

Risk factors of thromboembolism in nonvalvular atrial fibrillation patients with low CHA₂DS₂-VASc score

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Abstract

The risk of thromboembolism in patients with CHA₂DS₂-VASc score of 0 to 1 was low, and the anticoagulant therapy was not recommended. Although the CHA₂DS₂-VASc score was low, there were still many patients suffered from thrombotic events and stroke. We aim to investigate the risk factors of thrombotic events in nonvalvular atrial fibrillation (NVAF) patients with low CHA₂DS₂-VASc score.

We retrospectively enrolled 595 consecutive NVAF patients with low CHA₂DS₂-VASc score (male: CHA₂DS₂-VASc = 0, female: CHA₂DS₂-VASc = 1). The general clinical data, blood biochemical data, and echocardiography results of the 595 patients were collected. Multivariate logistic regression models were used to evaluate risk factors of thrombosis. Receiver operating characteristic curve was used to identify the optimal cut-off value of the independent risk factors. A *P* value of <.05 (2-sided) was considered to be statistically significant.

In multivariate analysis, lipoprotein (a) (Lp(a)) plasma level and left atrium diameter (LAD) were positively related to thromboembolism in NVAF patients with CHA₂DS₂-VASc score of 0 to 1 after adjustment for age, gender, and other variables (odds ratio [OR] = 1.02, 95% confidence interval [CI]: 1.01–1.03; OR = 1.13, 95% CI: 1.06–1.18). Lp(a) exerted a significant predictive value with area under the curve (AUC) of 0.62 (95% CI: 0.55–0.68, *P* < .01). The optimal cut-off value for Lp(a) predicting thrombotic events was 27.2 mg/dL (sensitivity 45.7%, specificity 73.4%). LAD showed a significant predictive value with AUC of 0.71 (95% CI: 0.64–0.78, *P* < .01). The optimal cut-off point for LAD predicting thrombotic events was 43.5 mm (sensitivity 47.1%, specificity 85.8%).

High Lp(a) plasma level and left atrial dilatation might be independent risk factors of thrombotic events for NVAF patients with low CHA₂DS₂-VASc score.

Abbreviations: AF = atrial fibrillation, AUC = area under the curve, CI = confidence interval, CT = computed tomography, LAD = left atrium diameter, LDL = low-density lipoprotein, Lp(a) = lipoprotein (a), MRI = magnetic resonance imaging, NVAF = nonvalvular atrial fibrillation, OR = odds ratio, ROC = receiver operating characteristic.

Keywords: CHA₂DS₂-VASc score, nonvalvular atrial fibrillation, thromboembolism

1. Introduction

Atrial fibrillation (AF), the most common sustained cardiac arrhythmia in clinical practice, can result in a series of adverse

outcomes. Thromboembolism is one of the most serious complications to increase mortality and disability in AF patients. Nonvalvular atrial fibrillation (NVAF) increases the risk of ischemic stroke by 5.6 times.^[1] Guidelines for the management of patients with AF had recommended that assessment of thrombotic risk in patients with NVAF should be based on the CHA₂DS₂-VASc scoring system.^[2] According to the guidelines, NVAF patients with CHA₂DS₂-VASc score of 0 to 1, defined as low thrombotic risk, were not necessary to take antithrombotic therapy.

Although low CHA₂DS₂-VASc score indicated low risk of thrombosis, there were still patients suffering from thromboembolism. A large-scale cohort study in Danish showed that the annual risk of ischemic stroke was 0.64% for NVAF patients with a CHA₂DS₂-VASc score of 0 in the absence of anticoagulants.^[3] Even in some studies, the annual incidence of stroke in Asia's AF population with CHA₂DS₂-VASc score of 0 was significantly higher than in the West.^[4,5] In recent years, some studies found that the CHA₂DS₂-VASc scoring system was not comprehensive prediction for thrombotic risk in NVAF patients, there were still other clinical factors associated with the risk of thrombotic events.^[6,7] In a cohort study of 15,806 patients with AF in Taiwan, the age threshold was reset. It was suggested that age younger than 50 years was a true low risk.^[8] Therefore, retrospective analysis of 595 NVAF patients' clinical

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data were made to identify the potential risk factors for thrombotic events in NVAF patients with CHA₂DS₂-VASc score of 0 to 1, and to help guiding clinical practice. The innovation of this study was to limit the NVAF population with CHA₂DS₂-VASc score of 0 to 1, which further purified the clinical factors.

