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ORIGINAL RESEARCH ARTICLE

Comparison of different thromboembolism risk scores with the predictive value of left atrial thrombosis and/or spontaneous ultrasound in patients with non-valvular atrial fibrillation

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ABSTRACT

Objective: To compare the predictive value of CHADS2, CHA2DS2-VASc, ATRIA and R2-CHADS2 scores and left atrial thrombosis and/or spontaneous ultrasound in patients with non-valvular atrial fibrillation (AF) Methods patients with non-valvular atrial fibrillation who were hospitalized in the Department of Cardiology of Sun Yat Sen Memorial. **Results:** 564 patients were included. The age of patients was (61.1 ± 10.1) years old, of which 63.3% were men. Hypertension was the most common complication, which was found in 49.6% of patients. Patients were divided into thrombus group ($n = 82$) and non-thrombus group ($n = 482$) according to the presence of left atrial thrombus and/or spontaneous ultrasound development CHADS2 score in thrombotic group (1[0,2]) was higher than that in non-thrombotic group (1[0,1]) ($P < 0.05$), and CHA2DS2-VASc score in thrombotic group (2[1,3]) was higher than that in non-thrombotic group (2[1,2]) ($P < 0.05$) 11.06%, 13.39%, 26.58%, 18.52% and 16.67% of patients with CHADS2 score of 0, 1, 2, 3 and 4 had left atrial thrombus and/or spontaneous ultrasound (P fortrend = 0.016), and 11.06%, 13.39% and 23.68% of patients with low, medium and high risk had left atrial thrombus and/or spontaneous ultrasound (P fortrend = 0.004); 10.81%, 10.19%, 16.57%, 21.05%, 21.05%, 16.67%, 14.29% of patients with CHA2DS2-VASc score of 0, 1, 2, 3, 4, 5, 6 or above had left atrial thrombosis and/or spontaneous ultrasound development (P fortrend = 0.019), and 8.75%, 13.90% and 19.35% of patients with low, medium and high risk had left atrial thrombosis and/or spontaneous ultrasound development (P fortrend = 0.004); The area under the ROC curve of ATRIA score and R2-CHADS2 score was 0.562. The samples based on this study had no statistical significance in the diagnosis of left atrial thrombosis and/or spontaneous ultrasound ($P > 0.05$). **Conclusion:** CHADS2 score and CHA2DS2-VASc score have considerable and limited diagnostic value for left atrial thrombosis and/or spontaneous ultrasound in patients with non-valvular atrial fibrillation.

Keywords: transfer hydrogenation; ortho-chloro aniline; γ-butyrolactone; atomic H2; basic sites; nano CoO-Cu-MgO

1. Introduction

Left atrial thrombus and dense spontaneous ultrasound (fatkin grade 3+ and 4+) are prerequisites for cardiogenic embolism in patients with non-valvular atrial fibrillation (AF). They have been proved to be independently related to thromboembolic events in patients with AF[1–5]. The prevention of stroke by oral anti-

coagulants is the cornerstone of atrial fibrillation management. The effective stratification of thrombus risk by scoring method is an important method to guide the clinical application of anticoagulants to prevent stroke. The author intends to explore the correlation between the four thrombus risk assessment methods recommended by the current guidelines, CHADS2 score[6], CHA2DS2-VASc score[7], published R2-CHADS2 score[8], ATRIA score[9], and left atrial thrombosis and/or spontaneous ultrasound development in patients with non-valvular atrial fibrillation who do not take anticoagulants for a long time.

2. Data and methods

The subjects of the study were hospitalized patients diagnosed with non-valvular atrial fibrillation and transesophageal echocardiography (TEE) in Sun Yat Sen Memorial Hospital of Sun Yat sen University from January 2007 to July 2019 Inclusion criteria: a) age > 18 years old; b) atrial fibrillation was diagnosed by routine ECG or 24 h ambulatory ECG; c) no history of taking anticoagulants before admission; d) the case data are complete exclusion criteria: (a) Valvular atrial fibrillation: rheumatic mitral stenosis, after mechanical or biological valve replacement and mitral valve repair. (b) Hyperthyroidism. (c) Malignant tumor. (d) Coagulation dysfunction.

The research method was retrospectively reviewed by electronic medical record system, including the following aspects: Age, sex, and gender, such as hypertension, diabetes mellitus, heart failure, stroke or transient ischemic attack, vascular disease. Laboratory data: Blood routine, liver and kidney function, blood lipid, coagulation function, etc.; auxiliary examination: tee results, left ventricular ejection fraction and left atrial diameter measured by transthoracic echocardiography make statistics on all data and establish spreadsheet at the same time, CHADS2, CHA2DS2-VASc, R2-CHADS2 and ATRIA scores were given to all patients with non-valvular atrial fibrillation.

