we focus on the presence of lumpy echo. [7]

D-Dimer Tests

Equivalent effectiveness of plasma D-dimer levels tested by different methods were proved by previous studies.[8] D-dimer values were classified into 'normal range' D-dimer (Group 1) and increased D-dimer group. The former was defined as D-dimer levels $\leq$ the ULRR while the increased D-dimer group was further divided into two groups: > ULRR but $\leq$ two times of the ULRR (Group 2), and > two times of the ULRR (Group 3). We also investigated the distribution of LAT in relation to the atrial thrombus exclusion (ATE) score[8] and CHA_2DS_2-VASc score.[9]

The atrial thrombus exclusion (ATE) score was defined as follows[8]: hypertension (1 point), heart failure (1point), history of stroke (1point) and D-Dimer level >270 ng/ml (1 point). The CHA_2DS_2-VASc score was defined as follows[9]: congestive heart failure (1 point), hypertension (1 point), age: 65–74 years (1 point), diabetes mellitus (1 point), previous transient ischemic attack(TIA) or stroke (2 points), peripheral artery disease (1 point), age: >75 years (2 points), female sex (1 point).

Statistical Analysis

Categorical variables in this study were expressed as numbers and percentages and compared with Chi-squared comparisons. Continuous variables were shown as mean ± standard deviation, SD. The stratification of D-dimer levels, ATE scores and CHA_2DS_2-VASc scores were reported for the whole included population and then according to sex subgroups. Odds ratios (OR) and 95% confidence intervals (CI) for possible risk factors (age, sex, body mass index [BMI, hypertension, diabetes mellitus [DM], stroke/transient ischemic attack [TIA] history, heart failure [HF], previous anticoagulation, LAD, left ventricular ejection fraction [LVEF], creatine level and hemoglobin) of different stratification of D-dimer levels were calculated with binary univariate and multivariate logistic regression, respectively. ROC curves with the largest Youden index were used to calculate the cut-off values of continuous variables. Variables categorized with cut-off value were then calculated by adjusted multivariate logistic regression analysis. Statistical analysis was performed using SPSS 24.0 software package (SPSS Inc).

Results

In the present analysis, 310 patients with AF and LAT were retrospectively reviewed. After excluding 66 patients with no

D-dimer test done within one day peri-examination period of TEE (N = 37) or with concurrent PE or DVT (N = 24) or stroke/systemic embolism (N = 5), 244 patients (mean age: 59.9 years, SD: 11.7; 53.3% female) were included in the final analysis. Patients with increased D-dimer levels (Group 2 and Group 3) were more likely to be female, have lower BMI, HF history, larger LAD, and lower hemoglobin; however, patients with normal range of D-dimer levels (Group 1) were more likely to have hypertension, DM history and higher baseline systolic blood pressure. Baseline characteristics are summarized in Table 1. In our study, a total of 57 patients took Warfarin, and 25 of them had "normal" D-dimer levels. Three were on dabigatran and six were on rivaroxaban, and all of them had "normal" D-dimer levels.

Distribution of D-Dimer Levels

There were altogether 103 (42.2%) patients in Group 1, 61(25.0%) in Group 2 and 80 (32.8%) in Group 3. The upper limit of the reference range (ULRR) of D-dimer of each method was 243 ng/ml for 186 patients (median: 279.00, interquartile range [IQR]: 479.00 ng/ml), 300ug/l for 4 patients (median: 187.50, IQR: 178.50 ng/ml), 1.5 mg/L for 25 patients (median: 1800.00, IQR: 4100.00 ng/ml) and 0.55 mg/L for 15 patients (median: 1490.00, IQR: 3550.00 ng/ml), respectively. Of these patients, 25 (10.2%) had ATE score of 0, 19 (16.7%) male AF patients had CHA_2DS_2-VASc score of 0 and 21(16.2%) female AF patients had CHA_2DS_2-VASc score of 1. 16 had overlapped ATE score of 0 and CHA_2DS_2-VASc score of 0 (N = 8 if male) or CHA_2DS_2-VASc score of 1(N = 8, if female) [Figure 1].

Males were more likely to have normal D-dimer levels compared with females (p = 0.01). The differences of the distribution of D-dimer, ATE score and CHA_2DS_2-VASc scores between male and female patients are shown in Figure 1.

