Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
50(2) 1–10

DOI: 10.1177/03000605221074520
journals.sagepub.com/home/imr
SAGE

Refinement of CHADS2 and CHA2DS2-VASc scores predict left atrial thrombus or spontaneous echo contrast in nonvalvular atrial fibrillation patients

Miaomiao Cao, Huihui Guo, Xiao Zhao, Xiyang Li and Chaofeng Sun

Abstract

Objective: To investigate the risk factors of left atrial thrombus (LAT)/spontaneous echo contrast (SEC) in patients with nonvalvular atrial fibrillation (AF).

Methods: This retrospective study analysed the data from consecutive patients with nonvalvular AF that underwent transoesophageal echocardiography. Logistic regression analysis was performed to identify risk factors of LAT/SEC. Receiver operating characteristic curve analysis was undertaken compare the new scales with CHADS2 and CHA2DS2-VASc scores.

Results: A total of 558 patients with AF were included in the study. LAT/SEC was detected in 137 (24.6%) patients. The independent risk factors of LAT/SEC beyond CHADS2 or CHA2DS2-VASc scores included non-paroxysmal AF and left atrial diameter >37.5 mm. These two variables were added into the CHADS2 or CHA2DS2-VASc score to build new scales. Areas under the curve for the new scales based on CHADS2 and CHA2DS2-VASc scores were significantly higher than the CHADS2 or CHA2DS2-VASc score both in the overall study cohort and in patients at a high risk of thromboembolism.

Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, China

Corresponding author:
Chaofeng Sun, Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China.
Email: cfsun123@126.com

Conclusions: Non-paroxysmal AF and increased left atrial diameter beyond the CHADS2 or CHA2DS2-VASc score were independent risk factors of LAT/SEC and may help to improve the current risk stratification, especially for patients with nonvalvular AF at a high risk of thromboembolism.

Keywords
Atrial fibrillation, left atrial thrombus, spontaneous echo contrast, thromboembolism

Date received: 30 July 2021; accepted: 24 December 2021

Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia, has a prevalence of 1.2% in China and has become a major public health burden as the age of the population has increased.[1] Thrombus formation and spontaneous echo contrast (SEC) occur within the left atrium, especially in the left atrial appendage (LAA) in the setting of AF due to reduced contractility and unsteady blood stasis, which have been demonstrated to be associated with an increased risk of thromboembolism.[2,3]

As reported, the prevalence of left atrial thrombus (LAT) in AF patients varies from 0.6% to 27% in different populations.[3] Although transoesophageal echocardiogram is the gold standard for the diagnosis of LAT/SEC, this invasive procedure restricts patients with heart failure, severe cardiac arrhythmia, oesophageal ulcers or varicose veins.[4] Several clinical risk factors, such as age, sex, congestive heart failure, hypertension, diabetes mellitus, stroke/transient ischaemic attack and vascular disease, known as CHADS2 and CHA2DS2-VASc scores, were used to build the risk prediction model of thromboembolism.[5] However, LAT/SEC occurs even in patients being treated with anticoagulant therapy.[6] Moreover, it has been demonstrated that other factors, such as left atrial diameter (LAD), LAA morphology and left ventricular mass, are associated with LAT/SEC.[3]

Therefore, this current study aimed to determine the risk factors beyond CHADS2 and CHA2DS2-VASc scores for LAT/SEC in patients with nonvalvular AF by assessing demographic and clinical characteristics in order to improve the current risk prediction models.

Patients and methods

Study population

This retrospective study reviewed data from consecutive patients with AF at the Department of Cardiovascular Medicine, First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi Province, China between November 2016 and December 2019. All patients underwent transoesophageal echocardiography. The exclusion criteria were as follows:(i) patients diagnosed with rheumatic heart disease; (ii) patients that underwent valve replacement or repair surgery; (iii) patients diagnosed with congenital heart disease; (iv) patients with cardiomyopathy including dilated, ischaemic and hypertrophic cardiomyopathy, or with pacemaker implantation; (v) patients with repeat transoesophageal

echocardiography (only the first admission was enrolled).