2. Methods

2.1. Study population

The study received approval from the Medical Ethics Committee of the Second Affiliated Hospital of Nanchang University. And the informed consent was waived because of the retrospective nature of this study.

We retrospectively screened consecutive NVAF patients who were admitted to the Second Affiliated Hospital of Nanchang University between January 1, 2009 and December 31, 2016. Then we graded them with CHA₂DS₂-VASc system. Considering the CHA₂DS₂-VASc score and first-onset thromboembolism, we divided the study population into thrombotic events group and control group. Enrolled patients had no long-term medication history before admission. The control group included the NVAF patients with CHA₂DS₂-VASc score of 0 to 1 (male: CHA₂DS₂-VASc=0, female: CHA₂DS₂-VASc=1). While the NVAF patients with previous CHA₂DS₂-VASc score of 0 to 1 hospitalized for first-onset thromboembolism, were enrolled in thrombotic events group. All selected patients were older than 18. Those who met one of the following conditions were excluded: diagnosed with Structural Heart Disease, thyroid disorder, kidney failure, chronic obstructive pulmonary disease; CHA₂DS₂-VASc score ≥ 1 in male, CHA₂DS₂-VASc score ≥ 2 in female; and with incomplete data.

2.2. Assessment of thrombotic events

The diagnosis of acute ischemic stroke was based on the diagnostic criteria developed by the American Heart Association and the American Stroke Association: acute onset, focal neurological deficit (one side of the face or limb weakness or numbness, language disorders, and other symptoms), a few were neurological deficits, there were responsible ischemic lesions in head recorded by computed tomography (CT) or magnetic resonance imaging (MRI), vascular causes were excluded, and cerebral hemorrhage was excluded by CT or MRI.^[9]

Peripheral arterial embolism includes limb arterial embolism, mesenteric artery embolization, renal artery embolization, and splenic artery embolization. The diagnostic criteria of peripheral arterial embolism are based on "Guidelines for the diagnosis and treatment of peripheral arterial disease"^[10] and could be proved by CT angiography or magnetic resonance angiography. Left atrial thrombus was diagnosed by transesophageal echocardiography and/or left atrial CT imaging.

2.3. Data collection

Subjects' general clinical data including gender, age, history of hyperlipidemia, history of smoking, history of drinking, systolic blood pressure, diastolic blood pressure, heart rate, and urinary protein positive rate on admission. Subjects' echocardiographic data and laboratory test results on empty stomach at the second day of admission were collected.

2.4. Statistical analysis

Statistical analysis was performed using Empower stats and SPSS version 19.0. The baseline data were described as mean \pm standard deviation ($\bar{x} \pm s$) for continuous variables and as percentages for categorical variables. Continuous variables were compared using the Student *t* test and categorical variables were compared using chi-squared test. Multivariate logistic regression models were used to evaluate risk factors of thrombosis. The receiver operating characteristic (ROC) curve was used to evaluate the ability of related risk factors to predict thromboembolism and to identify the optimal cut-off value, and the area under the curve (AUC) was used to determine the predictive value. A *P* value of $<.05$ (2-sided) was considered statistically significant in all analyses.

3. Results

3.1. Baseline characteristics

A total of 595 participants with an average age of 55.1 years (standard deviation, 8.5 years) were enrolled. There were 68 NVAF patients included in the thrombotic events group, with previous CHA₂DS₂-VASc score of 0 to 1 hospitalized for first-onset thromboembolism. And there were 527 NVAF patients with CHA₂DS₂-VASc score of 0 to 1 in the control group. The incidence of thrombotic events was 11.4%, including 51 males and 17 females. Of the participants in nonthrombotic events group, 68.9% were male. There were no patients with congestive heart failure, hypertension, age ≥ 65 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease.