Definition of thrombus and spontaneous ultrasound development thrombus is defined as the echo image with clear boundary, uniform density and different from the density of adjacent myocardial tissue in the left atrium. Spontaneous ultrasound development refers to the echo of cloud, vortex or prethrombotic state in the left atrium found by teethe patients with spontaneous ultrasound development included in this study were rated as 3+ and 4+ according to fatkin.

Thromboembolism risk score stratification a) CHADS2 score: 0 points are low risk, 1 point are medium risk, and greater than or equal to 2 points are high risk. b) CHA2DS2-VASc score: 0 is low risk (including women with a score of 1), 1 is medium risk (including women with a score of 2), and greater than or equal to 2 is high risk (excluding women with a score of 2). c) R2-CHADS2 score: 0 is low risk, 1 is medium risk, and greater than or equal to 2 is high risk. d) Atria score: 0–5 points are low risk, 6 points are medium risk, and more than 6 points are high risk.

Statistical treatment all statistical analyses were based on spss25.10. The measurement data meeting the normal distribution is expressed by mean ± standard deviation, and the measurement data of skew distribution is expressed by median (interquartile spacing). The data conform to the normal distribution and variance homogeneity test, the independent sample *t*-test is used for inter group comparison; If it does not meet the normal distribution or variance homogeneity test, Mann Whitney U test shall be used; the number of use cases (percentage) of counting data indicates that chi square test is used for comparison between groups P for trend adopts Cochran Armitage trend test. Calculate the area under the ROC curve of the four scoring methods based on the subject's working curve. Two-sided test was used, and the difference was significant when $p < 0.05$.

3. Results

A total of 564 patients with non-valvular atrial fibrillation were selected. According to whether there was left atrial thrombosis and/or spontaneous ultrasound, 82 cases (14.54%) in the thrombus group and 482 cases (85.46%) in the non-thrombus group.

Basic clinical data the age of patients is (61.1 ± 10.1) years old, of which 63.3% are men. Hypertension is the most common complication, which is seen in 49.6% of the selected patients CHADS2 and CHA2DS2-VASc scores in thrombus group were significantly higher than those in non-thrombus group ($P <$ 0.05), and there was no difference in ATRIA and R2-CHADS2 scores between the two groups. Compared with the non-thrombus group, the body mass index and the proportion of persistent atrial fibrillation and drinking increased in the thrombus group. In terms of complications, patients in the thrombus group were more complicated with congestive heart failure. In terms of laboratory indexes, the activities of lactate dehydrogenase, uric acid, C-reactive protein and prothrombin in the thrombotic group were higher than those in the non-thrombotic grouping terms of transthoracic color. Doppler ultrasound parameters, the left ventricular ejection fraction, left atrial anterior posterior diameter, left ventricular end diastolic diameter, diastolic ventricular septal thickness and right ventricular diameter in the thrombus group were higher than those in the non-thrombus group. There was no difference between the two groups in stroke/transient ischemic attack (TIA), hypertension, diabetes, creatinine, D-two dimer and other indicators ($P >$ 0.05). See **Tables 1** and **2**.

Table 1. Basic clinical data of patients with non-valvular atrial fibrillation.

Group	N	Age/year	Female/case	CHADS$_2$ score	CHA$_2$DS$_2$-VASc score	Atria score	R$_2$-CHADS$_2$ score
Thrombus group	82	62.5±9.1	30(36.6%)	1[0,2]*	2[1,3]*	3[1,5]	2[1,3]
Non thrombotic group	482	60.9±10.2	177(36.7%)	1[0,1]	2[1,2]	2[1,4]	1[0,3]
Total	564	61.1±10.1	207(36.7%)	1[0,1]	2[1,2]	2[1,4]	1[0,3]

Group	BMI/(kg/m^2)	Persistent atrial fibrillation/case	Smoking/case	Drinking/case	Stroke/TIA/case	Heart failure/case	CAD/example
Thrombus group	25.9±3.9*	21(25.6%)*	21(25.6%)	14(17.1%)*	6(7.3%)	18(22.0%)*	20(24.4%)
Non thrombotic group	24.6±3.5	57(11.8%)	123(25.5%)	42(8.7%)	28(5.8%)	22(4.6%)	116(24.1%)
Total	24.8±3.6	78(13.8%)	144(25.5%)	56(9.9%)	34(6.0%)	40(7.1%)	136(24.1%)