This study did not include identifiable personal information. Thus, a waiver of individual consent and ethics were reviewed and approved by the First Affiliated Hospital of Xi'an Jiaotong University Ethics Committee (no. XJTU1AF2020LSK-001). The reporting of this study conforms with STROBE guidelines.[7]

Data collection

All demographic, echocardiographic and laboratory data were collected from the electronic medical record system. The diagnosis and classification of AF were determined by at least two cardiologists independently according to the 2014 AHA/ACC/HRS guideline for the management of patients with AF based on the medical history, electrocardiogram or 24-h electrocardiogram Holter analysis.[8] The definition of nonvalvular AF was AF in the absence of mechanical or bioprosthetic heart valves, rheumatic mitral stenosis or mitral valve repair. The definition of non-paroxysmal AF was that the duration of the AF episode was sustained >7 days. The CHADS2 score (congestive heart failure, 1 point; hypertension, 1 point; age ≥ 75 years, 1 point; diabetes mellitus, 1 point; stroke/transient ischaemic attack (TIA), 2 points) and CHA2DS2-VASc score (congestive heart failure, 1 point; hypertension, 1 point; age ≥ 75 years, 2 points; diabetes mellitus, 1 point; stroke/TIA, 2 points; vascular disease, 1 point; age (65–74 years), 1 point; sex (female), 1 point) were calculated by determining the sum of the above scores of clinical risk factors.

Echocardiographic examination

Patients were classified into two groups based on the presence of LAT or SEC. For each patient, a transoesophageal echocardiogram was performed to exclude LAT within 2 days before catheter ablation or LAA occlusion. LAT was defined as a hyperechoic mass attached to the left atrial or LAA. Left atrial SEC was defined as dynamic 'smoke-like' echoes located in the LAA or left atrium. M-mode, two-dimensional and Doppler images were performed to evaluate heart structure and function. Echocardiographic data were analysed by two cardiologists.

Statistical analyses

All statistical analyses were performed using the SPSS® statistical package, version 18.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Continuous variables are presented as the mean $\pm$ SD or median (interquartile range), while categorical variables are presented as numbers and percentages. The distribution patterns of continuous variables were evaluated by the Kolmogorov–Smirnov test. Independent t-test, Mann-Whitney U-test and χ^2-test were used to compare two groups of continuous and categorical variables. Binary logistic regression analysis was performed using the stepwise forward method to identify the independent risk factors of LAT/SEC in patients with nonvalvular AF. Variables with a P-value <0.1 in the univariate analysis were entered into the multivariate models. Model one included the CHADS2 score, while model two included the CHA2DS2-VASc score. The Youden index was used to determine the optimal cut-off value of 37.5 mm for LAD. To build new-scoring systems, the odds ratios of each independent risk factor in model one were compared with the odds ratios of the CHADS2 score. The ratio was used to assign the score for each variable. Receiver operating characteristic (ROC) curve analysis and DeLong's test were performed to compare

the areas under the curve (AUCs) of CHADS2, CHA2DS2-VASc, and new scales based on CHADS2 and CHA2DS2-VASc for LAT/SEC in all patients and in the high-risk of thromboembolism group (CHA2DS2-VASc ≥ 2 and CHADS2 ≥ 2). A two-sided P-value < 0.05 was considered statistically significant.

Results

This retrospective study reviewed data from 595 patients with AF. Among them, 37 patients were excluded as follows:(i) four patients diagnosed with rheumatic heart disease; (ii) five patients underwent valve replacement or repair surgery; (iii) four patients diagnosed with congenital heart disease; (iv) 18 patients with cardiomyopathy including dilated, ischaemic and hypertrophic cardiomyopathy, or with pacemaker implantation; (v) six patients with repeat transoesophageal echocardiography (only the first admission was enrolled). The remaining 558 patients with nonvalvular AF were enrolled in this study.