In the thrombotic events group, there were 49 cases of acute cerebral ischemic stroke, lower limb artery embolization in 3 cases, renal artery embolization in 3 cases, 3 cases of splenic artery embolism (including renal artery combined splenic artery embolization in 1 case), mesenteric artery embolism in 1 case, and 10 cases of left atrial thrombus.

The comparisons of the baseline characteristics in the thrombosis group with control group are shown in Table 1. Compared with control group, the alcohol use rate (20, 29.4% vs. 99, 18.8%, *P*=.039), lipoprotein (a) (Lp(a)) plasma level (29.3 ± 24.5 mg/dL vs. 19.7 ± 18.7 mg/dL, *P*<.001), and left atrium diameter (LAD) (42.4 ± 9.1 mm vs. 36.8 ± 6.1 mm, *P*<.001) were significantly higher in the thrombotic event group. However, the LVEF ($59.3 \pm 5.8\%$ vs. $61.5 \pm 6.6\%$, *P*=.008) were obviously lower than in control group. Meanwhile, there was no significant difference in systolic blood pressure, heart rate, history of hyperlipidemia, history of smoking, FPG, plasma TG level, TC level, Cre level, left ventricular end-diastolic diameter, and other parameters in the 2 groups (Table 1).

3.2. Risk factors of thrombotic events in NVAF patients

To investigate the risk factors of thrombotic events in NVAF patients with CHA₂DS₂-VASc score of 0 to 1, multivariate regression analysis was used to evaluate the effects of the related factors on thrombosis. The results showed that the odds of Lp(a) plasma level and LAD were positively related to thrombosis, and these relationships remained statistically significant after adjustment for age, gender, and various other baseline parameters (Table 2). They were independent predictors of thrombotic events after adjusting for other covariables. The parameters not significantly associated with thrombotic events were not listed.

Table 1
Comparison of baseline characteristics in control group with thrombosis group.

	Total (n=595)	Control group (n=527)	Thrombosis group (n=68)	P
Male, n (%)	414 (69.6)	363 (68.9)	51 (75.0)	.302
Age, y	55.1±8.5	55.1±8.6	55.5±7.8	.705
BMI, kg/m ²	22.6±3.2	22.7±3.2	21.8±3.3	.52
Hyperlipidemia, n (%)	40 (6.7)	37 (7.0)	3 (4.4)	.419
Gout, n (%)	96 (16.1)	82 (15.6)	14 (20.6)	.38
Smoke, n (%)	188 (31.6)	163 (30.9)	25 (36.8)	.330
Alcohol intake, n (%)	119 (20)	99 (18.8)	20 (29.4)	.039
SBP, mm Hg	118.3±13.8	118.1±13.7	120.4±14.9	.143
DBP, mm Hg	73.4±9.7	73.2±9.7	75.4±9.8	.075
HR, bpm	80.9±18.2	80.6±18.2	83.5±18.0	.211
FPG, mmol/L	5.1±0.4	5.1±0.4	5.2±0.4	.143
TG, mmol/L	1.4±0.8	1.4±0.8	1.2±0.6	.160
TC, mmol/L	4.1±1.0	4.1±1.0	4.1±1.0	.496
HDL, mmol/L	1.0±0.3	1.0±0.3	1.0±0.2	.726
LDL, mmol/L	2.4±0.8	2.4±0.8	2.4±0.9	.797
Lp(a), mg/dL	20.8±19.7	19.7±18.7	29.3±24.5	<.001
BNP, pg/mL	88.0±15.1	88.0±15.1	88.2±15.1	.893
CRP, mg/L	6.3±5.3	6.2±5.1	7.2±6.2	.179
ESR, mm/h	14.6±10.7	14.4±10.8	15.9±10.5	.291
Cre, μmol/L	80.9±33.9	80.6±33.8	82.9±34.8	.610
eGFR, U/L	88.3±28.9	88.2±27.7	89.2±35.6	.785
PUP, n (%)	103 (17.3)	86 (16.3)	17 (25.0)	.075
UA, μmol/L	373.3±148.2	373.3±148.7	373.3±145.3	1.000
ALB, g/L	38.4±3.9	38.4±3.9	38.0±3.9	.421
AST, U/L	30.9±18.3	30.9±18.7	30.9±15.9	.995
ALT, U/L	24.7±16.5	24.8±16.9	23.7±13.2	.603
LAD, mm	37.4±6.7	36.8±6.1	42.4±9.1	<.001
RAD, mm	42.1±9.4	42.0±9.3	43.3±10.3	.269
LVEDD, mm	50.1±8.4	49.9±8.4	51.3±8.6	.202
LVEF, %	61.2±6.5	61.5±6.6	59.3±5.8	.008