Table 1. Baseline Characteristics of the Whole Study Population.

Variables	Normal D-dimer	Increased D-dimer	P value
Number	103	141	NA
Age	59.38 ± 10.89	60.44 ± 12.19	0.48
Female, N (%)	45 (43.69)	85 (60.28)	0.01
SBP, mm Hg	126.42 ± 17.44	126.38 ± 14.37	0.01
BMI, kg/m^2	25.10 ± 3.67	23.48 ± 3.42	0.001
Hypertension	49 (47.57)	30 (21.28)	<0.001
Diabetes mellitus	25 (24.27)	11 (7.80)	<0.001
Prior HF	50 (48.54)	87 (61.70)	0.05
Prior stroke/TIA	15 (14.56)	14 (9.92)	0.32
Malignant tumor	6 (5.83)	6 (4.26)	1.00
Previous anticoagulant	34 (33.01)	33 (23.40)	0.11
Creatinine	86.39 ± 95.35	87.12 ± 96.07	0.95
Hemoglobin, g/L	141.06 ± 20.33	133.47 ± 20.76	0.005
LAD, mm	46.90 ± 9.37	52.68 ± 11.04	<0.001
LVEF, %	56.20 ± 11.25	56.05 ± 10.05	0.92

N, number; BMI, body mass index; HF, heart failure; TIA, transient ischemic attack; LAD, left atrial diameter; LVEF, left ventricular ejection fraction

Factors Associated with Increased D-Dimer Levels

Using multivariate binary analysis, larger left atrial diameter (adjusted OR: 1.06, 1.03−1.10, p = 0.001) was associated with increased D-dimer. Patients with high body mass index (BMI), hypertension history and previous anticoagulation were more likely to show normal range D-dimer levels in the presence of LAT (Table 2). A cut-off value of 51.2 mm of LAD was found using ROC curves with sensitivity of 48.9% and specificity of 77.3%. In order to increase the clinical application, we used categorical variables of LAD of 51.2 mm by ROC curve with biggest Youden value and 3 times of higher risk of increased D-dimer was seen in those with LAD 51.2 mm than those with LAD <51.2 mm (OR:3.25, 95% CI:1.66−6.37, p < 0.001). The cut-off values for other continuous variables of age, BMI, creatinine, hemoglobin, LVEF were 77.5 years, 15.82 kg/m^2, 60.85 umol/L, 68.5 g/L, 43.5%, respectively.

Discussion

In the current analysis, a high prevalence (42.2%) of 'normal range' D-dimer was found in AF patients with LAT, especially in those with hypertension, high BMI and prior anticoagulation. D-dimer levels of those patients with larger left atrial diameter (LAD) were more likely to be increased.

Left atrial thrombus is an occult complication of AF,[10] which was often undetected before the development of ischemic stroke or systemic embolism. Although TEE is probably the most effective and applicable method for detecting atrial thrombi, it could only be performed by specially trained professionals and may be inconvenient in the setting of urgent cardioversion.

D-dimer has been proposed as a potential biomarker based on the finding that increased D-dimer levels were more likely to be seen in AF patients with atrial thrombi,[11] but no consistent cut-off point could be achieved due to the heterogeneity of cut-off points in different studies.[8, 12–14] The possibility of missed diagnosis could not be neglected, given the high prevalence (42.2%) of AF patients with LAT with normal D-dimer levels in this study. A similar concern was raised by Bejinariu et al,[6] whereby D-dimer failed to predict the thrombus formation in the left atrium. One possible reason was that D-dimer serves as an indirect marker of thrombotic activity, but the thrombi was usually in a stagnant state with a LAT. Also, a peripheral venous measurement of D-dimer levels may reflect systemic circumstances, rather than pathology within the left atrium (ie the presence of a LAT).