Among the 558 patients with nonvalvular AF (mean $\pm$ SD age, 63.18 ± 9.45 years; 326 [58.4%] male), the prevalence of LAT/SEC was 24.6% (137 of 558 patients). LAT was detected in 55 of 558 patients (9.9%). Among them, one patient was identified as having a thrombus in the left atrium. SEC was observed in 112 of 558 patients (20.1%). The median CHADS2 and CHA2DS2-VASc scores for the overall study cohort were 1 and 2, respectively.

The comparison of baseline characteristics, echocardiographic and laboratory data between patients with nonvalvular AF with and without LAT/SEC are presented in Tables 1 and 2. Compared with the patients in the non-LAT/SEC group ($n = 421$), patients with LAT/SEC ($n = 137$) were significantly older ($P = 0.008$). LAT/SEC was significantly more common in patients with non-paroxysmal AF, hypertension, chronic heart failure, previous stroke/TIA and in the high-risk thromboembolism population (CHA2DS2-VASc ≥ 2 and CHADS2 ≥ 2) ($P < 0.05$ for all comparisons). Patients with LAT/SEC presented with significantly increased LAD but with a significantly decreased left ventricular ejection fraction and significantly worse renal function compared with the patients in the non-LAT/SEC group ($P < 0.05$ for all comparisons).

In the univariate analysis, CHADS2 score, CHA2DS2-VASc score, non-paroxysmal AF, estimated glomerular filtration rate < 60 ml/min/1.73 m^2, left ventricular ejection fraction, left ventricular end-systolic dimension and LAD >37.5 mm were found to be significant risk factors of LAT/SEC (see supplementary materials, Table S1). All these factors were entered in the multivariate models and the results showed that non-paroxysmal AF, LAD >37.5 mm, CHA2DS2-VASc score and CHADS2 score were independent risk factors of LAT/SEC in patients with nonvalvular AF (Table 3). There was no statistical difference in the interaction between non-paroxysmal AF and LAD >37.5 mm (see supplementary materials, Table S2). To develop new scales based on the CHADS2 and CHA2DS2-VASc scores for predicting LAT/SEC, the odds ratios of each new independent risk factor in model one were compared with odds ratios of the CHADS2 score. The odds ratios of non-paroxysmal AF, LAD >37.5 mm and CHADS2 score in model one were 2.253, 1.967 and 1.402, respectively. Thus, 2 points were attributed to non-paroxysmal AF (as 2.253 divided by 1.402 equals 1.61), while 1 point each was attributed to LAD >37.5 mm (as 1.967 divided by 1.402 equals 1.40). Therefore, the total score of the new scale based on CHADS2 was 9 points, while the total score based on CHA2DS2-VASc was 12 points. The AUCs of CHADS2, CHA2DS2-VASc and the new scales based on CHADS2 and CHA2DS2-

Table 1. Baseline demographic and clinical characteristics of patients with nonvalvular atrial fibrillation (AF) with or without left atrial thrombus (LAT)/spontaneous echo contrast (SEC).

Characteristic	Non-LAT/SEC group $n = 421$	LAT/SEC group $n = 137$	Statistical analysis[a]
Age, years	62.57 ± 9.53	65.03 ± 8.95	$P = 0.008$
Male	247 (58.7%)	79 (57.7%)	NS
Non-paroxysmal AF	157 (37.3%)	87 (63.5%)	$P < 0.001$
CHF	10 (2.4%)	10 (7.3%)	$P = 0.005$
Hypertension	203 (48.2%)	81 (59.1%)	$P = 0.027$
Diabetes mellitus	64 (15.2%)	27 (19.7%)	NS
Stroke/TIA	22 (5.2%)	15 (10.9%)	$P = 0.019$
Vascular disease	25 (5.9%)	10 (7.3%)	NS
Smoker	129 (30.6%)	35 (25.5%)	NS
CHA2DS2-VASc score	2 (1–3)	2 (1–3)	$P < 0.001$
CHA2DS2-VASc score ≥ 2	222 (52.7%)	90 (65.7%)	$P = 0.008$
CHADS2 score	1 (0–1)	1 (0–2)	$P < 0.001$
CHADS2 score ≥ 2	84 (20.0%)	49 (35.8%)	$P < 0.001$
Oral anticoagulation	118 (28.0%)	46 (33.6%)	NS
Warfarin	2 (0.5%)	0 (0.0%)	NS
NOACs	116 (27.6%)	46 (33.6%)	NS