ALB = albumin, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, BNP = brain natriuretic peptide, Cre = creatinine, CRP = c-reactive protein, DBP = diastolic blood pressure, eGFR = estimated glomerular filtration rate, ESR = erythrocyte sedimentation rate, FPG = fasting plasma glucose, HDL = high-density lipoprotein, HR = heart rate, LAD = left atrium diameter, LDL = low-density lipoprotein, Lp(a) = lipoprotein (a), LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, PUP = positive urinary protein, RAD = right atrium diameter, SBP = systolic blood pressure, TC = total cholesterol, TG = triglyceride, UA = uric acid.

3.2.1. Multivariate logistic analysis of thrombotic events with plasma Lp(a). Table 2 shows the effect of plasma Lp(a) level on thrombosis in the multivariate regression analysis. Continuous plasma Lp(a) level was positively associated with thrombosis (odds ratio [OR]=1.02, 95% confidence interval [CI]: 1.01–

1.03). The incidence of thrombotic events was significantly higher in highest Lp(a) quartile than the lowest quartile. Compared with the lowest quartile (3.6±2.6 mg/dL), subjects in highest Lp(a) quartile (48.2±19.3 mg/dL) had a higher risk of thrombotic events (OR=2.48, 95% CI: 1.18–5.22) after adjusting for other

Table 2
Multivariate logistic analysis of thrombotic events with plasma Lp(a) level and LAD.

	Mean ± SD	Events (%)	Crude		Mode I		Mode II	
			OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Lp(a), mg/dL								
Continuous quartiles	20.8±19.7	68 (11.4%)	1.02 (1.01, 1.03)	<.001	1.02 (1.01, 1.03)	<.001	1.02 (1.01, 1.03)	.005
Quartile 1	3.6±2.6	12 (17.6%)	ref		ref		ref	
Quartile 2	10.7±2.0	13 (19.1%)	1.10 (0.48, 2.50)	.821	1.12 (0.49, 2.55)	.789	1.14 (0.49, 2.62)	.764
Quartile 3	20.5±4.4	16 (23.5%)	1.37 (0.63, 3.01)	.429	1.38 (0.63, 3.04)	.422	1.40 (0.63, 3.12)	.408
Quartile 4	48.2±19.3	27 (39.7%)	2.53 (1.23, 5.20)	.012	2.55 (1.23, 5.30)	.012	2.48 (1.18, 5.22)	.017
LAD, mm								
Continuous quartiles	37.4±6.7	68 (11.4%)	1.13 (1.09, 1.18)	<.001	1.13 (1.09, 1.18)	<.001	1.13 (1.09, 1.18)	<.001
Quartile 1	29.2±2.5	5 (7.4%)	ref		ref		ref	
Quartile 2	34.2±1.4	15 (22.1%)	2.38 (0.84, 6.72)	.103	2.39 (0.84, 6.76)	.049	2.45 (0.86, 6.97)	.094
Quartile 3	38.8±1.4	14 (20.6%)	2.38 (0.83, 6.79)	.106	2.36 (0.82, 6.74)	.110	2.56 (0.89, 7.40)	.083
Quartile 4	46.1±4.4	34 (50.0%)	6.63 (2.51, 17.53)	<.001	6.61 (2.49, 17.51)	<.001	6.64 (2.48, 17.77)	.003

Mode I adjust for gender and age. Mode II adjust for gender, age, hyperlipidemia, smoke, alcohol use, fasting plasma glucose, total cholesterol, triglyceride, low-density lipoprotein, and left ventricular ejection fraction.

CI = confidence interval, LAD = left atrium diameter, Lp(a) = lipoprotein (a), OR = odds ratio, SD = standard deviation.