Previous studies have shown the equivalent effectiveness of different plasma D-dimer testing methods.[8, 15] Therefore, we used the D-dimer value as a continuous variable with 270ng/ml as the recommended cut-off point according to the ATE score and found that 25 of the included AF patients had LAT

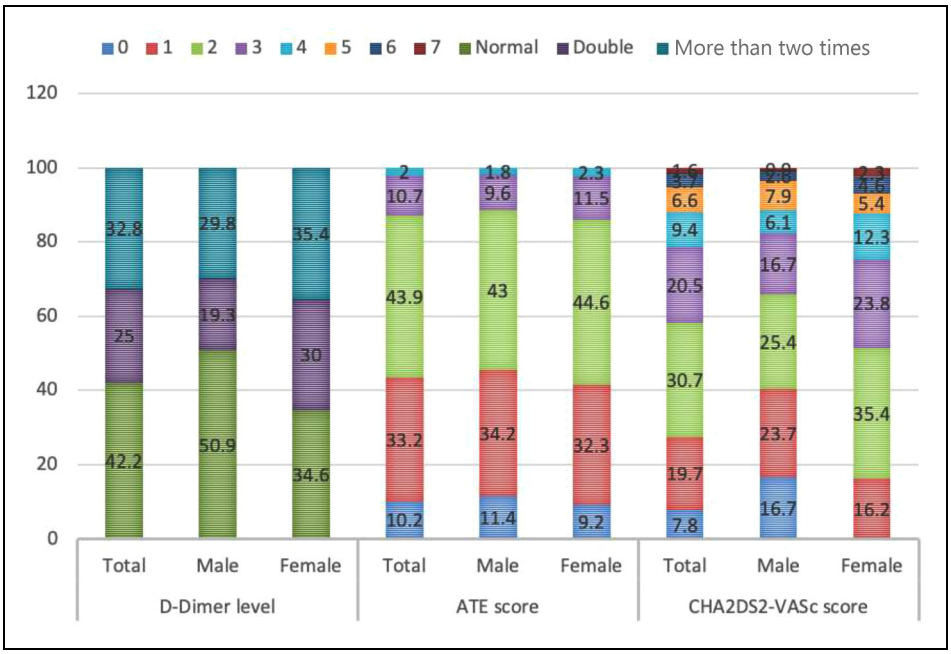

Figure 1. Distribution of D-dimer levels, ATE scores and CHA2DS2-VASc scores.
ATE, Atrial thrombus exclusion; ATE score: hypertension (1 point), heart failure (1point), history of stroke (1point) and D-Dimer level >270 ng/ml (1 point).
CHA_2DS_2VASc score: congestive heart failure (1 point), hypertension (1 point), age: 65–74 years (1 point), diabetes mellitus (1 point), previous TIA or stroke (2 points), peripheral artery disease (1 point), age: >75 years (2 points), female (1 point).

Table 2. Factors Associated with Increased D-Dimer.

	Unadjusted		Adjusted	
Factors	OR (95% CI)	p value	OR (95% CI)	p value
Age	1.01 (0.99 – 1.03)	0.48	1.03 (1.00 – 1.06)	0.05
Female	1.96 (1.17 – 3.28)	0.01	1.11 (0.57 – 2.18)	0.76
BMI	0.88 (0.81 – 0.95)	0.001	0.89 (0.80 – 0.98)	0.02
Hypertension history	0.30 (0.17 – 0.52)	<0.001	0.43 (0.19 – 0.97)	0.04
DM history	0.26 (0.12 – 0.57)	0.001	0.47 (0.18 – 1.21)	0.12
HF history	1.71 (1.02 – 2.86)	0.04	1.15 (0.61 – 2.18)	0.66
Previous stroke/TIA	0.65 (0.30 – 1.41)	0.27	0.67 (0.21 – 2.11)	0.50
Previous anticoagulation	0.62 (0.35 – 1.09)	0.10	0.47 (0.24 – 0.97)	0.04
Creatinine	1.00 (0.997 – 1.003)	0.95	1.002 (0.999 – 1.005)	0.26
Hemoglobin	0.98 (0.97 – 1.00)	0006	0.99 (0.98 – 1.01)	0.52
LAD	1.06 (1.03 – 1.09)	<0.001	1.06 (1.03 – 1.10)	0.001
LVEF	1.00 (0.97 – 1.02)	0.92	0.99 (0.96 – 1.03)	0.67