Data presented as mean $\pm$ SD, median (interquartile range) or *n* of patients (%).
[a]Independent *t*-test, Mann-Whitney *U*-test and χ^2-test were used to compare the continuous and categorical variables; NS, no significant between-group difference ($P \geq 0.05$).
CHF, chronic heart failure; TIA, transient ischemic attack; NOACs, novel oral anticoagulants.

VASc were 0.603, 0.606, 0.692 and 0.686, respectively. In the high-risk of thromboembolism group, the predictive value of CHADS2, CHA2DS2-VASc and the new scales based on CHADS2 and CHA2DS2-VASc were 0.547, 0.570, 0.714 and 0.712, respectively (Figure 1). Meanwhile, the AUCs of the new scales were significantly higher than those of the CHADS2 score or CHA2DS2-VASc score ($P < 0.001$ for all comparisons; DeLong's test) (see supplementary materials, Table S3).

Discussion

The main findings of this current study were as follows: (i) the prevalence of LAT in the present nonvalvular AF population was 9.9%, while the prevalence of SEC was 20.1%; (ii) binary logistic regression analysis suggested that non-paroxysmal AF and LAD >37.5 mm were independent risk factors for LAT/SEC in patients with nonvalvular AF; (iii) incorporating non-paroxysmal AF and LAD >37.5 mm can improve the predictive power of the CHADS2 and CHA2DS2-VASc scores for LAT/SEC in patients with nonvalvular AF, especially in the population of patients that is of high-risk of thromboembolism.

A previous meta-analysis suggested that approximately 89% of atrial thrombi were identified in the LAA in nonvalvular AF patients.[9] The LAA is a finger-like blind cavity with abundant comb muscles that extends from the main body of the left atrium and is separated by a narrow junction at the orifice of the LAA. Furthermore, the LAA originates from the primordial left atrium and has normal contraction and relaxation function during sinus rhythm.[10] However, AF results in

Table 2. Echocardiogram parameters and laboratory data for patients with nonvalvular atrial fibrillation (AF) with or without left atrial thrombus (LAT)/spontaneous echo contrast (SEC).

Characteristic	Non-LAT/SEC group $n = 421$	LAT/SEC group $n = 137$	Statistical analysis[a]
Echocardiogram parameters			
LVEF, %	67 (62–70)	64 (60–68)	$P = 0.001$
LAD, mm	35 (32–39)	39 (35–42)	$P < 0.001$
LVESD, mm	31 (29–34)	32 (29–36)	NS
LVEDD, mm	49 (46–52)	49 (47–53)	NS
Laboratory data			
Red blood cell count, 10^{12}/l	4.52 (4.20–4.90)	4.47 (4.14–4.92)	NS
White blood cell count, 10^9/l	6.01 ± 1.61	6.21 ± 1.51	NS
Monocyte count, 10^9/l	0.33 (0.26–0.42)	0.34 (0.26–0.42)	NS
Neutrophil count, 10^9/l	3.79 (2.97–4.61)	3.95 (3.16–4.82)	NS
Lymphocyte count, 10^9/l	1.69 ± 0.57	1.68 ± 0.56	NS
Platelet count, 10^9/l	185.03 ± 55.34	181.50 ± 52.00	NS
INR	1.15 ± 0.36	1.40 ± 0.70	$P < 0.001$
D-dimer, mg/l	0.56 ± 0.60	0.76 ± 1.21	NS
Fibrinogen, g/l	2.90 ± 0.70	3.11 ± 0.80	$P = 0.007$
eGFR < 60 ml/min/1.73 m^2	16 (3.8%)	12 (8.8%)	$P = 0.021$
Total cholesterol, mmol/l	3.49 (2.96–4.16)	3.48 (2.94–4.04)	NS
Triglyceride, mmol/l	1.21 (0.88–1.71)	1.11 (0.84–1.62)	NS