Group	Diabetes mellitus/case	Hypertension/case	Vascular disease/case	Creatinine/(umol/L)	Egfr/(mL/min/1.73 m^2)	Egfr < 60 (ml/min/1.73 m^2)/case
Thrombus group	43(52.4%)	13(15.9%)	4(4.9%)	94 ± 19	70 ± 21	37(46.3%)
Non thrombotic group	237(49.2%)	63(13.1%)	19(3.9%)	94 ± 20	68 ± 20	195(42.2%)
Total	280(49.6%)	76(13.5%)	23(4.1%)	94 ± 21	68 ± 20	232(42.8%)

Group	Proteinuria/case	Lactate dehydrogenase/(U/L)	CHOL/(mmol/L)	TG/(mmol/L)	HDL-C/(mmol/L)	LDL-C/(mmol/L)	UA/(umol/L)
Thrombus group	4(4.9%)	213 ± 71*	4.7 ± 1.1	1.4[1.0,1.9]	1.14 ± 0.32	2.90 ± 0.80	421 ± 111*
Non thrombotic group	12(2.5%)	187 ± 414.	4.6 ± 1.0	1.3[0.9,1.8]	1.17 ± 0.29	2.83 ± 0.75	384 ± 104
Total	16(2.8%)	191 ± 474.	4.6 ± 1.0	1.3[0.9,1.8]	1.17 ± 0.29	2.84 ± 0.76	389 ± 106

Group	D-Dimer/(mg/LFEU)	CRP/(mg/L)	PTA/%	Neutrophil/(×10^9/L)	Lymphocyte/(×10^9/L)	Medium leaching ratio
Thrombus group	0.29[0.14,0.51]	2.21[0.83,4.54]*	85 ± 29*	4.5 ± 1.5	2.00 ± 0.60	2.3[1.6,2.9]
Non thrombotic group	0.23[0.14,0.39]	1.25[0.57,3.93]	93 ± 24	4.5 ± 1.6	1.95 ± 0.69	2.3[1.6,3.0]

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Total	0.23[0.14,0.40]	1.38[0.59,4.06]	92 ± 25	4.5 ± 1.6	1.96 ± 0.68	2.3[1.6,3.0]

Note: TIA = transient ischemic attack, BMI = body mass index, CAD = coronary heart disease, EGFR = glomerular filtration rate, CHOL = total cholesterol, TG = triglyceride, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol, UA = uric acid, D-Dimer = D-dimer, CRP = C-reactive protein, PTA = prothrombin activity, NEUTROPHIL = neutrophil, LYMPHOCYTE = lymphocyte Compared with non thrombus group, *$P < 0.05$.

Table 2. Transthoracic color doppler ultrasound parameters in patients with non-valvular atrial fibrillation.

Group	N	LVEF	LAD/mm	LVDD/mm	IVSD/mm	RVD/mm
Thrombus group	82	0.61 ± 0.10*	42.3 ± 5.6*	50.2 ± 5.6*	10.6 ± 2.9*	23.2 ± 6.0*
Non thrombotic group	482	0.67 ± 0.07	35.8 ± 4.7	48.3 ± 4.2	9.5 ± 1.5	20.9 ± 4.2
Total	564	0.66 ± 0.08	36.8 ± 5.4	48.6 ± 4.5	9.7 ± 1.8	21.2 ± 4.5

Note: LVEF = left ventricular ejection fraction, LAD = left atrial anteroposterior diameter, LVDD = left ventricular end diastolic diameter, IVSD = diastolic ventricular septal thickness, RVD = right ventricular diameter Compared with non thrombus group, *$P < 0.05$.