Table 3**The diagnostic efficacy of Lp(a) cut-off value and LAD cut-off value.**

	Lp(a) cut-off value	LAD cut-off value
Sensitivity	45.7%	47.1%
Specificity	73.4%	85.8%
Positive predictive value	23.1%	41.0%
Negative predictive value	88.6%	88.6%
Positive likelihood ratio	1.718	3.32
Negative likelihood ratio	0.74	0.62
AUC (95% CI)	0.62 (0.55–0.68)	0.71 (0.64–0.78)
Diagnostic odds ratio	2.32	5.38
Youden index	0.19	0.33

AUC=area under the receiver operating characteristic curve, CI=confidence interval, LAD=left atrium diameter, Lp(a)=lipoprotein (a).

covariables. There was no significant difference in thrombotic risk among the other 3 quartiles.

3.2.2. Multivariate logistic analysis of thrombotic events with LAD.

The effect of LAD on thrombosis in the multivariate regression analysis is shown in Table 2. Both continuous and categorical LAD were significantly associated with thrombotic events. Continuous LAD was positively associated with thrombotic events (OR = 1.13, 95% CI: 1.09–1.18). Thrombotic risk was significantly higher in highest LAD quartile (46.1 ± 4.4 mm) compared with the lowest quartile (29.2 ± 2.5 mm) after adjusting for age, gender, and various other parameters (OR = 6.64, 95% CI: 2.48–17.77). Subjects in the second LAD quartile and third LAD quartile did not have significant different incidences compared with the lowest quartile (Table 2).

3.3. Lp(a) and LAD in predicting thrombotic events

Multivariable logistic regression analysis showed that hyper-Lp(a) and left atrial dilatation were thrombotic risk factors for NVAF patients with CHA₂DS₂-VASc score of 0 to 1. Compared with the lowest quartile, subjects in highest Lp(a) and LAD quartile had a higher risk of thrombotic events after adjusting for other covariables. To identify the optimal cut-off value, we used ROC curve to evaluate the ability of Lp(a) and LAD to predict thromboembolism.

On the basis of ROC curve analysis in Fig. 1, Lp(a) exerted a significant predictive value with AUC of 0.62 (95% CI: 0.55–0.68, $P < .01$). And the optimal cut-off value for Lp(a) predicting thrombotic events was 27.2 mg/dL, with a sensitivity of 45.7% and a specificity of 73.4%. The incidence of thrombosis in patients with Lp(a) \geq 27.2 mg/dL was 18.50%, which was significantly higher than the 8.7% in Lp(a) $<$ 27.2 mg/dL patients. The diagnostic efficacy of Lp(a) cut-off value was shown in Table 3, including sensitivity, specificity, positive and negative predictive value, positive and negative likelihood ratio, area under the ROC curve, diagnostic OR, and Youden index.

According to the ROC curve analysis in Fig. 2, LAD showed a significant predictive value with AUC of 0.71 (95% CI: 0.64–0.78, $P < .01$). And the optimal cut-off value for LAD predicting thrombotic events was 43.5 mm, with a sensitivity of 47.1% and a specificity of 85.8%. The incidence of thrombosis in patients with LAD \geq 43.5 mm was 29.9%, which was significantly higher than 7.4% in patients with LAD $<$ 43.5 mm. The diagnostic efficacy of LAD cut-off value was shown in Table 3.

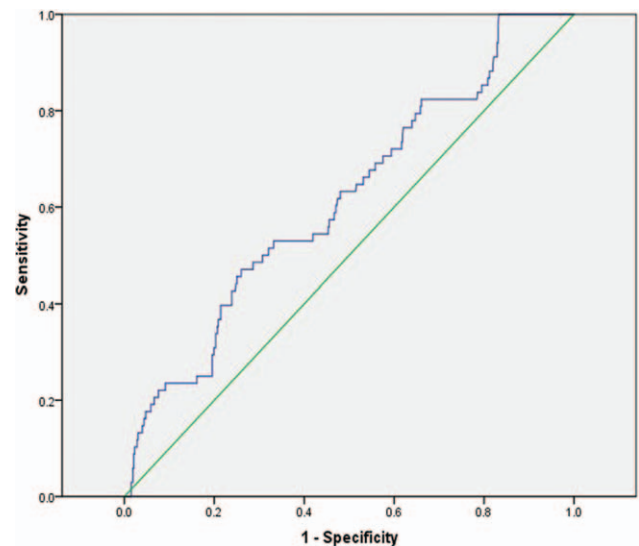


Figure 1. Receiver operating characteristic working curve of lipoprotein (a).