Data presented as mean $\pm$ SD, median (interquartile range) or *n* of patients (%).

[a]Independent *t*-test, Mann-Whitney *U*-test and χ^2-test were used to compare the continuous and categorical variables; NS, no significant between-group difference ($P \geq 0.05$).

LVEF, left ventricular ejection fraction; LAD, left atrial diameter; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; INR, international normalized ratio; eGFR, estimated glomerular filtration rate.

Table 3. Multivariate regression analysis of independent risk factors for left atrial thrombus (LAT)/spontaneous echo contrast (SEC) in patients with nonvalvular atrial fibrillation (AF).

Variables	Odds ratio	95% confidence interval	Statistical analysis
Model 1			
CHADS2 score	1.402	1.135, 1.731	$P = 0.002$
Non-paroxysmal AF	2.253	1.452, 3.496	$P < 0.001$
LAD > 37.5 mm	1.967	1.266, 3.055	$P = 0.003$
Model 2			
CHA2DS2-VASc score	1.236	1.069, 1.430	$P = 0.004$
Non-paroxysmal AF	2.201	1.418, 3.415	$P < 0.001$
LAD > 37.5 mm	2.036	1.313, 3.156	$P = 0.001$

LAD, left atrial diameter.

insufficient atrial contractility, which leads reduced blood flow within the LAA. All these factors, including morphology and decreased atrial function, predispose the patient to thrombus formation in the setting of AF. Atrial dilation, atrial or ventricular dysfunction, pre-existing comorbidities and elevated prothrombotic

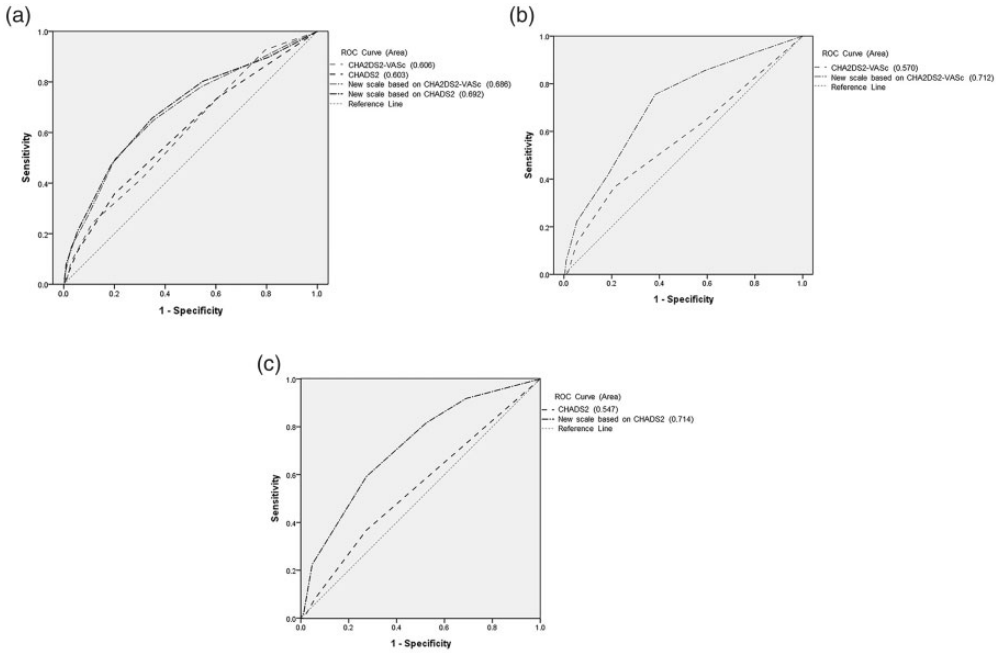

Figure 1. Receiver operating characteristic (ROC) curves and area under the curve for the CHADS2 score, CHA2DS2-VASc score, new scale based on CHADS2 and new scale based on CHA2DS2-VASc in the total study cohort (a) and in the high-risk of thromboembolism group (b, c).