Differences in scores and risk stratification among the four scoring systems: 226 cases with 0 CHADS2 score, 224 cases with 1 CHADS2 score, and 114 cases with 2 or above CHADS2 score; According to the results of trend test, the incidence of left atrial thrombosis and/or spontaneous ultrasound increased with the increase of score or risk stratification ($P < 0.05$); In ATRIA and R2-CHADS2 scores, the change of this trend is not statistically significant The score of high-risk patients was significantly lower than that of high-risk patients (ds2264/ds001) (28.37%), and the score of high-risk patients was significantly lower than that of high-risk patients (ds2264/ds001) (ds562/ds001) (28.37%), see **Table 3**. According to the recommendations of the guidelines, the patients received CHADS2 score, and 114 patients needed anticoagulant treatment, of which 23.68% had left atrial thrombosis and/or spontaneous ultrasound development; 226 patients did not need anticoagulant therapy, of which 11.06% had left atrial thrombosis and/or spontaneous ultrasound; In the CHA2DS2-VASc score, 217 patients need anticoagulant treatment, of which 19.35% have left atrial thrombosis and/or spontaneous ultrasound development, and 160 patients do not need anticoagulant treatment, of which 8.75% have left atrial thrombosis and/or spontaneous ultrasound development, see **Table 4**. According to the analysis of the selected patients in the thrombus group, there were 27 patients with high CHADS2 score (32.93%), 42 patients with high CHA2DS2-VASc score (51.22%), and the anticoagulant ratio of the thrombus group was higher than that of CHADS2 score ($P = 0.018$).
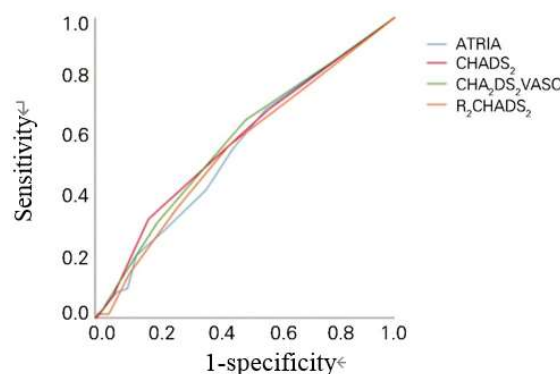
	ROC curve area (95% CI)	P value
CHADS₂ score	0.586 (0.518-0.654)	0.013
CHA₂DS₂VAS_C score	0.586 (0.520-0.653)	0.012
ATRIA score	0.562 (0.496~0.627)	0.074
R₂CHADS₂ score	0.562 (0.495-0.628)	0.074

Figure 1. Area under the curve of four thromboembolism scoring methods.

Comparison of area under ROC curve the area under ROC curve of CHADS2 score and CHA2DS2-VASc score was 0.586 ($P < 0.05$). There was no significant difference between the two scoring systems in the determination of left atrial thrombosis and/or spontaneous ultrasound development. The area under ROC curve of ATRIA score and R2-CHADS2 score was not statistically significant ($P > 0.05$), see **Figure 1**.

Table 3. Number of cases of left atrial thrombosis and/or spontaneous development corresponding to each score of four thromboembolism scores.

Scoring method	0	1	2	3
CHADS$_2$	25(11.06%,226)	30(13.39%,224)	21(26.58%,79)	5(18.52%,27)
CHA$_2$DS$_2$-VASc	12(10.81%,111)	16(10.19%,157)	28(16.57%,169)	16(21.05%,76)
R$_2$-CHADS$_2$	19(11.73%,162)	16(11.43%,140)	17(17.17%,99)	18(18.95%,95)
ATRIA	12(10.91%,110)	13(10.66%,122)	11(16.92%,65)	11(20.75%,53)
Scoring method	4	5	≥6	*P* fortrend
CHADS$_2$	1(16.67%,6)	0(0,2)	0(0)	0.016
CHA$_2$DS$_2$-VASc	8(21.05%,38)	1(16.67%,6)	1(14.29%,7)	0.019
R$_2$-CHADS$_2$	11(24.44%,45)	0(0,17)	1(16.67%,6)	0.113
ATRIA	11(14.10%,78)	7(13.21%,53)	17(20.48%,83)	0.062

Note: in parentheses are the incidence of left atrial thrombosis and/or spontaneous ultrasound development and the total number of patients corresponding to each score of four thromboembolism scores.

Table 4. Number of cases of left atrial thrombosis and/or spontaneous development corresponding to each layer of four thromboembolism scores.

Scoring method	Low risk	Medium risk	High-risk	*P* fortrend
CHADS$_2$	25(11.06%,226a)	30(13.39%,224)	27(23.68%,114c)	0.004
CHA$_2$DS$_2$-VASc	14(8.75%,160b)	26(13.90%,187)	42(19.35%,217d)	0.004
R$_2$-CHADS$_2$	19(11.73%,162)	16(11.43%,140)	47(17.94%,262)	0.058
ATRIA	65(13.51%,481)	9(39.13%,23)	8(13.33%,60)	0.428

Note: in parentheses are the incidence of left atrial thrombosis and/or spontaneous ultrasound development corresponding to each of the four thromboembolism scores and the total number of patients; a compared with b, $P < 0.001$; c compared with d, $P < 0.001$.