DM, diabetes mellitus HF, heart failure; TIA, transient ischemic attack; LAD, left atrial diameter; LVEF, left ventricular ejection fraction

even if their ATE score was 0. Similarly, CHA_2DS_2-VASc score has been associated with intra-atrial thrombus in previous studies.[16, 17] Among the participants of our study with LAT confirmed by TEE, 19 male had CHA_2DS_2-VASc score of 0 and 21 female had CHA_2DS_2-VASc score of 1. The use of oral anticoagulant drugs before D-dimer measurements increased the potential of normal range D-dimer levels in AF patients with LAT according to our results and previous paper.[18, 19]

Larger left atrial diameter was associated with increased D-dimer in AF patients with LAT in our study, which may be explained by D-dimer being a biomarker of degenerated fibrinogen during active thrombus formation,[20] which was more likely to be present and active in larger atria as shown in previous studies. [16, 21] We found that the larger LAD was associated with increased D-dimer. The probability of increased D-dimer was 1.06 times every 1 mm increase in LAD. In order to raise the clinical application, we used categorical variables of LAD of 51.2 mm by ROC curve with biggest Youden index and 3 times of higher risk of increased D-dimer was seen in those with LAD ≥51.2 mm than those with LAD <51.2 mm (OR:3.25,95% CI:1.66–6.37, $p < 0.001$). We obtained a P value of 0.05 for the variable of age, which is the boundary P value with an OR

value of 1.03 (1.00−1.06), so we did not count age as a strong predictor. Hypertension history and anticoagulation were factors associated with normal D-Dimer, as novel insights from our analysis. Of note, hypertension history showed a positive correlation with normal D-dimer and higher baseline systolic blood pressures in the Group 1 further supports this association. Despite the preventive effect of oral anticoagulation on the LAT, D-dimer was usually normal even if residual LAT remains after anticoagulation. Physicians should be encouraged to focus on possible existence of LAT in these patients as well as in those with hypertension history, higher BMI and previous anticoagulation even if patients had a normal range of D-dimer.

Limitations

There are several limitations in our study. First, this is a retrospective analysis collecting data from tertiary hospitals. Second, there is a selection bias of patients who received TEE examinations. These patients were usually scheduled for radiofrequency ablation and generally had fewer comorbidities and lower risks of LAT. Third, all the patients we included had TEE and LAT. However, because PE/DVT or stroke/systemic embolism could increase the D-dimer level,[22, 23] therefore, the stability of this study increased by excluding these conditions and then the probability of increase D-dimer caused by these diseases decreased to the utmost. Fourth, LAD was used as a more convenient measurement in the current analysis rather than left atrial size or left atrial volume, as LAD was more popular than other parameters in clinical practice. Fifth, our population were indeed heterogeneous, because the population we included had many underlying diseases, but all of them had AF and LAT which is the homogeneity in choosing them. Sixth, since TEE may not be appropriate for all patients with LAT in certain emergency situations, it was of great importance to find a biomarker. Unfortunately, although D-dimer is sometimes considered the most promising biomarker, 42.2% of the AF patients with LAT had normal D-dimer, which suggested a high possibility of misdiagnosis. Therefore, this study was performed to remind the clinicians that D-dimer might be normal in AF patients with hypertension, increased BMI, and previous anticoagulation, despite the existence of LAT. Actually, a more efficient and convenient biomarker is necessary for emergent screening of LAT, which needs further exploration.

Conclusions

A high prevalence (42.2%) of 'normal range' D-dimer levels was found in AF patients with LAT, especially in those with hypertension, increased BMI, and previous anticoagulation. D-dimer levels of those patients with larger LAD were more likely to be increased.

Abbreviations

LAT	Left atrial thrombus
AF	Atrial fibrillation
TEE	Transesophageal echocardiography
ATE	atrial thrombus exclusion
DVT	deep venous thrombosis
PE	pulmonary embolism
ULRR	upper limit of the reference range
OR	Odds ratios
CI	confidence intervals
BMI	body mass index
DM	diabetes mellitus
TIA	transient ischemic attack
HF	heart failure
LAD	left atrial diameter
LVEF	left ventricular ejection fraction

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Availability of Data and Material

Data and material could be provided when necessary.

Competing Interests:

The authors report no relationships that could be construed as a conflict of interest.

Consent for Publication

Yes.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethics Approval and Consent to Participate

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by clinical research ethics committee of our centers and individual consent for this retrospective analysis was waived.

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