indices further accelerate the progress of thrombus formation within the atrium.[11] The prevalence of LAT/SEC varies in different populations. For example, a previous meta-analysis reported a weighted mean prevalence of LAT of 9.8% (95% confidence interval, 7.6%, 12.5%) from 72 studies with 20 516 patients with AF.[12] This was similar to the current findings, in which the prevalence of LAT was 9.9% among patients with nonvalvular AF irrespective of anticoagulation treatment. Furthermore, another study reported that the prevalence of SEC in non-precipitated nonvalvular AF patients was 46.2%, when the prevalence of SEC in the current study was lower.[2] This might be because some patients with nonvalvular AF in the current study were prescribed oral anticoagulation therapy.

Evidence regarding the relationship between AF type and LAT/SEC or stroke is controversial.[13] A meta-analysis including 12 manuscripts with 99 996 patients with AF found that non-paroxysmal AF patients had a higher risk of thromboembolism than paroxysmal AF patients.[14] Similarly, a large survey including 6563 AF patients without anticoagulation suggested that persistent AF and permanent AF increased the risk of stroke by 1.44- and 1.84-fold compared with paroxysmal AF,[15] while another study found that persistent AF and permanent AF independently predicted LAT with odds ratios of 5.76 and 13.02, respectively.[16] This was consistent with the current results, in which non-paroxysmal AF was a strong and independent risk factor for LAT/SEC. However, other researchers also reported

that paroxysmal AF had a similar risk of stroke to that of non-paroxysmal AF.[17,18] The possible explanation may be associated with younger age, shorter AF duration, less atrial remodelling, fewer pre-existing comorbidities, a lower CHA2DS2-VASc score or more adequate oral anticoagulation treatment in paroxysmal AF than in non-paroxysmal AF.

The atrial substrate underlying AF has been well discussed previously.[19] Some indicators of structural remodelling in AF, such as LAD, can be easily detectable in clinical practice. Importantly, increased LAD in patients with AF has been shown to increase the risk of LAT/SEC.[20–22] This is in line with the current result that the median value of LAD in the LAT/SEC group was higher than that in the non-LAT/SEC group; and that a LAD >37.5 mm was an independent risk factor for LAT/SEC. Several pathophysiological mechanisms might be involved in this process. First, increased LAD was related to a longer AF duration or an increased AF burden, which are indirectly associated with more extensive inflammatory infiltration and endothelial dysfunction.[23] Secondly, an increased LAD further decreased blood flow velocity and deteriorated blood stasis.[20] It is noteworthy that the normal range of LAD varies across the sexes and different ethnic groups.[24] Therefore, indexing LAD by body surface area is a more applicable indicator for evaluating left atrial size. Additionally, although improved left atrial size has been observed in AF patients that received catheter ablation,[25] whether the risk of LAT/SEC can be improved by the reduction in left atrial size has yet to be investigated.