4. Discussion

AF is the most frequent cardiac arrhythmia in clinical practice. It occurs when a diffuse and chaotic pattern of electrical activity in the atria replaces the normal sinus rhythm.^[11,12] In a broad clinical context, NVAF is associated with consequent diastolic dysfunction and heart failure secondary to hypertension, coronary artery disease, myocarditis, aging, obesity, and diabetes mellitus.^[13–16] As the incidence of NVAF is increasing year by year,^[13,17] embolism complications is becoming a growing burden for healthcare systems. It was suggested that NVAF patient with a CHA₂DS₂-VASc score of 0 to 1 has a “real low risk” of thromboembolism. It was not necessary to take anticoagulant therapy for NVAF patient with a score of 0 to 1.^[2] However, the present study found that the incidence of thrombotic events was 11.4% in NVAF patients with CHA₂DS₂-VASc score of 0 to 1. It indicated that there was still a high

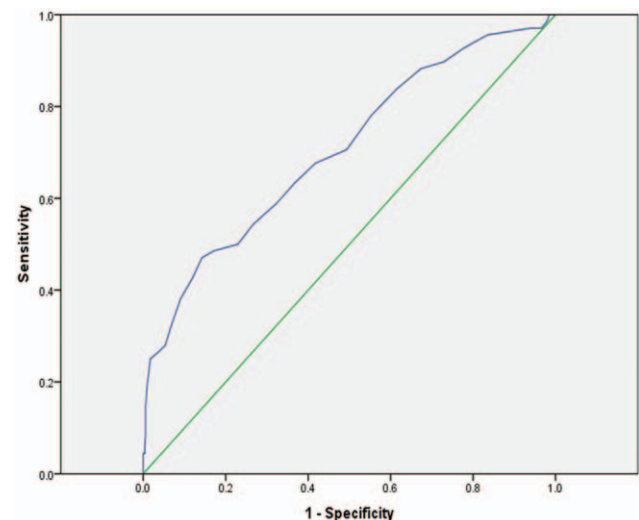


Figure 2. Receiver operating characteristic working curve of left atrial diameter.

incidence of thrombotic events in NVAF patients with CHA₂DS₂-VASc score of 0 to 1, who were considered as low risk of thrombosis in clinical. Therefore, the further research on the risk factors of NVAF has a great clinical significance. We found that Lp(a) plasma level and LAD were positively related to thrombosis in NVAF patients with CHA₂DS₂-VASc score of 0 to 1 after adjustment for age, gender, and other parameters.

4.1. Association between Lp(a) level and thrombotic events

Lp(a) is a special form of low-density lipoprotein (LDL), composed of apoB in LDL-like particle and apolipoprotein (a) (apo[a]), connected by a single disulfide bond. Lp(a) possesses structural homology with plasminogen.^[18] Epidemiological surveys showed that Lp(a) was closely related to cardiovascular disease. Lp(a) was also considered to be an independent risk factor for coronary heart disease.^[19] As early as 1987, Jurgens and Koltringer^[20] found that the Lp(a) was significantly different between patients with ischemic cerebrovascular disease and the healthy control group. Then, many studies found that Lp(a) was a risk factor for ischemic stroke.^[21,22] In 2017, Lange et al^[23] found that ischemic stroke patients with elevated Lp(a) had a higher risk of recurrence of vascular events in adult population. However, some studies still suggested that Lp(a) was meaningless in predicting ischemic stroke risk.^[24-26] Even some large prospective studies had shown that elevated Lp(a) forecast stroke risk in men only.^[27,28] Lp(a) is still controversial in predicting stroke, and the conclusions of each study are dissimilar.