4. Discussion

In 2006, ACC/AHA/ESC first recommended CHADS2 score for the assessment of thromboembolism risk in patients with non valvular atrial fibrillation. With the deepening of people's understanding of stroke risk factors of atrial fibrillation, CHA2DS2-VASc score has become the thromboembolism risk score recommended in the current guidelines after refining the age stratification and adding two risk factors of women and vascular diseases[10]. According to the recommendations of the guidelines, the study population was given CHADS2 score and CHA2DS2-VASc score. 114 and 217 patients needed anticoagulant treatment respectively. Among the patients who received anticoagulant treatment by the two scoring methods, 27 and 42 patients had left atrial thrombosis and/or spontaneous ultrasound development respectively. The anticoagulant ratio of thrombus group was higher than CHA2DS2-VASc score. In this study, the risk stratification of the same population with two scores shows that stroke risk assessment of patients with atrial fibrillation according to CHA2DS2-VASc score can more accurately enable high-risk patients to receive anticoagulant treatment and effectively reduce the risk of stroke or other embolic events in patients with atrial fibrillation.

The existence of left atrial thrombus is the contraindication of atrial fibrillation cardioversion and radiofrequency ablation. Tee is the most specific and sensitive method to detect left atrial thrombus in this study,

it is found that in low-risk patients, whether CHADS2 score or CHA2DS2-VASc score, left atrial thrombosis and/or spontaneous ultrasound development exist in varying degrees, suggesting that tee is an essential examination for all patients with atrial fibrillation before invasive treatment.

CHADS2 and CHA2DS2-VASc scores are useful risk stratification tools for predicting left atrial thrombosis/spontaneous ultrasound development, and there is no significant difference in the prediction ability between the two scores, but their prediction ability is limited (AUC = 0.586). Previous studies have also shown that the prediction ability of CHADS2 and CHA2DS2-VASc scores for patients with left atrial thrombosis is low to medium[11,12]. However, it still needs to be considered that this study is a retrospective study with insufficient data integrity, which may underestimate the predictive value of the two thromboembolism risk scores for left atrial thrombosis and/or spontaneous ultrasound development. In addition, in CHADS2 and CHA2DS2-VASc scores, some low-risk patients still have left atrial thrombosis and/or spontaneous ultrasound development. In this part of the population, there may be other risk factors related to thrombosis risk to be further found In addition to the risk factors in the current scoring system, studies have shown that left atrial enlargement, N-terminal pro brain natriuretic peptide, proteinuria, left atrial appendage morphology and function are independent risk factors for stroke in patients with atrial fibrillation[13–16], but data were not collected for further analysis in this study Uric acid, alcohol consumption, lactate dehydrogenase and other indicators shown in this study may also be related to the risk of thrombosis in patients with atrial fibrillation. Perhaps the addition of necessary echocardiographic parameters, biomarkers and other factors can further improve the current risk stratification method of thromboembolism and make a more systematic and accurate assessment of the risk of thrombosis in patients with atrial fibrillation.

In 2013, Piccini et al.[8] verified that the decrease of EGFR (estimated global filtration rate) was an independent predictor of thromboembolism in patients with atrial fibrillation, second only to previous stroke or transient ischemic attack. After incorporating crcl (Creative clearance) <60 mL/min as a risk factor, they proposed R2-CHADS2 score In the same year, Singer et al.[9] further refined the age in consideration of the interaction between age and stroke history, adopted different scoring systems according to whether the stroke history was combined or not, and proposed ATRIA score. The four thromboembolism scoring methods in this study come from different research populations, and their performance and classification accuracy are related to their derived cohort R2-chads2 score comes from an anticoagulation cohort and excludes patients with creatinine clearance rate less than 30 mL/min[8], which is different from the population selected in this study to some extent In addition, renal dysfunction as a risk factor for thrombosis is included in the R2-CHADS2 and ATRIA scores. However, in real world studies[17] is found to be associated with renal dysfunction and hypertension, diabetes, heart failure and vascular disease in elderly patients, which will affect the predictive value of R2-CHADS2 score and ATRIA score in this study. Thromboembolism risk score is committed to helping busy clinical work make anticoagulation decisions, which needs to be simple and practical. Atria score is more cumbersome and complex than other scores, which limits its clinical application.

The proportion of low-risk patients based on cha2ds2 ASC score in this study is higher than that in previous studies (4.9%~8.6%)[11,18,19], which may be because this subject is a retrospective study. There are few examinations for the evaluation of peripheral arterial disease and composite aortic plaque in the study population, and there is no good evaluation of vascular disease in CHA2DS2-VASc score, resulting in some patients not being further separated from low-risk patients It is also because this study recommends that female patients with atrial fibrillation without other thromboembolic risk factors be included in the low-risk stratification according to the latest atrial fibrillation guidelines, which increases the proportion of low-risk patients with CHA2DS2-VASc score.

Conflict of interest

The authors declare no conflict of interest.

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