The CHADS2 and CHA2DS2-VASc scores are widely used for stratifying the risk of thromboembolism and guiding anticoagulation treatment for AF patients. High CHADS2 and CHA2DS2-VASc scores have been reported to be associated with LAT.[26] In the current study, either CHADS2 or CHA2DS2-VASc score provided an independent but limited predictive value for LAT/SEC. This was consistent with a previous report that the predictive value of CHADS2 or CHA2DS2-VASc for LAT ranged from 0.55 to 0.7.[5] The possible explanation is that the components of the CHADS2/CHA2DS2-VASc scores mainly contribute to the atherosclerotic process, instead of focusing on the formation of thromboembolism.[27] The current study suggested the predictive powers of CHADS2 and CHA2DS2-VASc for LAT/SEC were improved by the additions of variables including non-paroxysmal AF (2 points) and LAD >37.5 mm (1 point), especially in the population of patients at a high risk of thromboembolism. Therefore, refinement of CHADS2 and CHA2DS2-VASc scores may provide better prediction of high−risk AF patients.

This current study had several limitations. First, selection bias might exist because this study was a retrospective study from a single centre. Patients with nonvalvular AF that did not undergo transoesophageal echocardiography or did not have the indication of catheter ablation may be different from those included in the study. Secondly, data were retrieved from the electronic medical record system and some important data were not available. For example, the type of non-paroxysmal AF could not be traced and the degree of SEC and LA volumes were not available from the medical record system. Approximately 25% of individuals did not have information on height or weight; therefore, the LAD index could not be determined completely. Thirdly, this current study included a limited number of AF patients irrespective of oral anticoagulation and, thus, may not represent the general AF population.

In conclusion, the independent risk factors for LAT/SEC were non-

paroxysmal AF and increased LAD, which added predictive value to the CHADS2 and CHA2DS2-VASc scores for LAT/SEC in patients with nonvalvular AF, especially in the high-risk of thromboembolism group. This highlights the fact that these additional risk factors of LAT/SEC may help to improve the current risk prediction model for thromboembolism.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

ORCID iD

Miaomiao Cao https://orcid.org/0000-0002-4863-4454

Supplemental material

Supplemental material for this article is available online.

References

1. Sun GZ, Guo L, Wang XZ, et al. Prevalence of atrial fibrillation and its risk factors in rural China: a cross-sectional study. *Int J Cardiol* 2015; 182: 13–17.
2. Soulat-Dufour L, Lang S, Etienney A, et al. Correlation between left atrial spontaneous echocardiographic contrast and 5-year stroke/death in patients with non-valvular atrial fibrillation. *Arch Cardiovasc Dis* 2020; 113: 525–533.
3. Zhan Y, Joza J, Al Rawahi M, et al. Assessment and Management of the Left Atrial Appendage Thrombus in Patients With Nonvalvular Atrial Fibrillation. *Can J Cardiol* 2018; 34: 252–261.
4. Hahn RT, Abraham T, Adams MS, et al: Guidelines for performing a comprehensive transesophageal echocardiographic examination: recommendations from the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists. *J Am Soc Echocardiogr* 2013; 26: 921–964.
5. Huang J, Wu SL, Xue YM, et al. Association of CHADS2 and CHA2DS2-VASc Scores with Left Atrial Thrombus with Nonvalvular Atrial Fibrillation: A Single Center Based Retrospective Study in a Cohort of 2695 Chinese Subjects. *Biomed Res Int* 2017; 2017: 6839589.
6. Bertaglia E, Anselmino M, Zorzi A, et al. NOACs and atrial fibrillation: Incidence and predictors of left atrial thrombus in the real world. *Int J Cardiol* 2017; 249: 179–183.
7. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147: 573–577.
8. January CT, Wann LS, Alpert JS, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2014; 64: e1–e76.
9. Mahajan R, Brooks AG, Sullivan T, et al. Importance of the underlying substrate in determining thrombus location in atrial fibrillation: implications for left atrial appendage closure. *Heart* 2012; 98: 1120–1126.
10. Beigel R, Wunderlich NC, Ho SY, et al. The left atrial appendage: anatomy, function, and noninvasive evaluation. *JACC Cardiovasc Imaging* 2014; 7: 1251–1265.
11. Watson T, Shantsila E and Lip GYH. Mechanisms of thrombogenesis in atrial fibrillation: Virchow's triad revisited. *Lancet* 2009; 373: 155–166.
12. Di Minno MND, Ambrosino P, Dello Russo A, et al. Prevalence of left atrial thrombus in patients with non-valvular atrial fibrillation A systematic review and meta-analysis of the literature. *Thromb Haemost* 2016; 115: 663–677.