Due to the structural homology, Lp(a) could compete with plasminogen on the fibrin binding sites, inhibit plasminogen activity, and reduce the vitality of the fibrinolysis system after thrombosis, which eventually weakened the fibrinolysis. Besides, Lp(a) could promote the secretion of plasminogen activator inhibitor-1 in vascular endothelial cells and hepatocytes, which caused plasma fibrinolysis and coagulation system imbalance. These could make the coagulation function prevail and promote thrombosis.^[29,30] Furthermore, Lp(a) could bind heparin and heparan sulfate, which closed the substrate, causing its inhibition of thrombosis inactivation.^[31] It suggested that elevated Lp(a) could facilitate coagulation-fibrinolytic system during thrombosis.

To define the relationship between Lp(a) and thrombotic events in the NVAF patients, we first screened the NVAF patients with low CHA₂DS₂-VASc score, and targeted the risk factors outside the CHA₂DS₂-VASc score range. The results showed that elevated Lp(a) was an independent risk factor for thrombotic events in NVAF patients with CHA₂DS₂-VASc score of 0 to 1. Patients in the fourth quartile of the Lp(a) distribution had an increased risk for thromboembolism compared with patients in the first 3 quartiles of the Hcy distribution.

4.2. Association between LAD and thrombotic events

Researches had proved that LAD enlargement was a risk factor for AF occurrence, recurrence, and even death events.^[32] However, it was controversial whether LAD increasing thrombotic risk in AF patients. Some studies suggested that LAD enlargement had no significant association with thromboembolism in AF patients.^[33,34] In the subgroup of the AFFIRM study,^[19] researchers did not think LAD was a risk factor for embolism in AF patients. It could be explained by the reason that

the study population excluded patients who had increased LAD and part of patients had oral anticoagulants. Recently, Hamatani et al^[35] found that AF patients with the LAD > 45 mm had a higher stroke rate in the AF study. The experiment suggested that the enlargement of LAD was a risk factor for the embolism in AF patients. But the LAD expansion group was significantly higher than the control group in the age, course of AF, the proportion of nonparoxysmal AF, CHA₂DS₂-VASc score, and the use of oral anticoagulants, which were the defects of AF study. Therefore, its conclusions are restricted. It still needs to be confirmed that whether stroke risk is achieved by LAD expansion.

The present study screened the NVAF patients with CHA₂DS₂-VASc score of 0 to 1, which controlled the risk factors in CHA₂DS₂-VASc scoring system. Importantly, our study confirmed that LAD enlargement was an independent risk factor for thrombotic events in NVAF patients with low CHA₂DS₂-VASc score. Thrombotic risk was significantly higher in highest LAD quartile (46.1 ± 4.4 mm) compared with the lowest quartile (29.2 ± 2.4 mm) after adjusting for age, gender, and various other parameters. It implied that left atrium dilatation could increase thrombotic risk in NVAF patients, which might be associated with hemodynamic disorders, decreased blood flow velocity in left atrial appendage, decline of left ventricular compliance, dysfunction of vascular endothelial and excessive activation of coagulation system.^[36,37] On the other hand, left atrium dilatation increased the eddy currents caused by left atrium's irregular contraction in AF patients, which would damage the atrial intima and then cause wall thrombosis.^[38]

4.3. Limitations of the study

The study was a retrospective single center analysis. There was controversy over the fact that whether above variables were causes or consequences. Most of the selected cases were the serious patients in clinical disease spectrum, so there was a certain choice bias. Moreover, there were still some shortages such as racial specificity of Lp(a) plasma concentration and the small sample size.

4.4. Future directions

In the future, we need prospective multicenter cohort studies for comprehensive analysis to identify the potential risk factors for thrombotic events in NVAF patients, and to help guiding clinical practice.

5. Conclusion

Our results showed that Lp(a) plasma level and LAD were positively related to thromboembolism in NVAF patients with CHA₂DS₂-VASc score of 0 to 1 after adjustment for age, gender, and other variables. High Lp(a) plasma level and left atrial dilatation might be independent risk factors of thrombotic events for NVAF patients with low CHA₂DS₂-VASc score.

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