13. Boriani G and Pettorelli D. Atrial fibrillation burden and atrial fibrillation type: Clinical significance and impact on the risk of stroke and decision making for long-term anticoagulation. *Vascul Pharmacol* 2016; 83: 26–35.
14. Ganesan AN, Chew DP, Hartshorne T, et al. The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis. *Eur Heart J* 2016; 37: 1591–1602.
15. Vanassche T, Lauw MN, Eikelboom JW, et al: Risk of ischaemic stroke according to pattern of atrial fibrillation: analysis of 6563 aspirin-treated patients in ACTIVE-A and AVERROES. *Eur Heart J* 2015; 36: 281–287a.
16. Kapłon-Cieślicka A, Budnik M, Gawałko M, et al. Atrial fibrillation type and renal dysfunction as important predictors of left atrial thrombus. *Heart* 2019; 105: 1310–1315.
17. Hohnloser SH, Pajitnev D, Pogue J, et al. Incidence of stroke in paroxysmal versus sustained atrial fibrillation in patients taking oral anticoagulation or combined antiplatelet therapy: an ACTIVE W Substudy. *J Am Coll Cardiol* 2007; 50: 2156–2161.
18. Banerjee A, Taillandier S, Olesen JB, et al. Pattern of atrial fibrillation and risk of outcomes: The Loire Valley Atrial Fibrillation Project. *Int J Cardiol* 2013; 167: 2682–2687.
19. Goldberger JJ, Arora R, Green D, et al. Evaluating the Atrial Myopathy Underlying Atrial Fibrillation Identifying the Arrhythmogenic and Thrombogenic Substrate. *Circulation* 2015; 132: 278–291.
20. Hamatani Y, Ogawa H, Takabayashi K, et al. Left atrial enlargement is an independent predictor of stroke and systemic embolism in patients with non-valvular atrial fibrillation. *Sci Rep* 2016; 6: 31042.
21. Ning WN, Li Y, Ma C, et al. The Refinement of Risk Stratification for Atrial Thrombus or Spontaneous Echo Contrast in Nonvalvular Atrial Fibrillation. *Int Heart J* 2017; 58: 885–893.
22. Lin WD, Xue YM, Liu FZ, et al. Left atrial enlargement and non-paroxysmal atrial fibrillation as risk factors for left atrial thrombus/spontaneous Echo contrast in patients with atrial fibrillation and low CHA2DS2-VASc score. *J Geriatr Cardiol* 2020; 17: 155–159.
23. Sanfilippo AJ, Abascal VM, Sheehan M, et al. Atrial enlargement as a consequence of atrial fibrillation. A prospective echocardiographic study. *Circulation* 1990; 82: 792–797.
24. Khoo CW, Krishnamoorthy S, Lim HS, et al. Assessment of left atrial volume: a focus on echocardiographic methods and clinical implications. *Clin Res Cardiol* 2011; 100: 97–105.
25. Xiong B, Li D, Wang J, et al: The Effect of Catheter Ablation on Left Atrial Size and Function for Patients with Atrial Fibrillation: An Updated Meta-Analysis. *PLoS One* 2015; 10: e0129274.
26. Shah M, Mobaligh N, Niku A, et al. Predictors of left atrial appendage thrombus despite NOAC use in nonvalvular atrial fibrillation and flutter. *Int J Cardiol* 2020; 317: 86–90.
27. Huang J, Liao HT, Fei HW, et al. Association of Thromboembolic Risk Score with Left Atrial Thrombus and Spontaneous Echocardiographic Contrast in Non-Anticoagulated Nonvalvular Atrial Fibrillation Patients. *Cardiology* 2018; 140: 87–95.